BOOK OF FULL TEXTS

12TH INTERNATIONAL CONFERENCE ON MEDICAL & HEALTH SCIENCES

August 23 – September 1, 2026, Japan

EDITORS

Prof. Dr. Mahire BAYRAMOĞLU AKKOYUN
Prof. Dr. Gökhan OTO

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ORGANIZING INSTITUTION

CONGRESS ID

CONGRESS TITLE

12TH INTERNATIONAL CONFERENCE ON MEDICAL & HEALTH SCIENCES

DATE

August 23 – September 1, 2026

PLACE

Japan

Face-to-face & Online (Zoom)

PARTICIPANT COUNTRIES (30)

Türkiye, Nigeria, India, Morocco, Azerbaijan, Pakistan, Romania, Albania, Indonesia, Georgia, Israel, Tunisia, Iran, Ethiopia, Bulgaria, North Macedonia, Algeria, Hungary, Portugal, Bangladesh, Kosovo, Egypt, Vietnam, China, Philippines, Spain, Benin, Iraq, Malaysia, Moldova

273	29	119	154
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12th INTERNATIONAL CONFERENCE ON MEDICAL & HEALTH SCIENCES

August 23 - September 01, 2026 / Japan

CONGRESS PROGRAM



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IN-PERSON SESSION - 1

28.08.2026	HALL-1

TOKYO LOCAL TIME: 09:00-11:00

United Nations University, Shibuya, Tokyo

HEAD OF SESSION: Prof. Dr. Melekber SÜLÜŞOĞLU DURUL

Authors	Affiliation	Presentation Title
Melekber SULUŞOGLU DURUL	*Kocaeli University*	The Importance of Antioxidant Properties of Fruit Species for Human Health
Mehtap GUNEY	*Van Yuzuncu Yil University,*	What is Role of Flavonoid Sources in Rumen Fermentation
Suna CAKMAK	*Siirt University*	Biological Control from a One Health Perspective: Indirect Contributions of Trichoderma, Arbuscular Mycorrhizal Fungi, and Natural Enemies to Human Health
Züleyha DURAK Tülay GURSOY Şenol KUBİLAY	*Van Yuzuncu Yil University*	Adsorption Of Crystal Violet Dye on Our Local Soil:Characterization, Isotherm, Thermodynamics, And Kinetics
Halide TEMELCI Yusuf SECGIN Zulal ONER Muhammet CAKMAK Serkan ONER	*İzmir Bakırçay University*	Sex Prediction from Cranial Images Using Deep Learning: A Comparative Evaluation of a Dual-Stream Hybrid Architecture Based on Maxvit, Convnext, And Efficientnetv2 Models
Berfin ÖKSÜZ	*Van Yuzuncu Yil University*	Evaluation of the Effect of Honey on Wound Healing
Nilgün ONURSAL	*Siirt University*	Adsorption Technologies and the Health Effects of Heavy Metals: A Multidisciplinary Review with Examples from the World and Türkiye
Nilgün ONURSAL	*Siirt University*	HEAVY METAL POLLUTION AND BIOLOGICAL EFFECTS IN MARINE ECOSYSTEMS

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IN-PERSON SESSION - 1

28.08.2026	HALL-2

TOKYO LOCAL TIME: 09:00-11:00

United Nations University, Shibuya, Tokyo

HEAD OF SESSION: Prof. Dr. Hülya KOYUNCU

Authors	Affiliation	Presentation Title
Özden KUTLAY Tülay AKAN Şerife Nur BULAT Rumeysa CINAR	*Afyonkarahisar Health Sciences University*	Assessment of the Hepatorenal and Pulmonary Effects of Phoenixin-14 Via Cytokine Profiling In An L-Arginine-Induced Rat Model of Toxicity
Hulya KOYUNCU	*Bursa Technical University*	Heavy Metals in Public Health: Removal from Wastewater
Tuba TARHAN Ahmet ULU Burhan ATES	*Mardin Artuklu University*	Design and Investigation of Physical and Mechanical Properties of Senps-Encapsulated Mucoadhesive Nanofiber Buccal Patches for The Treatment of Oral Infections
Tülay AKAN	*Afyonkarahisar Health Sciences University*	Effects of Chemerin on Inflammatory Cytokines and Cell Migration in the Hela Cell Line
Nur ATES SAHINKAYA Nilufer DEMIRSOY	*Eskişehir Osmangazi University*	Beyond Weight Loss: An Ethical and Value-Based Evaluation of Quality-of-Life Measurement Instruments Following Bariatric Surgery
Ferdane Ozlem AKARSU Nurdan KIRIMLIOGLU	*Eskişehir Osmangazi University*	Self-Management in Epilepsy: An Evaluation from the Perspectives of Patient-Centered Care and Medical Ethics
Ayşegül BILDIIK Umay ÇILINGIR BORAZANCI	*Aydın Adnan Menderes University*	The Effect of Borage Oil on Inflammation In 2,4-Dinitrochlorobenzene-Induced Atopic Dermatitis-Like Skin Lesions in Balb/C Mice
Selda YILDIZ Nilufer DEMIRSOY	*Eskişehir Osmangazi University*	Ethical Blindness as the Missing Link Between Malpractice Fear and Defensive Medicine: A Proposed Conceptual Framework
Fatmagül YUR Neval BURKAY	*Muğla Sıtkı Koçman University*	The Future of Health Strategy: Aging Management Through Nutrigenetics and Longevity
Nazmi KANAD Gülçin OZALP GERCEKER Müjgan ERCAN KARADAG Özge FENERCIOGLU İbrahim EKER Sibel TURMUS	*Afyonkarahisar University of Health Sciences*	Evaluation Of the Effect of Specimen Collection Training Provided to Nurses in The Pediatric Hematology and Oncology Clinic on Biochemistry Specimen Rejection Rates According to Ifcc Laboratory Errors and Patient Safety Specifications

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IN-PERSON SESSION - 2

28.08.2026	HALL-1

TOKYO LOCAL TIME: 11:30-13:30

United Nations University, Shibuya, Tokyo

HEAD OF SESSION: Prof. Dr. Nurhan DOĞAN

Authors	Affiliation	Presentation Title
Sinan SARACLI Nermin TEPE Emrah OZCAN Gülseren BUYUKSERBETCI	*Balıkesir University*	The Potential Role of Ventral Lateral Anterior (Vlan) And Ventral Lateral Posterior (Vlpn) Thalamic Nuclei In Migraine Patients
Mehmet Sinan EVCIL Seray DOGAN	*Afyonkarahisar Health Sciences University*	Endodontic Treatment of a Tooth with Internal Root Resorption Using Mta
Hüseyin CALI Pınar ALKIM ULUTAS	*Aydın Adnan Menderes University*	Effects of Intermittent Fasting on Some Biochemical Parameters in Rats with Experimental Diabetes
Kübra SARICAN Pınar ALKIM ULUTAS	*Aydın Adnan Menderes University*	Investigation of the Protective Effects of Systemic and Oral Glutathione in Rats with Experimentally Induced Acute Inflammation
Ece ARMAGAN Dilara KUŞ ÖNDER	*Aydın Adnan Menderes University*	An Examination of Digital Consumer Experiences with Probiotic Products (OTC): A Qualitative Study
Esma Bilge SAHIN	*Muğla Sıtkı Koçman University*	Effects Of Thymol and Carvacrol Loaded Gelatin Sponges on Fibroblast Proliferation, Antibacterial Activity, And Coagulation İn The Treatment of Alveolar Osteitis
Dilek BOSTAN BUDAK	*Çukurova University*	Factors Affecting Young People's Entry into and Retention in Agriculture
Cahit GÜNGÖR Dilek BOSTAN BUDAK	*Çukurova University*	Effects Of Drought Shocks on Rural Household Welfare, Credit Access and Borrowing Behavior
Sevim CIFTCI YEGIN	*Giresun University*	The Aging Process: Epigenetic Approaches
Nurhan DOGAN İsmet DOGAN	*Afyonkarahisar Health Sciences University*	All-Cause And Cause-Specific Mortality Among Children Aged 0–17 Years in Türkiye, 2015–2024

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IN-PERSON SESSION - 2

28.08.2026	HALL-2

TOKYO LOCAL TIME: 11:30-13:30

United Nations University, Shibuya, Tokyo

HEAD OF SESSION: Prof. Dr. Meltem SOYLU

Authors	Affiliation	Presentation Title
Aslı SARITAŞ Amine ÇUBUKÇU Sidar GÜL	*Siirt University*	The Relationship Between E-Health Literacy and Menstrual Myths Among Young People: The Case of Siirt University
Aybüke KAYA Özlem ÇAKIN	*Hatay Mustafa Kemal University*	A Regional Study on Farmers'; Perceptions and Approaches to Land Consolidation in Türkiye
Aybüke KAYA Reyhan YAKAR	*Hatay Mustafa Kemal University*	Evaluation Of the Agricultural Labor Wage Structure in Türkiye
Hasan SARITAS Abdullah YILMAZ	*Siirt University*	Associations Among Surgical Fear, Pain Catastrophizing, And Early Mobilization Experiences in Patients Undergoing Laparoscopic Abdominal Surgery
Adem YAGAN	*Van Yüzüncü Yıl University*	A Biopsychosocial Approach to Low Back Pain: Causes and Lifestyle Modifications
Ozan AYDEMIR Adem YAGAN Berfin YUCEL AYDEMIR	*Van Yüzüncü Yıl University*	The Role of Lifestyle and Screening in Colorectal Cancer Prevention: A Primary Care Perspective
Meltem SOYLU	*Alanya Alaaddin Keykubat University*	The Missing Link in the Prevention of Iodine Deficiency: Catering Services
Meltem SOYLU	*Alanya Alaaddin Keykubat University*	Seaweeds: Are They a Sustainable Food of the Future for Turkish Cuisine?

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27.08.2026 / ONLINE / SESSION-1 / HALL-1

Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

Zoom Meeting ID: 844 6001 0824 / Zoom Passcode: 123456

HEAD OF SESSION: Mustafa KAPLAN

Authors	Affiliation	Presentation Title
Fatima SHAHBAZOVA Elif KAYA TİLKİ	*Anadolu University*	Evaluation of the Antioxidant Activity of Brimonidine Tartrate-Loaded Nanoparticles in A Tbhp-Induced Oxidative Stress Model
Bilge Nur SERIN Fuat ERDEM	*Düzce University*	Retrospective Evaluation of the Contribution of Lipid Parameters, Parathyroid Hormone, and 25-Hydroxyvitamin D Levels to Achievement of Remission and Duration of Remission in Patients with Hematological Malignancies
Gonca KARAYAGIZ MUSLU Recep KARA	*Muğla Sıtkı Koçman University*	Beyond Screen Time: Mapping Digital Over-Connectedness onto Adolescent Occupational Balance Through The A-Obs Framework
Mustafa KAPLAN Gökhan OTO	*Van Yuzuncu Yil University*	The Cytoprotective Effects of Ferula Pseudalliacea Rech. F.Methanol Extract in Rats with Bleomycin-Induced Pulmonary Fibrosis
Yusuf Sevinç Gökhan OTO	*Van Yuzuncu Yil University*	The Protective Effect of Pistacia Terebinthus L. Fruit and Gum Against Isotretinoin-Induced Hepatic Damage in Rats
Nurdan KARISAN	*Mehmet Akif Ersoy University*	Artificial Intelligence and Digital Twin-Based Vulnerable Group Management in Disasters: An International Model Proposal
Reza SABİRİ Gülbeyaz BARAN DURMAZ	*Dicle University*	Pain Management in Pediatric Intensive Care Patients and The Role of Nurses
Bilge Nur SERIN Fuat ERDEM	*Düzce University Hospital,*	Lipid Parameters, Parathyroid Hormone, and 25 - Hydroxyvitamin D Levels on Remission and Duration of Remission in Patients Diagnosed with Hematologic Malignancies

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Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

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HEAD OF SESSION: Muhammed Ahmed SELCUK

Authors	Affiliation	Presentation Title
Neryal TAHTA Salih GOZMEN	*Izmir City Hospital*	Atypical Presentations of Pediatric Hodgkin and Non-Hodgkin Lymphoma: A Single-Center Pilot Study
Nilüfer SEN	*Gazi University*	Hydration and Body Composition
Aykut EKIYOR	*Ankara Haci Bayram Veli University*	The Perception of Turkey Health Tourism Positioning Within Transnational Social Networks
Aykut EKIYOR	*Ankara Haci Bayram Veli University*	Positioning of Turkey Health Tourism Brand Value Through Transnational Social Networks
Hülya ADMIS Gülay ACAR Aynur Emine CİCEKCIBASI Güldane MAGAT	*Karabük University*	Morphometric and Morphological Analysis of the Greater Palatine Foramen and Its Association with Maxillary Sinus Pneumatization: A Cone-Beam Computed Tomography Study
Hatice BULUT	*Süleyman Demirel University*	Femtech in Women's Health: Smart Rings, Ovulation Tracking with Wearable Devices, and Digital Nursing
Ayşe Zehra OZDEMIR Sıdıka ERTURK TOKER	*Istanbul University*	Plasma, Serum or Dried Blood Spots? An Analytical Chemistry Perspective on Imatinib Therapeutic Drug Monitoring
Osman Deniz KULAC Hülya OZDEMIR	*Van Yuzuncu Yil University*	A Retrospective Investigation of the Effects of Postoperative Prophylactic Antibiotic Therapy Profiles on Length of Hospital Stay Following Spinal Fusion Surgery
Muhammed Ahmed SELÇUK	*Siirt University*	Heavy Oestrus Ovis Infestation in a Sheep

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27.08.2026 / ONLINE / SESSION-1 / HALL-3

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HEAD OF SESSION: Ayşe Kübra SAP KINAR

Authors	Affiliation	Presentation Title
Ayşe Kübra SAP KINAR	*Uşak University*	Association Between Digital Media Use, Social Life Characteristics, and Social Cognition in Retired Adults Aged 55 Years and Older
S. BENABDI M. AMANI K. DAHO H. ALLALI D. BOUMENDIL	*Pediatric Emergency Hospital Canastel Oran*	Urgent Placement of Dialysis Catheter in Children: Challenges and Anesthetic Issues
Ezgi DARICI KURT Miray Nilüfer ÇIMŞIT KEMAHLI Mehmet Reşit ASOGLU	*Bahceci IVF center*	Cost-Effectiveness Of Omitting Routine Endocrine and Ultrasound Monitoring During Hormone Replacement Therapy Cycles for Frozen Embryo Transfer in Good-Prognosis Patients: A Cost-Effectiveness Analysis
Gülsüm KAYA Cengiz KARACAER	*Yalova University*	Evaluation of Hematological Parameters and Systemic Inflammatory Markers in Helicobacter pylori Infection
Ümmü Gülşen BOZOK	*Ankara Medipol University,*	Exosomes in Ischemia-Reperfusion Injury: Experimental Evidence and Emerging Clinical Significance
Ayşe INKAYA Havva KACAN	*Kastamonu Education and Research Hospital*	The Effect of a Nurse-Led Coping Psychoeducational Program for Family Caregivers of Palliative Care Patients on Care Burden, Coping Strategies, and Burnout: A Semi-Experimental Study
Nisanur GULER Havva KACAN	*Kastamonu Education and Research Hospital*	The Effect of Intolerance of Uncertainty on Coping Strategies Among Parents of Children with Autism Spectrum Disorder and Psychiatric Diagnoses: A Comparative Study
Sinan ELIACIK Sena YANIKOGLU	*Hitit University*	Dietary Patterns in Parkinson' S Disease: An Updated Mini-Review (2024–2026)

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HEAD OF SESSION: Ibrahim Umar

Authors	Affiliation	Presentation Title
Andrea Lehoczki Vince Fazekas-Pongor Dávid Major Mónika Fekete	*Institute of Preventive Medicine and Public Health*	Fermented Foods as Modulators of the Gut Microbiome: Implications for Metabolic, Immune and Brain Health
Gheorghe Giurgiu Manole Cojocaru	*Deniplant-Aide Sante Medical Center*	Inflammation Now the Key Target for Seborrheic Dermatitis
Gazi Abu Horaira Sultan Ahmed Jobair Siaf Ahmed Khan Rezvy Taimiah Bin Harun	*University of Lisbon*	The Impact of International Migration and Remittances on Health Outcomes of Rural Households in Bangladesh
Iqra Farzeen Asma Ashraf Muhammad Muzammil Nazir Sehrish Muzaffar	*Government College University*	Mechanistic Insight into Anti-Inflammatory Activity of Fagonia Cretica Via COX Inhibition and Multimodal Pharmacological Evaluation
Amal Ghribi Mariem Ben Hmida Houda Ben Ayed Nouha Ketata Hanen Maamri Sourour Yaich	*Hedi CHAKER University*	Satisfaction among Mothers Regarding Childhood Vaccination Sessions at a Tunisian Primary Health Center
Amal Ghribi Nouha Ketata Houda Ben Ayed Mariem Ben Hmida Hanen Maamri Sourour Yaich	*Hedi CHAKER University*	Depression among Teachers in Southern Tunisia: Prevalence and Associated Factors
Ibrahim Umar Titus Matthew Yakubu Usman Mu'azu Nasiru Kontagora	*Umaru Sanda Ahmadu College of Education*	Innovations in Medical Biotechnology, Genetics, and Molecular Biology: A Critical Review of Challenges, Limitations, and Future Directions
Shukria Islam Tanjum Islam Kotha Nusrat Afrin	*University of Global Village*	How Social Media Reviews Influence Consumers for Selecting Restaurant
Sudhangshu Chakraborty Soumen Prakash Kabi	*Asansol Engineering College*	Smart Urban Ecosystems Enabled by Intelligent Internet of Things Networks

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HEAD OF SESSION: K. Thamizhmaran

Authors	Affiliation	Presentation Title
Madalina Sorop Ion Petre Bogdan Sorop Tiberiu Buleu Daian Ionel Popa Florina Buleu Izabella Petre	*"Victor Babes" University of Medicine and Pharmacy Timisoara*	Interleukin-6 and Gestational Age in Pregnant Women with COVID-19 and Hypertensive Disorders of Pregnancy
Mihai Loichita Ion Petre Ionut Faur Razvan Bobora Alexandru – Marius Furau Izabella Petre	*"Victor Babes" University of Medicine and Pharmacy Timisoara*	Hematologic Dynamics During Platinum-Based Treatment in Patients with Stage III Cervical Cancer
Anwar Mallongi Atjo Wahyu Apollo Apollo Wahiduddin Wahyuni Salewe Muh Taufik Hidayat Stang Ernyasih A. Muh. Faudzul Adziim	*Hasanuddin University*	Calculating the Health Risks using Monte Carlo Simulations due to Carbon Dioxide and Particulate Matter 10 Pollutants in Cement Industrial Area, Pangkep Indonesia
Adrian Loichita Ion Petre Narcisa Carmen Mladin Alexandru – Marius Furau Ioana Marin Izabella Petre	*"Victor Babes" University of Medicine and Pharmacy Timisoara*	Maternal Arterial Stiffness and Adverse Neonatal Outcomes in Hypertensive Pregnancies: Linking Vascular Dysfunction to Perinatal Risk
Tahri Nouhayla Mikou Karima Nabloussi Abdelghani	*Sidi Mohamed Ben Abdellah University*	Field Evaluation of EMS-Induced Sesame (Sesamum indicum L.) Mutants for Adaptation to Early Sowing under Semi-Arid Conditions
Samin Shafigh Yu-Hsin Chen	*Wenzhou Medical University*	A Review on Non-Pharmacological Interventions for Sleep Disorders
El Mostafa Benharaf Ali Barhoumi Ahmed Moufti Mohamed Taoufik Mohammed Chafi Abdellah Zeroual Mohammed El Idrissi	*Sultan Moulay Slimane University*	Computational Insights into Novel Organic Photosensitizers for Dye-Sensitized Solar Cell Applications
Saemira Durmishi Rezarta Lalo Mitilda Gugu	*"Ismail Qemali" University*	Health Information Sources and Their Association with Lifestyle Behaviors Among Pregnant Women: A Cross-Sectional Study in Vlora, Albania
K. Thamizhmaran R. Vimali	*Government College of Engineering*	An Analysis of the Role of 5G and 6G Networks in Enabling Smart Healthcare Services

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27.08.2026 / ONLINE / SESSION-1 / HALL-6

Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

Zoom Meeting ID: 844 6001 0824 / Zoom Passcode: 123456

HEAD OF SESSION: Poonam Dhiman

Authors	Affiliation	Presentation Title
Fateme Asadi TOURANLOU	*Tehran University of Medical Sciences*	Artificial Intelligence and Machine Learning Applications in Predictive Microbial Risk Assessment for Food Safety: A Systematic Review of Emerging Approaches
Mahira Firudin kizi Amirova	*Azerbaijan Medical University*	Bidirectional Microbiota-Immune-Nervous System Interactions in Neurological Disorders
Ilochi N. Ogadinma Wodu F. Emomotimi	*Federal University Otuoke*	Study Of the Effect of Organosulphur Extract of Onion and Garlic Juice on Heavy Metal-Induced Renal Toxicity in Male Wistar Rats
Tuhina Sinha Priya Chaudhuri	*Amity University*	Global Health Governance and Sovereign Compliance: Re-evaluating the Human Right to Health Under the WHO&39; s International Health Regulations
Omer Shujat Bhatti M. Asad Ghufran Atta Ullah Shah	*School of Architecture Planning*	Transforming Adversity into Opportunity: Assessing User Satisfaction in Hospital Transformation In Lieu Of a Pandemic Through the Multi Corridor Expansion Model for Epidemic Management and Environmental Design Enhancement
Shom Prakash Kushwaha Syed Misbahul Hasan Pushpendra Soni	*Integral University*	Pharmacophore Mapping for Anti-Lung-Cancer Agents
Mina Gholami Samaneh Mahmood-Aghdam Alireza Ahmadi Hedieh Rahmati Mehrnaz Izadpanah Abdolreza Daneshvar Amoli Mansoureh Farhangniya Shiva Mohammadi Mohammad Hossein Sanati Zahra Elyasi Gorgi	*Iranian Biological Resource Center*	A Renewable Biobank of EBV-Immortalized Lymphocytes from Globozoospermia Patients to Advance Reproductive Genetics and Andrology Research
Poonam Dhiman	*Sai Mohan College of Education*	Healthcare Education Progressive Role in Biomedical Waste Management and Environmental Sustainability

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Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

Zoom Meeting ID: 844 6001 0824 / Zoom Passcode: 123456

HEAD OF SESSION: Ruhul Amin

Authors	Affiliation	Presentation Title
Ruhul Amin	*Comilla University*	Patient Satisfaction with Public Healthcare Services in Bangladesh: An Inclusive Assessment of Accessibility, Quality, Equity, and Service Delivery.
Iram Liaqat	*Overnment College University*	Flagellar assembly role in Salmonella FlhA deleted strain biofilm formation
Mohd Usman Mohd Siddique Azim Ansari	*SVKM NMIMS Global University*	AI-Enabled Multiscale Molecular Modelling and Advanced Data Analytics for the Identification of Phenolic Lead Molecules Against Human Metapneumovirus
Rajeev Kumar	*Manav Rachna International Institute of Research and Studies*	Sustainable Adsorptive Removal of Pharmaceuticals from Wastewater: One Step for Healthcare
Skender Demaku Arbnorë Aliu Donika Sylejmani Anita Ismajli Shqipe Berisha	*JES's SND College of Pharmacy*	Stem Cell-Based Tissue Repair and Regeneration
Madhuri Gaikwad	*University of Prishtina "Hasan Prishtina"*	Physicochemical, Biological, and Heavy Metal Analysis and Assessment of Water and Sediment at the Lluzhan Spa, Podujevë, Kosovo
Hadia Tabbasum Shazia Perveen Sumaira Kanwal	*The Women University Multan*	Antidiabetic, Antioxidant and Tissue Protective Effects of Alumina, Iron-Alumina composite and Silica-Chitosan hybrid Nanoparticles in Alloxan-Induced Diabetes in Rabbits
Milea Diana	*Constantin Stere" University of European Political and Economic*	The Role of Forensic Medicine and Psychiatry in Identifying and Documenting Forced Marriage
Izabella PETRE Narcisa Carmen MLADIN Daian Ionel POPA Florina BULEU Elena BUSUIOC Maryam KRROSHEN Ion PETRE	*"Victor Babes" University of Medicine and Pharmacy Timisoara*	Progressive Arterial Stiffening in Hypertensive Pregnancies: A Longitudinal Assessment of Maternal Vascular Adaptation

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Tokyo Local Time: 17:30-19:30 Ankara Local Time: 11:30-13:30

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HEAD OF SESSION: Selin Engür Öztürk

Authors	Affiliation	Presentation Title
Erbil ARIK Eyüp ZENGIN	*Marmara University*	Double Retrograde Trans-Femoral Access Technique (Dore-Tract) For Endovascular Treatment of Combined Iliac and Femoral Artery Stenosis: Technical Description and Preliminary Experience
Ahmet AKKOCA Burcu GULTEKIN	*Necmettin Erbakan University*	Therapeutic Effects of Elamipretide on Cardiac Electrical, Hemodynamic, And Histopathological Parameters in a Rat Model Of 5-Fluorouracil-Induced Cardiotoxicity
Şevval YEYIT BOZDEMIR Havva KACAN	*Kastamonu Üniversitesi*	Artificial Intelligence Applications İn Psychiatric Nursing: Areas of Use and Limitations
Nilgün OKSEL Zeliha Cansel OZMEN	*Tokat Gaziosmanpaşa University*	The Relationship Between Hypothalamic-Pituitary-Gonadal and Thyroid Axis Hormones and Semen Analysis Parameters: A Retrospective Evaluation
Ayşe Beyza BEKGOZ Hüseyin Nejat KUCUKDAG	*Düzce University*	Investigation of the Relationship Between Troponin T Levels and Platelet Count and Platelet Indices in Emergency Department Admissions with Suspected Acute Coronary Syndrome
Gökhan GUNDOĞDU Çağrı KALE	*Van Yüzüncü Yıl University,*	Effect of Chasteberry (*Vitex agnus-castus* L.) Seed Volatile Oil Added to The Diet on Performance, Carcass and Some Antioxidant Parameters in Quail (*Coturnix coturnix japonica*) Exposed to Stocking Density Stress
Selin ENGUR OZTURK	*Pamukkale University*	Dose-Dependent Vascular Tolerability of Hydrocortisone in the in Ovo Chorioallantoic Membrane Model: A Filter-Disc-Based Study
Sinan DEGIRMENCIOGLU Ali SEVGILI	*Bozova Mehmet-Enver Yıldırım State Hospital,*	Direct Laryngoscopy-Assisted I-Gel Placement for Flexible Bronchoscopic Cryotherapy in Severe Post-Intubation Tracheal Stenosis: A Case Report
Mehtap GENC Ahmet SANLI Emre CIYDEM	*Karamanoğlu Mehmetbey University*	The Relationship Between Belief in Sexual Myths and Sexual/Reproductive Health Stigma Among Women of Reproductive Age: The Mediating Role of Cognitive Distortions

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HEAD OF SESSION: Ali Yücel Kara

Authors	Affiliation	Presentation Title
Ali Yucel KARA	*Izmir Katip Celebi University*	Physiological Effects of Mortality Salience: Autonomic Nervous System Responses and Neuroendocrine Findings
Oguzhan AKPINAR Umut Yasin OZDEMIR	*University of Health Sciences Bursa*	Occult Renal Mass as The Probable Primary Source of Solitary Brain Metastasis of Unknown Origin: A Multidisciplinary Diagnostic Approach
Halil Can YILDIZ Esin ÖZLEK	*Van Yüzüncü Yıl University*	Non-Surgical Endodontic Treatment in a Tooth with a Large Periapical Lesion: A Case Report
Halil Can YILDIZ Esin ÖZLEK	*Van Yüzüncü Yıl University*	Root Canal Treatment of a Tooth with a Periapical Lesion: A Case Report
Omer UNAL	*Samsun University*	Evaluation of Neurophysiological Dynamics Between Sleep Stages Through Quantitative Electroencephalogram Spectral Analysis
Nilufer AKGUN UNAL	*Ondokuz Mayıs University*	Investigation Of the Effects of Ventricular Arrhythmias on Cardiac Autonomic Modulation Through in Silico Time-Domain Signal Analysis
Saniye Merve CENGIZ Ahmet Fatih CENGIZ Gökhan COBAN Ahmet Emin DEMİRBAS Abdullah Kemal ZENGIN	*Mersin University*	Management Of Bimaxillary Prognathism, Gummy Smile, And Skeletal Class Ii Malocclusion with Bimaxillary Orthognathic Surgery and Genioplasty: A Case Report
Saniye Merve CENGIZ Ahmet Fatih CENGIZ Ömer Faruk BAKI	*Mersin University*	Orthodontic Management of a Missing Maxillary Central Incisor Following Trauma: A Case Report

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Tokyo Local Time: 17:30-19:30 Ankara Local Time: 11:30-13:30

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HEAD OF SESSION: Serhat SUNAR

Authors	Affiliation	Presentation Title
Serhat SUNAR	*Kafkas University*	Toxicological Effects of Ivermectin, A Commonly Used Antiparasitic, On the Male Reproductive System and Sperm Quality
Serhat SUNAR	*Kafkas University*	Effects Of Environmental Factors on Sperm Quality in Different Rabbit Breeds: A Comparative Review
Selçuk ALBAYRAK Oğuz MERHAN	*Kafkas University*	Preliminary Evaluation of Clinical, Acute-Phase Protein, And Biochemical Findings in Common Buzzards (Buteo Buteo) And European Honey Buzzards (Pernis Apivorus) Admitted to Wildlife Rehabilitation
Selçuk ALBAYRAK	*Kafkas University*	Masking Phenomenon in Raptors and Introducing the Observation-First Clinical Approach (Ofca)
Efsun SOMAY Sibel BASCIL	*Baskent University*	The Host Tissue Repair Vulnerability Index (HTRVI): A Composite Biomarker for Predicting Osteoradionecrosis in Locally Advanced Nasopharyngeal Carcinoma
Medine SIMSEK Taha Emre KOSE	*Recep Tayyip Erdoğan University*	Asymptomatic Internal Root Resorption Identified on Routine Radiographic Examination: A Case Report
Medine SIMSEK Taha Emre KOSE	*Recep Tayyip Erdoğan University*	Incidentally Detected Retained Pellets on Routine Panoramic Radiography: A Case Report
Esma OSMAN Esra GUNEY	*İnönü University*	The Impact of Healthy Lifestyle Behaviors on Fertility and the Role of Midwives in Supporting Fertility
Esma OSMAN Esra GUNEY	*İnönü University*	Alternative Birth Methods: Water Birth, Planned Home Birth, Vaginal Birth After Cesarean, And Epidural Birth

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Tokyo Local Time: 17:30-19:30 Ankara Local Time: 11:30-13:30

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HEAD OF SESSION: Kanchi Ravi Padma

Authors	Affiliation	Presentation Title
Kanchi Ravi Padma	*Women's University*	Artificial Intelligence for Intelligent Disaster Management: Advancing Smart Agriculture and Healthcare Resilience
Rosa Aulia Ananda Safani Ranti Ekasari Lilis Widiastuty Fatmawaty Mallapiang	*Universitas Islam Negeri Alauddin Makassar*	Analysis of Lead Levels in Automotive Painting Workers in Makassar City
Balasubramani G L Rinky Rajput Manish Gupta Pradeep Dahiya Jitendra K Thakur Rakesh Bhatnagar Abhinav Grover	*Jawaharlal Nehru University*	Structure-Based Drug Repurposing to Inhibit the DNA Gyrase of Mycobacterium Tuberculosis
Nodar Sulashvili Margarita Beglaryan Nino Didbaridze Nana Gorgaslidze Lasha Tchelidze Magda Davitashvili Irina Imerlishvili Vira Kravchenko Marika Sulashvili Nato Alavidze Nino Abuladze David Aphkhazava Igor Seniuk Marina Giorgobiani Lela Grigolia Kakhaber Robakidze	*Georgian National University SEU*	Scientific Discourse on Epilepsy: Immunological and Other Pathogenetic Mechanisms, Diagnostic Challenges, Pharmacological Management, Drug-Related Complications, Current Advances in Diagnosis, Precision Therapeutics, Clinical Outcomes and Future Research Perspectives Worldwide
Aleksandar STOYANOV Dario ZEHTINSKI Martin SHOPOV Tonislav VLAHOV Rumyana STOYANOVA	*Technical University of Sofia*	The Role of Chatgpt in Providing Mental Health Information and Support: A Literature Review
Rana Osman Rama Mousa Alaa Sheta	*Nile University*	Vision Transformer-Based Breast Cancer Classification from Histopathological Images
Adamu Amanu Asari Ameyu Godesso Zewdie Birhanu	*Jimma University*	Health Literacy Status Among Adolescents and Implications in Ethiopia
Boutaina Yahyai Rajae Agnaou Meyrem Doubi Chaimae Torres Fatima Zahra Hafid Driss Hmouni Brahim Bourkhiss	*Biotechnology and Plant Protection*	Moroccan Middle Atlas Medicinal Flora: Methodological Framework For Phytochemical and Anti-Inflammatory Bioactivity Screening
Pooja Rasal Gaurav Kasar Aman Upaganlawar Pranoti Nikama Akanksha Punekar Sayali Patil Chandrashekhar Wake	*JES's SND College of Pharmacy*	Natural Compounds in the Prevention and Management of Neurological Disorders: Therapeutic Potential and Future Perspectives

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HEAD OF SESSION: Bledar Kraja

Authors	Affiliation	Presentation Title
Bledar Kraja	*University of Medicine Tirana*	The Impact of Physical Activity, Obesity and Body Mass on Colorectal Cancer Risk: Mechanisms and Preventive Strategies
Bismillah Iftikhar	*Essentials Healthcare Lahore*	Optimizing Vitamin D3 Bioavailability: Development of High-Dose Oral Shot Formulation (Vol-D)
Gowhar Ahmad Wani Shifanath A. S. Thasneem K. A.	*B.S. Abdur Rahman Crescent Institute of Science and Technology*	Health Insurance and Financial Protection in India: Challenges and Prospects
Muhammad Saleh Faisal	*Khyber Medical College*	Pharmacogenetic Role of UGT1A6 Gene Polymorphism in Antiepileptic Drug Response
Varun V. Joshi Nitu L. Wankhede Aman B. Upaganlawar Chandrashekhar D. Upasani	*SNJB's Shriman Sureshdada Jain College of Pharmacy*	Neuroprotective Potential of Natural Compounds Against Streptozotocin- Induced Diabetic Peripheral Neuropathy: A Preclinical Study
Nwaforbe Frank L. Adekola Saheed A Bakare Mustapha Umar Musah Khadijat Toyin	*Federal University of Environment and Technology Koroma/Saakpenwa Rivers State*	Use of Digital Interventions for Hygiene Promotion among Primary School Students in Nigeria: A Narrative Review
Divyadharshini R Jai Shyam S Karthika H	*R.M.K. Engineering College*	Low-Cost Healthcare Technologies
Dhikroh Oriyomi Adekola Khadijat Toyin Musah Saheed Ayodeji Adekola Sodiq Adetunji Adekola	*University of Abuja*	Access to and Outcomes of Epidural Labour Analgesia in Low-Resource Settings: A Comparative Analysis of Urban vs. Rural Healthcare Facilities in Nigeria
Fatima El hilah Nadia Belahbib Jamila Dahmani Lahcen Zidane	*Ibn Tofail University*	Pharmacological Validation of Moroccan Medicinal Plants in the Management of Chronic Diseases: A Critical Synthesis

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27.08.2026 / ONLINE / SESSION-2 / HALL-6

Tokyo Local Time: 17:30-19:30 Ankara Local Time: 11:30-13:30

Zoom Meeting ID: 844 6001 0824 / Zoom Passcode: 123456

HEAD OF SESSION: Brahmi Zahia

Authors	Affiliation	Presentation Title
T.N.Kosayeva A.T.Amiraslanov B.E.Abbasov	*Azerbaijan Medical University*	Pd-L1 Expression in Epithelial Ovarian Tumors: Clinicopathological Implications
Bledar Kraja Fatjona Kraja	*University of Medicine*	Determinants of Survival in Albanian Patients with Gastric Cancer: A Retrospective Cohort Study
Fatjona Kraja Erald Karaulli	*University of Medicine*	Personalizing Local Treatment in Early-Stage Breast Cancer: Which Patients May Safely Avoid Adjuvant Radiotherapy?
Boutaina Yahyai Rajae Agnaou Meyrem Doubi Chaimae Torres Fatima Zahra Hafid Driss Hmouni Brahim Bourkhiss	*Biotechnology and Plant Protection*	Moroccan Middle Atlas Medicinal Flora: A Methodological Framework for Phytochemical and Anti-Inflammatory Bioactivity Screening
Brahmi Zahia Gherissi Djallel Eddine	*University of Souk-Ahras*	Integrated Estradiol Profiling and Transrectal Ultrasonography Reveal Distinct Reproductive Responses in Dromedary Camels
Deven S. Aspalani Anuja B. Bahirat Pushpraj S. Shelke Buddhagosh J. Khandezod Sushant R. Gite Pooja U. Gunjal Prajakta P. Mande	*Savitribai Phule Pune University*	Digital Twin-Based Personalized Pharmacotherapy: Integrating Pharmacokinetics, Pharmaceutical Formulation and Patient-Specific Data for Precision Healthcare
Dovonou Mehinto Flore Houndji Pamphile	*University of Abomey-Calavi*	Influence Of Climatic Factors on the Prevalence of Water-Related Diseases in the Municipality of Lokossa (Benin)
Usman Kris Joko Suharjo Tunjung Pamekas Lidia Yunirti Manik	*University of Bengkulu*	Promoting The Formation of Solo Garlic by Vernalization of Different Sources of Planting Materials

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Tokyo Local Time: 17:30-19:30 Ankara Local Time: 11:30-13:30

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HEAD OF SESSION: Sawaira Moeen

Authors	Affiliation	Presentation Title
Z Ait Said L Harchaoui S Ouafi	*Research Laboratory on Arid Zones*	Exploring the Antioxidant and Anti-inflammatory Potential of Solenostemma argel Phenolic Extracts
Brahim Elhilali Moulay Lafdil Belghiti Abdelhak Saidi Abdelkader Chahlaoui	*Moulay Ismaïl University*	Evaluating Physico-Chemical and Organic Pollution Dynamics Using the WQI And OPI At Ouislane Wadi (Meknes), Morocco
Sawaira Moeen Muhammad Ikram	*Government College University Lahore*	Designing G-C 3 N 4 /PVP@Ca(OH) 2 Ternary Heterostructure Catalysts for Efficient Degradation of Dyes and Antibacterial Activity
Zdravka Harizanova Ferihan Popova Fanka Gerginska Sabri Sabri Zlatizara Todorova Lilia Grozlekova Vyara Zaykova Polina Ivanova	*Medical University of Plovdiv*	A Band-shaped Pes Anserinus Insertion: An Anatomical Variant with Implications for Tendon Graft Harvesting
Reda Chahir Océane Pertegaz Salma Chakir Noureddine Hammani Hinde Aassila Marie Potier-Cartereau Naoual Oukkache	*Hassan I University*	Characterization and Anticancer Properties of Venom-Derived Peptides from the Moroccan Scorpion Androctonus mauritanicus and the Cobra Naja haje: Proteomic Insights, Inhibition of Cell Proliferation and Migration, and Modulation of Ion Channels in Human Glioblastoma Models
Melkamu Adamu Belaynew Asmamew Genet Yohanes Almeken Berihun and Melkeneh Wondie	*Gambella University*	Illegal Wildlife Hunting Patterns, Techniques, and Local Community Aspects in the case of Jikaw District, Southwest Ethiopia
Aishwarya S Priyanka K Varshana Deepa M Samiksha R K	*R.M.K. Engineering College*	Medical Sciences
Fozia Anjum Muhammad Shahid	*Government College University Faisalabad*	Microbial Production of Glutathione Under Optimal Conditions Using Poultry Waste

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Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

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HEAD OF SESSION: Merve Türkegün Şengül

Authors	Affiliation	Presentation Title
Deniz OZKAN VARDAR	*Lokman Hekim University*	A New Approach Methodology-Based Comparative Assessment of the Thyroid-Disrupting Potential of Bisphenol A, Bisphenol S, And Bisphenol F
Mine TOPAL Emine YASSIBAS	*Gazi University*	Avoidant/Restrictive Eating Disorder in Patients with Celiac Disease
Özge Sultan BALIKCI Ezgi SESEN	*Ankara Medipol University*	Paralinguistic Features of Infant-Directed Speech (Motherese) in Mother-Child Interaction in Language Development: A Systematic Review
Merve TURKEGUN SENGUL	*Alanya Alaaddin Keykubat University*	Causal Inference from Observational Studies: Methodology and Reporting Principles for Target Trial Emulations
Havva KACAN Şevval YEYIT BOZDEMIR	*Kastamonu University*	An Examination of Nursing Approaches to Common Mental Disorders in Adolescence in Light of Current Evidence
ŞEVİN AKSOY SACİDE PEHLIVAN	*Istanbul University*	Genetic And Epigenetic Mechanisms of Restricted and Repetitive Behaviors İn Autism Spectrum Disorder: Their Relationship with Emotion Regulation and Emotion Dysregulation
Ayça TOPRAK SEMIZ	*Recep Tayyip Erdoğan University*	Repurposing Of Existing Drugs for Nsaid-Induced Gastric Ulcers: Insights from Recent Experimental Studies
Hülya SARAY KILIC	*Bilecik Şeyh Edebali University*	Fear Of Falling in Surgical Patients: A Narrative Review of Prevalence, Risk Factors, Clinical Outcomes, And Nursing Interventions
Kaya OZEN	*Gazi Yaşargil Training and Research Hospital*	Atherosclerosis: Comparison Of Global and National Perspectives in Prevention, Diagnosis, And Treatment

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HEAD OF SESSION: Özge Çimen

Authors	Affiliation	Presentation Title
Kevser PAMUK Eren SARITAS Nazmiye YILDIRIM	*Afyonkarahisar Health Sciences University*	Examining Postgraduate Theses Involving Laughter Yoga Interventions in Türkiye: A Document Analysis
Fatma Ayşe UZ Çağdaş AKTAN	*Bandırma Onyedi Eylül University*	Non-Coding Rna Networks and Molecular Signaling Pathways in the Development of Castration-Resistant Prostate Cancer
Elif MANSUROGLU Gülbin OZCELIKAY	*Ankara University*	Pharmacist-Administered Vaccination in Turkey: A Legal Document Analysis
Özge CIMEN	*Nuh Naci Yazgan University*	Evidence-Based Nursing Practices in Burn Patient Care
Bengisu ARSLANTAS Zeynep BIRSU CINCIN	*ADAM European Center for Lifelong Learning, Research & Development*	A Modular 3D-Printed Titanium Microscrew–Assisted Platform for Stable and Reproducible EEG Recordings in Behavioral Neuroscience
Bengisu ARSLANTAS Dilara KOCABAL Zeynep BIRSU CINCIN	*ADAM European Center for Lifelong Learning, Research & Development*	Mixture-aware systems pharmacology maps hazelnut-oil constituents onto phase-specific human wound-repair states
Tarana SULEYMANOVA Aytac ALLAHVERDIYEVA Günel ALIYEVA	*Azerbaijan Medical University*	Microbiological Diagnostic Methods for Catheter-Associated Urinary Tract Infections Following Surgical Procedures
Zekeriya CETINKAYA	*Kayseri State Hospital*	Evaluation of Thyroid Functions, Vitamin B12, Folate, Ferritin and Metabolic Parameters in Patients with Ptosis: A Controlled Study
Işıl KURT Gamze KUŞ Hayal GÜLER	*Hatay Mustafa Kemal University*	Association of Pain Intensity and Functional Status with Adipose Tissue, Muscle Strength, And Physical Activity in Individuals with Chronic Low Back Pain

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HEAD OF SESSION: Nazife Nur AKBULUT

Authors	Affiliation	Presentation Title
Ahmet CALISKAN Betül KARABUDAK Sena AKSOY Harun EROL Bekir SALIH Hacı Mehmet KAYILI	*Karabük University*	N-Glycan Profiling of Renal Cell Carcinoma for Maldi Mass Spectrometry
Ahmat Adam AMIR Esra Nur AKYILDIZ Sena AKSOY Betül KARABUDAK Bekir SALIH Hacı Mehmet KAYILI	*Karabük University*	Meat Product Authentication Based On N-Glycan Profiles
Fatih SARGIN	*Antalya City Hospital*	Liver Laceration Following Polytrauma, Hemopneumothorax, And Multiple Complications During an Extended Intensive Care Stay: A Case Report
Nazife Nur AKBULUT	*Recep Tayyip Erdoğan University*	Investigation Of Findings Before and After Voice Therapy in a Case with Unilateral Vocal Fold Atrophy and Muscle Tension Dysphonia
Ramazan USTUN Erbil SEVEN Ayşe SEKER Harun EYYUPKOCA	*Bolu Abant İzzet Baysal University*	Decrease in B3-Tubulin and Neurofilament Heavy Chain (Nfh) Immunoreactivity Following Optic Nerve Crush Injury in Mice: A Comparative Analysis of Control and Injury Groups
Harun EYYUPKOCA	*Van Yüzüncü Yıl University*	The Brain in Crisis: Neurophysiological Foundations of Acute Stress, Triage, And Simulation Training in Pre-Hospital Emergency Health Services
Rüştü ERSOY SAKAYRA Muhammed Mustafa AKAR	*Atatürk University*	Rehabilitation of Complete Edentulism with Screw-Retained Implant-Supported Fixed Prostheses Using a Digital Workflow:A Case Report
Aynur Karadağ GÜREL Gökhan GÖRGIŞEN Hamdullah YANIK	*University of Health Sciences*	Identification of Common Peripheral Blood Transcriptomic Biomarkers Across Female Cancers

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Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

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HEAD OF SESSION: Umar Baba Shaaba

Authors	Affiliation	Presentation Title
Umar Baba Shaaba	*Ahman Pategi University*	Artificial Intelligence Adoption and Financial Reporting Quality: Evidence from Small and Medium-Sized Enterprises in Nigeria
Umar Baba Shaaba	*Ahman Pategi University*	The Role of Forensic Accounting in Combating Financial Fraud and Enhancing Corporate Governance in Emerging Economies
Nurliani Erni Suhardi Suhardi	*Mulawarman University*	Phenotypic Diversity and Correlation of Body Condition Score with Bali Cattle Body Size
Bornare Ashwini	*JES's SND College of Pharmacy*	Advanced Nanotechnology-Based Drug Delivery Systems
Ranti Ekasari Dian Kurnia Ningsih Nurul Fasya Faisal Nur Inayah Rustan Randi Surya Rannu Muhammad Zulfikar Djafar	*Universitas Islam Negeri Alauddin Makassar*	Work Posture Assessment Among Retail Cashiers: A Descriptive Ergonomic Study in Makassar, Indonesia
Chahid SLIMANI Abdellah BAHTAT	*Sidi Mohamed Ben Abdellah University*	Artificial Intelligence and Medical Decision-Making: Redefining Physician Autonomy, Patient Consent, and Liability
Maria Fareed Siddiqui Umar Raees	*University of Lahore*	Navigating the Infodemic: COVID-19 Literacy and Treatment Misconceptions Among Medical and Non-Medical Workers in Punjab
Mohammad Moneruzzaman Khandaker Shahida Kanwal Mohd Hailmi Sajili	*Universiti Sultan Zainal Abidin*	Enhancing Growth, Cellular Structure, and Anthracnose Resistance in Chilli Using Sargassum polycystum Extracts
Abdelaadim Khriss Aissa Kerkour Elmiad Mohammed Badaoui Filip Šuligoj	*Mohammed Premier University*	Learning Anatomical Spatial Relationships for Landmark Detection in Full-Leg Radiographs

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Tokyo Local Time: 15:00-17:00 Ankara Local Time: 09:00-11:00

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HEAD OF SESSION: BKIRI Abderrahim

Authors	Affiliation	Presentation Title
Mark Anthony N. Polinar Mary Adeline B. Delos Cientos Joanna Marie U. Ato April Marie N. Mahipos Jenalyn B. Boctot	*Mabolo National High School*	Social Media Platform Utilization and Perceived Business Growth among Food Micro, Small, and Medium Enterprises (MSMEs)
Muawuya Ibrahim Gumi A.M K. Abdullahi Shamsudeen Muhammad Muhammad Lema Aisha Muhammed	*Abdullahi Fodio University of Sci. and Tech.*	Assessment of Anthocyanin Pigmentation Diversity among Rice (Oryza glaberrima Steud.) Varieties Using Spectral Pigment Indices
Hari Nandhini A Ramya G	*Bharath Institute of Higher Education and Research*	3D-Printed Medicines: The Future of Personalized Drug Therapy
Nyayiru Kannaian Udaya Prakash Srinivasan Bhuvaneswari	*Technology and Advanced Studies*	The Atmospheric Presence of Aspergillus Fumigatus, A Who Priority Pathogen in Chennai, India: Historical Evidence From 1996-1998
Olaniyi Habib ALIU Jamiu Rotimi OLASINA	*Federal Polytechnic Ilaro*	Lightweight Convolutional Neural Networks for Automated Malaria Parasite Detection in Blood Smear Microscopy Images
BKIRI Abderrahim	*Faculty of Sciences of Kénitra*	Valorization Of Waste Rocks from Tte Former French Mining Company Of MIBLADEN: Recovery of Lead and Barite.
Oluwatosin Emmanuel AKINSUROJU	*Federal University*	Resource-Utilisation and Internal Efficiency of Medical and Health Sciences Programmes in Universities in Ekiti State, Nigeria: Implications for Quality and Sustainable Health Workforce Development
Mariami Managadze	*Tbilisi State Medical University*	The Problem of Microplastics in Environmental Medicine
Olaniyi Habib ALIU Jamiu Rotimi OLASINA	*Federal Polytechnic*	Explainable AI for Student Dropout Risk Prediction in Nigerian Polytechnics

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HEAD OF SESSION: Bhavesh Bhamare

Authors	Affiliation	Presentation Title
Ilochi. N. Ogadinma Adeolu Esther Abiola	*Federal University Otuoke*	The Impact of Hygiene Education in Reducing Respiratory Infection Among 400 Level Nursing Students in Madonna University
Ilochi. N. Ogadinma Adeolu Esther Abiola	*Federal University Otuoke*	Exploring The Effect of Noncompliance with Malaria Treatment on Academic Performance Among Undergraduate Students
A.O. Ibegbu I. Mullaney L. Fyfe D. MacBean	*Federal UniversityNdufu*	Stress Predisposes Neuronal Cells to changes in G-Protein Coupled Receptor Gene Expression in Cortical Neurons in culture
Ilochi N. Ogadinma Anyanwu C. Frances	*Federal University Otuoke*	Cognitomotor Effect of an Allium Specie And Its Bioactive Agent on Heavy Metal- Induced Toxicity
Parviz Abbasov Parvin Najafguliyeva	*Azerbaijan State Advanced Training Institute for Doctors*	Comparative Outcomes of Laparoscopic TAPP and Open Lichtenstein Mesh Repair in the Surgical Treatment of Inguinal Hernia
Sorin Burlica Elena Ramona Dragomir Ion Petre Roxana Furau Florina Buleu Cezar Pântea Izabella Petre	*"Victor Babes" University of Medicine and Pharmacy Timisoara*	Vitamin D Status and Reproductive Hormonal Profiles in Early versus Physiological Menopause: A Comparative Study
Kawthar El Ahmadi Khadija Haboubi Phuong Nguyen-Tri	*Abdelmalek Essaâdi University*	Biological Valorization of Cannabis sativa L. Extracts and By-Products Obtained by Supercritical CO_2: Antimicrobial and Anti-Inflammatory Potential
Bhavesh Bhamare	*University: S.N.D. College of Pharmacy*	3D-Printed Medicines and the Future of Personalized Healthcare: Economic, Social and Pharmaceutical Implications
Mahima verma	*I.K. Gujral Punjab Technical University*	Role of Functional Foods in Women's Health: From Menarche to Menopause

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HEAD OF SESSION: Ghazaleh Elahi

Authors	Affiliation	Presentation Title
Ghazaleh Elahi	*Golestan University of Medical Sciences*	Molecular Identification of ESBLs Genes (bla TEM, bla SHV and bla CTX) among Non-fermenting Gram-negative Bacteria Isolated from Hospitalized Patients in Mazandaran Province, Iran
Ghazaleh Elahi *Abdollah Ardebili*	*Golestan University of Medical Sciences*	Evaluation Of Biofilm-Related Phenotypic and Genotypic Characteristics in Clinical Acinetobacter Baumannii Isolates from Gorgan, Northern Iran
Moses Adeolu AGOI Success Eniola OGBOYE Samuel Olayiwola AJAGA Oluwanifemi Opeyemi AGOI	*Lagos State University of Education*	Reimagining Continuing Medical and Health Sciences Education Through Mobile Microlearning: Evidence-Based Evaluation of Knowledge Retention, Professional Competence, And Clinical Practice
Hari Nandhini A Ramya G	*Bharath Institute of Higher Education and Research*	Pharmacogenomics: Personalized Medicine Based on Genetic Makeup.
Ibrahim Samaila Usman Samaila	*Umaru Musa Yar'adua University*	The Application of Nanoparticles as a Therapeutic Agent
Usman Samaila Ibrahim Samaila	*Umaru Musa Yar'adua University*	Green Hybrid Nanoparticles for Biomedical Applications
Salehova G.B. Emrahova F.B.	*The K.Y. Farajova Institute of Scientific Research in Pediatrics*	Choledochal Cyst Associated with Pancreatic Exocrine Insufficiency and Electrolyte Imbalances
Aytan Agayeva Kamala Namazova Sabuhi Yusifov Rashad Guliev Nazrin Agayeva	*Academician M. Topchubashov Scientific Surgery Center*	International Standards and Local Practice in Papillary Thyroid Cancer: A Comparative Analysis
Rabar Mohammed HUSSEIN	*Noble Technical Institute*	Climate Change Impacts on Freshwater Ecosystems in the Kurdistan Region, Iraq

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HEAD OF SESSION: Gülşah TOLLU

Authors	Affiliation	Presentation Title
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Gülşah TOLLU Erdal YABALAK	*Mersin Univercity*	Subcritical Water-Derived Ceratonia Siliqua L. Seed Extract as a Natural Antimicrobial Agent Against Pathogenic Bacteria and Fungi
İsmail Musab GÜLAÇAR Aynur Karadağ GÜREL Gökhan GÖRGİŞEN	*University of Health Sciences,*	Liquid Biopsy and Next-Generation Sequencing (Ngs): The Role of Ctdna in Cancer Management
Asma RAHMANI TANGROUDI Seval YILMAZ	*Atılım University*	Investigation Of Oculomotor Function and Digital Fatigue in Individuals with Non-Specific Neck Pain
Miray ACAR Gamze Sevri EKREN AŞICI Senem AKKOÇ FEIZI DEH NAYEBI	*Aydın Adnan Menderes University*	In Vitro Evaluation of The Antiproliferative Effect of a Newly Synthesized Benzimidazole Derivative on the Human Breast Cancer Mcf-7 Cell Line
Kadir Han ALVER	*Pamukkale University*	Evolving Procedural Profile of Interventional Radiology: A Five-Year Single-Center Trend Analysis
Muhammed KOSTEKCI	*Kırşehir Ahi Evran University*	The Role of Child Development Specialist in Community-Based Social Work in The Context of Migration and Poverty
Muhammed KOSTEKCI	*Kırşehir Ahi Evran University*	The Impact of the “Nfluencer” Culture on Children’s Identity Development and The Protective Role of Social Services
Kübra Aslantaş Akar Muhammed Mustafa Akar	*Kafkas University*	The Role of Endodontic Treatment in the Prevention of Tooth Loss: The Importance of Preserving the Natural Tooth

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HEAD OF SESSION: Nasrin ZIAYEE

Authors	Affiliation	Presentation Title
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Nasrin ZIAYEE	Ahlul-Bayt International University Tehran	Green Chemistry Framework for Women's Reproductive Health: Engineering Biodegradable Formulations to Mitigate Transgenerational Bioaccumulation of Endocrine-Disrupting Chemicals
Jitendra AHERKAR	*Atmiya University,*	Mental Well-being of Generation Beta: Challenges in a Hyperconnected World
Bushra ANSARI	*Aligarh Muslim University*	Therapeutic Potential of Short-Chain Fatty Acids in Parkinson's Disease: An Integrated Metabolomics Approach
Le Quang NGỌC Nguyen Thi THOM Nguyen Xuan DUY	*Institute of Sociology and Psychology,*	Access to Central-Level Hospitals among Older Adults in Rural Vietnam
Valery V. BELAKHOV	*Technion – Israel Institute of Technology*	Discovery of New Group of Organofluorine Derivatives of Heptaene Macrolide Antifungal Antibiotic Amphotericin B
Valery V. BELAKHOV	*Technion – Israel Institute of Technology*	Development of a New Unified Technological Method for the Isolation and Chemical Purification of Polyene Macrolide Antibiotics with Protection Against Inactivation
Valery V. BELAKHOV	*Technion – Israel Institute of Technology*	Design, Synthesis, Biological Activity, And Use Prospects of New Functionally Substituted Monosaccharides as Highly Effective and Environmentally Safe Pesticides
Chahinez BOUDJEMAI Mourad DJEZIRI Hassiba ZEMMOURI	*Advanced Technologies Laboratory*	Antioxidant and Proteolytic Enzyme Activities Across Organs of Octopus vulgaris as Indicators of Physiological Status

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HEAD OF SESSION: Anamika Basu

Authors	Affiliation	Presentation Title
Sumayya Akram Matloob Ahmad Sana Aslam	*Government College University Faisalabad*	Synthesis and Biological Evaluation of Pyridylpiperazine-Based Carbodithioates as Urease Inhibitors
Imane Elbelghiti Noureddine Slimani Zohra Lemkhente Fatima Boubrik Ahmed Belmouden	*Ibn Zohr University*	Isolation, Characterization and Therapeutic Applications of Bacteriophages against Pathogenic Bacteria of the ESKAPE group
Nabil ZAARA Jamila DAHMANI Souad SKALLI Amina TOUHAMI OUAZZANI Allal DOUIRA	*Ibn Tofail University*	The Influence of Climatic Factors and the Cultivation System on the Physicochemical Characteristics of Olive Oil from the Moroccan Variety Picholine (Olea Europaea L.) Cultivated in The Northern and Central Region of Morocco
Anamika Basu	*Gurudas College Affiliated to University of Calcutta*	Conserved Molecular Pathways of Coal Dust Exposure: Cross-Species Insights from Zebrafish and Human Transcriptomics
Oussama Mahmoudi	*Mohamed-Cherif Messaadia University*	Antimicrobial Resistance in Animal Production: Mechanisms, Selective Pressures, and Mitigation Strategies within the One Health Framework
Abubakar Abdulkadir Abuabdin	*Business Administration, Federal University*	AI-Powered Consumer Insights and the Marketing of Green Innovations: A STEAM Approach to Sustainable Consumption in Nigeria
Nayab Parveen	*National Institute of Educational Planning and Administration*	The Role of Rehabilitation and Assistive Technology in Improving Quality of Life Among People with Physical Disabilities
Lhoucine Naanaai Abdellah El Aissouq Youness Moukhliss Hicham Zaitan Mohammed Bouachrine Fouad Khalil	*Sidi Mohamed Ben Abdellah University*	Design Of Novel Hydrazide–Hydrazone Derivatives Against MGC803 Gastric Cancer Cells Using 3D-QSAR, ADMET, Network Pharmacology, Docking and MD Simulations
BELLIL Dassine GHAROUT-SAIT Alima DJOUDI Ferhat BELLIL Zahra MENDIL Ouidad MANSEUR Lyticia DIB-SAIT Sabrina	*Université de Bejaia*	Comparative Assessment of Decontamination Strategies for the Isolation of Mycobacterium spp. from Diverse Animal Samples

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HEAD OF SESSION: Sarah Shahid

Authors	Affiliation	Presentation Title
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Rabiu Haruna Idris Abdulrashid Rahmat Adam Abdulkadir Idris Zulaihat Yakubu Muhammad	*Federal University Dutse*	Postoperative Appearance and Facial Satisfaction Outcomes among Adults with Repaired Cleft Lip and Palate in Jigawa State, Nigeria
Yassine Koubi Youness Moukhliss Oumayma Abdssadk Marwa Alaqarbeh Hamid Maghat Tahar Lakhlifi Mohammed Bouachrine	*Moulay Ismail University of Meknes*	Computational Structure – Biological Activity and Retrosynthesis Investigations Of 1,2,3-Triazole-Quinoline Hybrid Molecules as Potential Respiratory Virus Inhibitors
Dabeer Ahmed Khan Syed Abid Mehdi Kazmi Sohail Rafi Amna Aamir Khan Mazhar Ali Bhutto	Dr. Ziauddin Hospital	Comparative Effects of Kinetic Chain Exercises on Pain and Arterial Occlusion Pressure in Acute Anterior Knee Pain: A Randomized Controlled Trial
Anjitha. A B. Rajendran	University of Kerala	Health and Wellness Tourism in Kerala: The Role of Ayurveda and Medical Science
Soukaina Hamou Mustapha Moufassih Ousama Tarahi Anas Mazid Said Agounad Hafida Idrissi Azami	Ibn Zohr University	Evaluating the Impact of Machine Learning Classification Methods on Correlation-Based SSVEP Decoding
Ranjita Sinha Mithu Dey Induprama Mandal	Asansol Engineering College	AI-Powered Environmental Monitoring for Sustainable Ecosystem Management
Ranjita Sinha Mithu Dey Anubhab Dassharma	Asansol Engineering College	Microbial Fuel Cells for Environmental Sustainability and Wastewater Treatment

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HEAD OF SESSION: Karim Nadir

Authors	Affiliation	Presentation Title
El Mahdi Bouabdalli Mohamed El Jouad Samira Touhtouh Ilyass El kadmiri Nathalie Gaumer Mostapha Siniti Abdelowahed Hajjaji	*Sidi Mohamed Ben Abdellah University*	Engineering Structure–Property Relationships in Eu 3 $^{+}$-Doped Strontium Phosphate Glasses for Advanced Photonic and Photovoltaic Applications
El Mahdi Bouabdalli Mohamed El Jouad Samira Touhtouh Fouad Belhora Nathalie Gaumer El Kebir Hlil Abdelowahed Hajjaji	*Sidi Mohamed Ben Abdellah University*	A Synergistic Multiphysics and Judd–Ofelt Framework for High-Efficiency Red Emission in Eu 3 $^{+}$-Doped Silicophosphate Sol–Gel Glasses
Karim Nadir Hassan Benchelha	Université Ibn Tofail	Socioeconomic Status, Motivation, Self-Esteem, and Nonverbal Intelligence as Determinants of Academic Achievement: An Integrative Structural Model
Huma Ikram Ambreen Hasnat Saniya Tauqeer Hafsa Abdullah Syeda Yumna Darakhshan J. Haleem	University of Karachi	Levothyroxine Rescues Hypothyroidism- and Scopolamine-Induced Memory Deficits in a Rat Model: Role of Hippocampal Serotonergic Modulation
Lorena SALIAJ Marinel SALIAJ	Mediterranean University of Albania	Longitudinal Statistical Analysis Of Gastrointestinal Symptom Dynamics Following Helicobacter Pylori Eradication
Anum Shahzadi Ali Haider Muhammad Ikram	COMSATS University Islamabad	Graphene Oxide/Chitosan-Layered Double Hydroxides: Efficient Dye Degrader And Antibacterial Agent With Computational Validation
Mohammed El Goual Mouad Benaicha	Mohammed First University	Numerical Assessment Of Heat Extraction Enhancement In Photovoltaic–Phase Change Material (PV–PCM) Collectors
Bendaoud Ahmed Mohammed Salah Zeroual Abdellah	Chouaib Doukkali University	Synthesis and Anticorrosion Efficiency of a Benzo[d]oxazole Derivative for E24 Steel: Insights from DFT and Molecular Dynamics Simulations
Orges Lena Jasemin Todri	UCAM Universidad Católica San Antonio de Murcia	Postural Reeducation for Low Back Pain in Elite Athletes: A Randomized Controlled Trial
Diyana Zhelyazkova Svetlin Aleksandrov Dobromira Shopova	Medical University-Plovdiv	Combined Fixed–Removable Prosthetic Rehabilitation Of The Maxilla In A Partially Dentate Patient: A Clinical Case Report
Aher Asmita Changdeo Bhamare Bhavesh Sanjay Kolhe Yogita Babasaheb Gaikwad Chanchal Navnath Thorat Siddhi Deepak	S.N.D College Of Pharmacy	Smart Nanocarriers for Personalized Medicine: Integrating Nanotechnology, Artificial Intelligence and Targeted Drug Delivery

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HEAD OF SESSION: Gamze SAATÇİ

Authors	Affiliation	Presentation Title
Gamze SAATÇİ	*Kırşehir Ahi Evran University*	The Role of Nurses in Recognizing, Stopping, and Correcting Medical Errors
Gamze SAATÇİ	*Kırşehir Ahi Evran University*	Alarm Fatigue and Patient Safety in Healthcare Services
Nahit SAYLAK	*Dicle University*	Rhinoplasty In Brachycephalic Cats: Surgical Techniques and Clinical Outcomes
Sümbüle Köksoy Vayisoğlu Demet Harbalioğlu	*Mersin University*	The Effect Of Self-Applied Ear Massage On Sleep Quality In Earthquake-Affected Women
Ahliman Amiraslanov Tamara Guliyeva	*Azerbaijan Medical University*	Association Between Pten Gene Deletion And Treatment Outcomes In Patients With Soft Tissue Sarcoma
Arkhmammedova Gulshan Karimli Nurane Hasanova Vafa	*Azerbaijan Medical University*	Comparative Assessment Of Dental Disease Prevention Among Pregnant Women
Kerimbekova Gulnara	*Azerbaijan Medical University*	Current Approaches To The Clinical Features, Diagnosis, And Management Of Cutaneous Leishmaniasis
Shahla Yusubova Elmira Aliyeva Qasim Bayramov Shafag Mammadova	*Azerbaijan Medical University*	Features of Immunological Processes And Interactions With The Body In The Pathogenesis Of Periodontal Diseases
Ravana GULIYEVA Nigar ALIYEVA Sevinc AMIRASLANOVA Aytən HÜSEYNOVA İlhama SAFAROVA Sevinc ABDULLAZADƏ Surayya İSMAYILOVA İSMİKHAN	*Baku State University*	The Chemistry Of Addiction: Psychoactive Plant Metabolites, Neurobiological Targets, And The Duality Of Therapeutic Potential And Toxicity
Ravana GULIYEVA Səadət AZADƏLİYEVA İlhama SAFAROVA Narmin MAMMADOVA Milana AKİFLİ Diana AHMADOVA	*Baku State University*	From Molecules To Mind: The Gut–Brain Axis As A Molecular Link Between Microbiota, Neurotransmitters, Inflammation, And Mental Health
S. M. YAGUBOVA T. S. SULTANOVA, A. A. ALAKBAROV I. I. KARIMOVA G. N. ALIYEVA G. A. HUSEYNOVA	Azerbaijan Medical University	Digital Pathology And Its Applications In Modern Medicine
I. E. YUSUBOV	Azerbaijan Medical University	The Role Of Esophagogastroduodenoscopy In The Diagnosis And Treatment Of Postoperative Complications

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PEDİATRİK YOĞUN BAKIM HASTALARINDA AĞRI YÖNETİMİ VE HEMŞİRENİN ROLÜ

PAIN MANAGEMENT IN PEDIATRIC INTENSIVE CARE PATIENTS AND THE ROLE OF NURSES

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ÖZET

Giriş: Bu derleme, pediatrik yoğun bakım hastalarında ağrının değerlendirilmesi, ağrı yönetiminde kullanılan yöntemler ve hemşirenin rolünün incelenmesi amacıyla hazırlanmıştır.

Çocuklarda ağrı, pediatrik yoğun bakım ünitelerinde en sık karşılaşılan semptomlardan biri olup hastalıklar, travmalar, cerrahi girişimler ve tanı-tedavi amaçlı uygulamalardan kaynaklanabilmektedir. Bu derlemede çocuklarda ağrının fizyolojisi, değerlendirilmesi, ağrıya neden olan faktörler ve farmakolojik ile farmakolojik olmayan ağrı yönetimi yaklaşımları güncel literatür doğrultusunda ele alınmıştır.

Pediatrik yoğun bakım hastalarının günlük bakım süreçlerinde çok sayıda ağrılı girişime maruz kaldıkları bildirilmektedir. Tedavi edilmeyen ağrı; solunum komplikasyonları, artmış oksijen tüketimi, yara iyileşmesinde gecikme, uzamış hastanede yatış süresi ve olumsuz psikolojik sonuçlarla ilişkilidir. Çocuklarda ağrının değerlendirilmesi yaşa, gelişim düzeyine ve iletişim becerilerine bağlı olarak güçleşmektedir. Bu nedenle NIPS, FLACC, Wong-Baker Yüz İfadeleri Ölçeği, VAS ve PIPP gibi yaşa uygun değerlendirme araçlarının kullanılması önerilmektedir. Ağrı yönetiminde opioidler, non-opioid analjezikler, lokal anestezikler ve sedatif ilaçlar kullanılmakla birlikte; dikkat dağıtma, müzik terapisi, masaj, pozisyon verme, gevşeme teknikleri, aile katılımı ve terapötik iletişim gibi farmakolojik olmayan yöntemlerin de etkili olduğu bildirilmektedir. Hemşireler ağrının tanılanması, düzenli değerlendirilmesi, uygun girişimlerin uygulanması ve sonuçların izlenmesinde temel role sahiptir.

Sonuç: Pediatrik yoğun bakım hastalarında etkili ağrı yönetimi, multidisipliner yaklaşım ve düzenli ağrı değerlendirmesini gerektirmektedir. Hem farmakolojik hem de farmakolojik olmayan yöntemlerin birlikte kullanılması ağrı kontrolünü güçlendirmektedir. Hemşirelerin bilgi, deneyim ve farkındalık düzeylerinin artırılması, çocuklarda ağrı yönetiminin etkinliğini artırarak bakım kalitesinin geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: Çocuk, ağrı, pediatrik yoğun bakım, ağrı yönetimi, hemşirelik.

ABSTRACT

Introduction: This review was prepared to examine pain assessment, pain management methods, and the role of nurses in pediatric intensive care patients.

Pain is one of the most common symptoms encountered in pediatric intensive care units and may result from illnesses, trauma, surgical interventions, and diagnostic or therapeutic procedures. This review discusses the physiology of pain in children, pain assessment, factors contributing to pain, and both pharmacological and non-pharmacological pain management approaches in light of current literature.

Pediatric intensive care patients are frequently exposed to numerous painful procedures during their daily care. Untreated pain has been associated with respiratory complications, increased oxygen consumption, delayed wound healing, prolonged hospital stay, and adverse psychological outcomes. Pain assessment in children can be challenging due to age, developmental level, and communication abilities. Therefore, the use of age-appropriate assessment tools such as the Neonatal Infant Pain Scale (NIPS), Face, Legs, Activity, Cry, Consolability (FLACC) Scale, Wong-Baker Faces Pain Rating Scale, Visual Analog Scale (VAS), and Premature Infant Pain Profile (PIPP) is recommended. Pain management includes the use of opioids, non-opioid analgesics, local anesthetics, and sedative agents. In addition, non-pharmacological interventions such as distraction techniques, music therapy, massage, positioning, relaxation techniques, family involvement, and therapeutic communication have been

reported to be effective. Nurses play a key role in pain identification, regular assessment, implementation of appropriate interventions, and monitoring of outcomes.
Conclusion: Effective pain management in pediatric intensive care patients requires a multidisciplinary approach and regular pain assessment. The combined use of pharmacological and non-pharmacological methods strengthens pain control. Increasing nurses' knowledge, experience, and awareness can enhance the effectiveness of pain management in children and contribute to improving the quality of care.
Keywords: Child, pain, pediatric intensive care, pain management, nursing.

Giriş

Ağrı, çocukluk döneminde sıklıkla karşılaşılan ve biyolojik, psikolojik, sosyal ve çevresel birçok faktörden etkilenen karmaşık bir deneyimdir. Çocuklarda ağrı yalnızca fiziksel rahatsızlığa neden olmakla kalmamakta; büyüme ve gelişme süreçlerini, psikolojik durumu, aile ilişkilerini ve yaşam kalitesini de olumsuz yönde etkilemektedir (Derebent & Yiğit, 2006; Dinçer et al., 2011). Çocukluk döneminde yaşanan ağrı deneyimlerinin uzun dönemli sonuçları bulunmakta olup, bu dönemde gelişen korkuların yetişkinlikte de devam ettiği bildirilmektedir. Kanada'da yapılan bir çalışmada yetişkinlerin yaklaşık dörtte birinde iğne korkusunun bulunduğu ve bu korkunun çoğunlukla çocukluk dönemindeki deneyimlerden kaynaklandığı belirtilmiştir (Taddio & Appleton, 2010).
Özellikle pediatrik yoğun bakım ünitelerinde (PYBÜ) tedavi gören çocuklar, hastalık süreçleri, cerrahi girişimler, tanı ve tedavi amaçlı işlemler nedeniyle çok sayıda ağrılı uyaranla karşı karşıya kalmaktadır. Yoğun bakım ortamında ağrının etkin şekilde değerlendirilmesi ve yönetilmesi, kaliteli bakımın temel bileşenlerinden biridir (Ismail et al., 2018; Srouji & Ratnapalan, 2010). Ancak çocukların gelişimsel özellikleri, iletişim güçlükleri, sedasyon uygulamaları ve mekanik ventilasyon gibi durumlar ağrının değerlendirilmesini zorlaştırmaktadır. Buna rağmen ağrının etkin şekilde kontrol altına alınması kritik öneme sahiptir.

Çocuklarda Ağrının Tanımı ve Fizyolojisi

Uluslararası Ağrı Araştırmaları Derneği (IASP) ağrıyı, "gerçek veya potansiyel doku hasarı ile ilişkili ya da buna benzeyen hoş olmayan duyusal ve emosyonel deneyim" olarak tanımlamaktadır (International Association for the Study of Pain [IASP], 2010)). Ağrı bireysel bir deneyimdir ve her çocuk tarafından farklı şekillerde algılanabilir. Önceki deneyimler, kültürel özellikler, aile tutumları ve çevresel faktörler ağrı algısını etkileyebilmektedir (Oulton, 2002).
Ağrının fizyolojik temelinde nosiseptör adı verilen reseptörler yer almaktadır. Bu reseptörler mekanik, termal ve kimyasal uyaranları algılayarak merkezi sinir sistemine iletmektedir. Doku hasarı sonrasında ortaya çıkan inflamatuvar süreçler nosiseptörleri uyararak ağrı hissinin artmasına neden olmaktadır (Conk et al., 2013; Erdine, 2003). Çocuklarda sinir sisteminin gelişim süreci devam etmekte olduğundan ağrılı uyaranlara verilen yanıt yetişkinlerden farklı özellikler gösterebilmektedir.

Çocuklarda Ağrı Deneyimi ve Sonuçları

Geçmiş yıllarda çocukların ağrıyı yetişkinlerden daha az hissettikleri düşünülmekteydi. Ancak günümüzde yapılan çalışmalar, çocukların ağrıyı yoğun şekilde deneyimlediklerini ve yetersiz ağrı yönetiminin ciddi sonuçlar doğurabildiğini göstermektedir (Helms & Barone, 2008). Bu nedenle ağrı, günümüzde "beşinci yaşamsal bulgu" olarak kabul edilmektedir.
Çocuklarda ağrı akut veya kronik nedenlere bağlı olarak gelişebilir. Yaralanmalar, cerrahi girişimler, travmalar, intravenöz kateter uygulamaları, entübasyon, aspirasyon ve pansuman değişiklikleri gibi birçok tıbbi işlem ağrıya neden olabilmektedir (Jacob & Puntillo, 2000). Ağrının yeterince kontrol altına alınamaması, çocuklarda hem fizyolojik hem de psikolojik sorunlara yol açmaktadır (Elçigil, 2011).
Fizyolojik açıdan değerlendirildiğinde ağrı; kalp hızında artış, kan basıncında yükselme, oksijen tüketiminde artış, immün sistem baskılanması ve yara iyileşmesinde gecikme gibi sonuçlara neden olabilmektedir (Ismail et al., 2018). Özellikle yoğun bakım hastalarında bu durum hastanede kalış süresinin uzamasına yol açabilmektedir.
Psikolojik açıdan ise ağrı; korku, anksiyete, uyku bozuklukları, huzursuzluk ve davranış değişiklikleri ile ilişkilidir (Seyoum et al., 2015; Kopf & Patel, 2010). Çocuklarda ağrıya bağlı gelişen olumsuz deneyimlerin ilerleyen yaşlarda sağlık hizmetlerinden kaçınma davranışına neden olabileceği bildirilmektedir (Taddio & Appleton, 2010).

Çocuklarda Ağrının Değerlendirilmesi

Dünya Sağlık Örgütü (WHO), Uluslararası Ağrı Araştırmaları Derneği (IASP) ve Avrupa Ağrı Federasyonu tarafından ağrının giderilmesinin temel bir insan hakkı olduğu vurgulanmaktadır (Conk et al., 2013). Bu nedenle çocuklarda ağrının doğru şekilde değerlendirilmesi ve uygun müdahalelerin planlanması büyük önem taşımaktadır.

Çocuklarda ağrı değerlendirmesi erişkinlere göre daha karmaşıktır. Bunun başlıca nedenleri arasında çocuğun yaşına bağlı iletişim güçlükleri, gelişimsel farklılıklar, korku ve kaygı gibi faktörler yer almaktadır (Conk et al., 2013;). Ağrının değerlendirilmesinde mümkün olduğunda çocuğun öz bildirimi temel alınmalıdır. Ancak iletişim kurulamayan durumlarda davranışsal ve fizyolojik göstergeler değerlendirilmelidir (American Academy of Pediatrics & American Pain Society, 2001). Çocuklarda yaygın olarak kullanılan ağrı değerlendirme ölçekleri arasında Yenidoğan Ağrı Ölçeği (NIPS), Görsel Analog Skala (VAS), Wong-Baker Yüz İfadeleri Ölçeği, FLACC Ölçeği, N-PASS, EDIN, COVERS ve Prematüre Bebek Ağrı Profili (PIPP) bulunmaktadır. Bu ölçekler çocuğun yaşına ve gelişim düzeyine uygun olarak seçilmektedir (Conk et al., 2013).

Pediatrik Yoğun Bakım Hastalarında Ağrı

Pediatrik yoğun bakım ünitelerinde ağrıya neden olan faktörler oldukça çeşitlidir. Akut ve kronik hastalıklar, travmalar, cerrahi girişimler, mekanik ventilasyon uygulamaları, aspirasyon işlemleri, kateter uygulamaları ve pozisyon değişiklikleri ağrıya neden olan başlıca etkenler arasında yer almaktadır (Conk et al., 2013).

Stevens ve arkadaşları tarafından yapılan çalışmada yoğun bakımda yatan çocukların günde ortalama 13 ağrılı işleme maruz kaldığı bildirilmiştir (Stevens et al., 2011). Bu durum çocukların sürekli stres altında kalmasına ve olumsuz fizyolojik yanıtların ortaya çıkmasına neden olmaktadır.

Özellikle travmatik beyin yaralanması bulunan çocuklarda ağrı yönetimi daha büyük önem taşımaktadır. Travmatik beyin hasarı, çocukluk çağında önemli bir morbidite ve mortalite nedenidir. Kafa travması geçiren çocuklarda ağrının etkin şekilde yönetilmesi, nörolojik iyileşmenin desteklenmesi ve sekonder komplikasyonların önlenmesi açısından kritik öneme sahiptir (NSW Rural Paediatric Emergency Clinical Guidelines, 2014).

Pediatrik Yoğun Bakımda Ağrı Yönetiminde Hemşirenin Rolü

Ağrı yönetimi hemşirelik bakımının temel sorumluluklarından biridir. Yoğun bakım ortamında çocuğu en yakından izleyen sağlık profesyoneli hemşire olduğundan, ağrının değerlendirilmesi ve uygun girişimlerin planlanmasında kilit rol üstlenmektedir (Elçigil, 2011; Pawar & Garten, 2010).

Hemşirelerin ağrı yönetimindeki başarısı; bilgi düzeyleri, klinik deneyimleri, tutumları ve ağrıya ilişkin inançları ile yakından ilişkilidir (Bennett, 2001). Deneyimli hemşirelerin ağrıyı daha erken fark ettikleri ve uygun müdahaleleri daha hızlı uyguladıkları bildirilmektedir.

Ancak pediatrik ağrı yönetiminde bazı engeller bulunmaktadır. Bunlar arasında çocukların ağrılarını ifade etmekte zorlanmaları, sağlık çalışanlarının bilgi eksikliği, analjezik kullanımına ilişkin endişeler ve yoğun iş yükü yer almaktadır (Twycross & Collins, 2013; Walsh et al., 2013;Khalil, 2018). Bu nedenle hemşirelerin güncel bilimsel kanıtlar doğrultusunda eğitimlerinin desteklenmesi gerekmektedir.

Farmakolojik Ağrı Yönetimi

Pediatrik yoğun bakım hastalarında ağrı yönetiminde farmakolojik yöntemler sıklıkla kullanılmaktadır. Kullanılan ilaçlar arasında lokal anestezikler, steroid olmayan antiinflamatuvar ilaçlar (NSAİİ), parasetamol, opioidler, sedatifler ve analjezik ajanlar yer almaktadır (Conk et al., 2013). Lokal anestezikler özellikle ağrılı girişimlerden önce kısa süreli ağrı kontrolü sağlamak amacıyla kullanılmaktadır. Parasetamol ve NSAİİ'ler hafif ve orta şiddetteki ağrıların tedavisinde etkili ajanlardır ve opioid gereksinimini azaltabilmektedir. Şiddetli ağrı durumlarında morfin ve fentanil gibi opioidler tercih edilmektedir. Morfin güçlü bir μ-opioid agonisti olup özellikle postoperatif ve malign ağrı tedavisinde kullanılmaktadır. Fentanil ise morfinden yaklaşık yüz kat daha güçlü analjezik etkiye sahiptir ve hızlı etki başlangıcı nedeniyle yoğun bakım ortamlarında yaygın olarak kullanılmaktadır (Gopisetti & Playfor, 2019). Sedasyon amacıyla midazolam sıklıkla tercih edilmektedir. Ayrıca ketamin hem sedatif hem de analjezik özellikleri nedeniyle ağrılı girişimlerde etkili bir seçenek olarak kullanılmaktadır (Devecioğlu & Çıtak, 2014; Playfor et al., 2006).

Farmakolojik Olmayan Ağrı Yönetimi

Farmakolojik olmayan yöntemler, ilaç tedavisini destekleyen önemli uygulamalardır. Bu yöntemler arasında gevşeme teknikleri, derin nefes alma egzersizleri, masaj, müzik terapisi, dikkat dağıtma yöntemleri, uygun pozisyon verme ve aile desteği yer almaktadır (Boldt et al., 2014; Faigeles et al., 2010).

Özellikle çocuklarda ebeveyn varlığının güven duygusunu artırdığı ve ağrı algısını azalttığı gösterilmiştir (Kopf & Patel, 2010). Ayrıca farmakolojik olmayan yöntemlerin uygulanmasının analjezik gereksinimini azalttığı, stres düzeyini düşürdüğü ve çocuğun bakım sürecine uyumunu artırdığı bildirilmektedir (Bausewein et al., 2008; Yıldırım, 2006).

Sonuç

Pediatrik yoğun bakım hastalarında ağrı sık görülen ve çok boyutlu bir sorundur. Ağrının etkin şekilde değerlendirilmesi ve yönetilmesi, çocukların yaşam kalitesinin artırılması ve komplikasyonların önlenmesi açısından büyük önem taşımaktadır. Hemşireler, ağrı değerlendirmesi ve yönetiminde merkezi bir role sahiptir. Farmakolojik ve farmakolojik olmayan yöntemlerin birlikte kullanılması, çocuklarda daha etkili ağrı kontrolü sağlamaktadır. Güncel kanıtlara dayalı uygulamaların yaygınlaştırılması ve sağlık profesyonellerinin bu konuda sürekli eğitilmesi, pediatrik yoğun bakım hastalarında ağrı yönetiminin geliştirilmesine önemli katkı sağlayacaktır.

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HEMATOLOJİK MALİGNİTE TANISI ALAN HASTALARDA LİPİD PARAMETRELERİ, PARATHORMON VE 25-HİDROKSİVİTAMİN D DÜZEYLERİNİN REMİSYON VE REMİSYONDA KALIŞ SÜRESİ ÜZERİNE ETKİSİNİN RETROSPEKTİF OLARAK

RETROSPECTIVE EVALUATION OF THE CONTRIBUTION OF LIPID PARAMETERS, PARATHYROID HORMONE, AND 25-HYDROXYVITAMIN D LEVELS TO ACHIEVEMENT OF REMISSION AND DURATION OF REMISSION IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

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ABSTRACT

Objective

Hematological malignancies comprise a heterogeneous group of diseases affecting the blood and lymphatic system, with considerable variability in disease course and treatment response. Recent evidence suggests that lipid metabolism, vitamin D, and parathyroid hormone (PTH) are associated not only with metabolic disorders but also with cancer development and prognosis. However, no comprehensive study has simultaneously evaluated the impact of these parameters on remission outcomes across all major hematological malignancies.

The aim of this study was to retrospectively evaluate the effects of baseline lipid parameters (HDL, LDL, triglycerides, and total cholesterol), PTH, and 25-hydroxyvitamin D [25(OH)D] levels on remission achievement and remission duration in adult patients with hematological malignancies. In addition, differences in these parameters among various hematological malignancy subgroups were investigated.

Materials and Methods

Study Design and Participants

This retrospective descriptive study included 545 newly diagnosed patients treated at the Hematology Clinic of Atatürk University Faculty of Medicine Research Hospital between January 2014 and December 2020.

Inclusion and Exclusion Criteria

Patients diagnosed with hematological malignancies during the study period who had complete records of lipid profile, 25(OH)D, and PTH levels were included. Patients with missing laboratory data, irregular follow-up, or diagnosis outside the study period were excluded.

Data Collection

Demographic characteristics, diagnosis, baseline laboratory findings (HDL, LDL, triglycerides, total cholesterol, 25(OH)D, and PTH), time from diagnosis to remission (days), and time from remission to relapse (months) were obtained from medical records and the electronic hospital database.

Statistical Analysis

Statistical analyses were performed using NCSS 2020 software. Normality was assessed with the Shapiro–Wilk test. Group comparisons were conducted using the Mann–Whitney U test, Kruskal–Wallis test with Dunn–Bonferroni post hoc analysis, Chi-square test, and Fisher's exact test. Pearson's and Spearman's correlation analyses were performed where appropriate. A two-sided p value <0.05 was considered statistically significant.

Results

Among the 545 patients included in the study, 339 (62.2%) were male and 206 (37.8%) were female. The mean age was 59.90 ± 17.76 years. The most common diagnostic groups were chronic

lymphoproliferative diseases (CLPD, 33.8%), plasma cell disorders (PCD, 23.7%), and acute myeloid leukemia (AML, 21.7%). At the end of follow-up, 285 patients (52.3%) remained in remission, whereas 260 (47.7%) experienced relapse. The mean time from diagnosis to remission was 35.99 ± 13.97 days, and the mean remission duration was 32.64 ± 23.78 months.

Comparison According to Diagnostic Groups: Patients with plasma cell disorders had significantly higher HDL levels than the other diagnostic groups (p=0.001). LDL levels were significantly higher in patients with chronic lymphoproliferative diseases than in those with chronic myeloproliferative diseases (p=0.005). Triglyceride levels were significantly higher in patients with acute lymphoblastic leukemia compared with those with plasma cell disorders (p=0.033). Total cholesterol levels were significantly lower in patients with chronic myeloproliferative diseases than in those with chronic lymphoproliferative diseases and plasma cell disorders (p=0.017). No significant differences were observed in 25(OH)D levels among diagnostic groups (p>0.05). PTH levels were significantly lower in patients with plasma cell disorders than in all other groups (p=0.001).

Comparison According to Clinical Outcome
Patients who remained in remission were significantly younger than those who relapsed (54.19 vs. 66.17 years, p=0.001). HDL, LDL, and total cholesterol levels were significantly higher in the remission group than in the relapse group (p=0.003, p=0.003, and p=0.037, respectively). No significant differences were observed in vitamin D or PTH levels between the two groups.

Factors Affecting Remission Duration
Patients with HDL levels ≥40 mg/dL had significantly longer remission duration (p=0.004). Patients with LDL levels >130 mg/dL had significantly shorter remission duration (p=0.001), whereas patients with total cholesterol levels >200 mg/dL had significantly longer remission duration (p=0.001). The longest remission duration was observed in patients with chronic lymphoproliferative diseases and was significantly longer than that observed in patients with AML and ALL. No significant association was found between vitamin D levels and remission duration (p>0.05). Patients with PTH levels <12 pg/mL had significantly shorter remission duration than those with normal PTH levels (p=0.048).

Conclusion
In this retrospective study, the effects of lipid parameters, PTH, and vitamin D levels on remission outcomes in patients with hematological malignancies were evaluated.
Higher HDL and total cholesterol levels emerged as protective factors associated with an increased likelihood of achieving remission and prolonged remission duration, suggesting that lipid parameters may serve as prognostic biomarkers in hematological malignancies.
Lower LDL levels, particularly in patients with chronic myeloproliferative diseases, were associated with shorter remission duration. This finding may reflect increased cholesterol utilization by proliferating malignant cells.
Elevated triglyceride levels in patients with acute lymphoblastic leukemia indicate that metabolic parameters should be closely monitored in this subgroup.
Lower PTH levels observed in plasma cell disorders are consistent with the pathophysiology of these diseases and are likely related to PTH suppression secondary to hypercalcemia and renal involvement.
No prognostic effect of vitamin D levels on remission duration was demonstrated. This finding may be attributable to the high prevalence of severe vitamin D deficiency in the study population (82.6% of patients had serum 25(OH)D levels <20 ng/mL).
Although the retrospective single-center design and the inability to evaluate confounding factors such as nutritional status, comorbidities, and medication use represent important limitations, this study constitutes one of the largest investigations conducted on this subject in Türkiye. Overall, lipid parameters appear to be simple, inexpensive, and readily available prognostic biomarkers for the follow-up of patients with hematological malignancies. Prospective multicenter studies are warranted to validate these findings.
Keywords: Hematological malignancies; Lipid profile; High-density lipoprotein; 25-Hydroxyvitamin D; Parathyroid hormone; Remission; Prognostic biomarkers.

ÖZET

Amaç: Hematolojik malignitelerde prognozun öngörülmesinde kullanılabilecek kolay ulaşılabilir biyobelirteçlere ihtiyaç duyulmaktadır. Bu çalışmada, tanı anında ölçülen lipid profili, parathormon (PTH) ve 25-hidroksivitamin D [25(OH)D] düzeylerinin remisyona ulaşma ve remisyonda kalış süresi ile ilişkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif çalışmaya, Atatürk Üniversitesi Tıp Fakültesi Araştırma Hastanesi Hematoloji Kliniğinde 2014–2020 yılları arasında yeni hematolojik malignite tanısı alan 545 erişkin hasta dahil edildi. Hastalar akut miyeloid lösemi, akut lenfoid lösemi, kronik miyeloproliferatif hastalıklar, kronik lenfoproliferatif hastalıklar, plazma hücre hastalıkları ve myelodisplastik sendrom gruplarında değerlendirildi. Tanı anındaki HDL, LDL, total kolesterol, trigliserit, PTH ve 25(OH)D düzeyleri ile tedavi sonrası remisyona ulaşma ve remisyonda kalış süreleri arasındaki ilişkiler istatistiksel olarak analiz edildi.

Bulgular: Hastaların yaş ortalaması 59,9±17,8 yıl olup %62,2'si erkekti. Takip süresince olguların %52,3'ü remisyonda kalırken %47,7'sinde nüks gelişti. Ortalama remisyona ulaşma süresi 35,99±13,97 gün, nüks gelişen hastalarda ortalama remisyonda kalış süresi ise 32,64±23,78 ay olarak bulundu. Remisyonda kalan hastalarda HDL düzeyleri nüks gelişen hastalara göre anlamlı olarak daha yüksekti (p=0,003). Total kolesterol düzeyleri ise nüks grubunda anlamlı derecede daha yüksekti (p=0,037). Trigliserit, PTH ve 25(OH)D düzeyleri açısından remisyon ve nüks grupları arasında anlamlı farklılık saptanmadı (p>0,05).

Sonuç: Tanı anındaki HDL düzeyinin yüksek olması daha uzun remisyon süresi ile ilişkili bulunurken, yüksek total kolesterol düzeyleri daha olumsuz klinik seyir ile ilişkilendirildi. Bulgularımız lipid metabolizmasının hematolojik malignitelerde prognostik önem taşıyabileceğini düşündürmektedir. Rutin biyokimyasal parametrelerden elde edilen bu göstergelerin prognostik belirteç olarak kullanımını doğrulamak amacıyla daha geniş örneklemli, prospektif ve çok merkezli çalışmalara gereksinim vardır.

Anahtar Kelimeler: Hematolojik malignite, HDL, lipid profili, total kolesterol, 25-hidroksivitamin D, parathormon, remisyon.

GİRİŞ

Hematolojik maligniteler; kemik iliği, kan ve lenfoid dokudan köken alan, biyolojik davranışları, tedaviye yanıtları ve prognozları bakımından heterojen özellikler gösteren malign hastalık grubunu oluşturmaktadır. [1] Akut ve kronik lösemiler, lenfomalar, plazma hücre hastalıkları ile myelodisplastik sendromlar bu grubun başlıca hastalıklarını oluşturmaktadır. Son yıllarda moleküler tanı yöntemleri ve hedefe yönelik tedavilerde kaydedilen önemli gelişmelere rağmen, hastalar arasında tedavi yanıtı ve sağkalım açısından belirgin farklılıklar devam etmektedir. Bu nedenle hastalık prognozunun öngörülmesinde kullanılabilecek, kolay ulaşılabilir ve düşük maliyetli biyobelirteçlerin belirlenmesi güncelliğini koruyan araştırma alanlarından biridir.

Kanser hücrelerinde artmış enerji gereksinimi ve hücre membranı sentezi nedeniyle lipid metabolizmasında belirgin değişiklikler meydana gelmektedir. Kolesterol ve lipoproteinler yalnızca enerji metabolizmasında görev alan moleküller olmayıp aynı zamanda hücre proliferasyonu, inflamasyon, immün yanıt ve sinyal iletim mekanizmalarında da önemli rol oynamaktadır. Özellikle yüksek yoğunluklu lipoprotein (HDL) antiinflamatuvar ve antioksidan özellikleri nedeniyle tümör biyolojisini etkileyebilecek potansiyel bir biyobelirteç olarak değerlendirilmektedir. Buna karşın düşük HDL ve yüksek total kolesterol düzeylerinin çeşitli solid tümörler ile bazı hematolojik malignitelerde daha kötü klinik sonuçlarla ilişkili olabileceğini gösteren çalışmalar bulunmaktadır. [2–8]

D vitamini ve parathormon (PTH) da hematopoetik sistem üzerinde etkili olduğu düşünülen biyolojik belirteçler arasında yer almaktadır. D vitamininin hücre farklılaşması, immün düzenleme, apoptozis ve tümör hücre proliferasyonunun baskılanması üzerine etkileri deneysel ve klinik çalışmalarda gösterilmiştir. PTH düzeylerindeki değişikliklerin ise kemik iliği mikrosistemi ve mineral metabolizması üzerinden hastalık seyrini etkileyebileceği öne sürülmektedir. Bununla birlikte, hematolojik malignitelerde D vitamini ve PTH düzeylerinin prognostik değeri konusunda literatürde çelişkili sonuçlar bulunmaktadır. [9–12]

Bugüne kadar yapılan çalışmaların büyük çoğunluğu belirli hematolojik malignite alt gruplarına odaklanmış olup, lipid parametreleri ile D vitamini ve PTH düzeylerini birlikte değerlendirerek farklı hematolojik malignitelerde remisyona ulaşma ve remisyonda kalış süresi üzerine etkilerini inceleyen kapsamlı araştırmalar sınırlıdır. Bu nedenle, kolay uygulanabilir laboratuvar parametrelerinin prognostik değerinin ortaya konulması klinik uygulamada risk sınıflandırmasına katkı sağlayabilir.

Bu çalışmada, 2014–2020 yılları arasında hematolojik malignite tanısı alan erişkin hastalarda tanı anında ölçülen HDL, LDL, total kolesterol, trigliserit, 25-hidroksivitamin D ve parathormon düzeylerinin remisyona ulaşma ve remisyonda kalış süresi ile ilişkisi retrospektif olarak değerlendirilmiş; ayrıca bu biyokimyasal parametrelerin farklı hematolojik malignite grupları arasındaki dağılımı incelenmiştir. Elde edilen bulguların, hematolojik malignitelerde prognozun öngörülmesinde kullanılabilecek pratik ve düşük maliyetli biyobelirteçlerin belirlenmesine katkı sağlaması amaçlanmıştır.

GEREÇ VE YÖNTEM

Çalışma Tasarımı ve Hasta Popülasyonu

Bu çalışma, Atatürk Üniversitesi Tıp Fakültesi Araştırma Hastanesi Hematoloji Kliniğinde 01 Ocak 2014–31 Aralık 2020 tarihleri arasında yeni hematolojik malignite tanısı alan erişkin hastaların dosyalarının incelendiği tek merkezli, retrospektif gözlemsel bir araştırma olarak planlandı. Çalışmaya tanısı Dünya Sağlık Örgütü (WHO) sınıflamasına göre doğrulanmış ve tanı anında lipid profili, parathormon (PTH) ve 25-hidroksivitamin D [25(OH)D] ölçümleri bulunan hastalar dahil edildi.

Hastalar tanılarına göre akut miyeloid lösemi (AML), akut lenfoid lösemi (ALL), kronik miyeloproliferatif hastalıklar (KMPH), kronik lenfoproliferatif hastalıklar (KLPH), plazma hücre hastalıkları (PHH) ve myelodisplastik sendrom (MDS) olmak üzere altı gruba ayrıldı. Çalışmaya yalnızca 18 yaş ve üzerindeki erişkin hastalar dahil edildi.

Tanı anında biyokimyasal verileri eksik olan, takip bilgilerine ulaşılamayan, daha önce hematolojik malignite nedeniyle tedavi almış olan veya nüks hastalığı ile başvuran olgular çalışma dışında bırakıldı.

Veri Toplanması

Çalışmaya ait veriler hastanenin elektronik hasta kayıt sistemi ve arşiv dosyalarından retrospektif olarak elde edildi. Demografik özellikler (yaş ve cinsiyet), hematolojik malignite tanısı, tanı tarihi, tedavi sonrası remisyon durumu, nüks gelişimi ve takip süreleri kaydedildi.

Tanı anında ölçülen biyokimyasal parametreler arasında yüksek yoğunluklu lipoprotein kolesterol (HDL), düşük yoğunluklu lipoprotein kolesterol (LDL), total kolesterol, trigliserit, parathormon (PTH) ve 25-hidroksivitamin D [25(OH)D] düzeyleri değerlendirildi. Tüm laboratuvar ölçümleri hastanenin biyokimya laboratuvarında rutin klinik uygulamalar kapsamında gerçekleştirildi.

Çalışma Değişkenleri

Çalışmanın birincil sonlanım noktası tedavi sonrasında remisyona ulaşılması ve remisyonda kalış süresi olarak belirlendi. Remisyonda kalış süresi, remisyonun sağlandığı tarihten ilk nüksün saptandığı tarihe kadar geçen süre olarak hesaplandı. Nüks gelişmeyen hastalarda son poliklinik kontrol tarihi takip sonu olarak kabul edildi.

Remisyon durumu hastaların hematoloji takip kayıtları esas alınarak değerlendirildi. Ayrıca tanı anından remisyon gelişimine kadar geçen süre gün olarak hesaplandı.

Lipid parametreleri ve biyokimyasal değişkenler klinik laboratuvarın referans aralıkları dikkate alınarak kategorik gruplar halinde değerlendirildi. HDL düzeyi <40 mg/dL ve ≥40 mg/dL, LDL düzeyi ≤130 mg/dL ve >130 mg/dL, total kolesterol <120 mg/dL, 120–200 mg/dL ve >200 mg/dL, trigliserit <150 mg/dL ve ≥150 mg/dL, 25(OH)D düzeyi <20 ng/mL, 20–30 ng/mL ve ≥30 ng/mL, PTH düzeyi ise <12 pg/mL, 12–88 pg/mL ve >88 pg/mL olarak sınıflandırıldı.

İstatistiksel Analiz

İstatistiksel analizler IBM SPSS Statistics (Version 20.0, IBM Corp., Armonk, NY, ABD) paket programı kullanılarak gerçekleştirildi. Sürekli değişkenlerin dağılımı Kolmogorov–Smirnov testi ile değerlendirildi. Normal dağılım gösteren veriler ortalama±standart sapma, normal dağılım göstermeyen veriler medyan (minimum–maksimum) olarak ifade edildi. Kategorik değişkenler sayı ve yüzde olarak sunuldu.

İki bağımsız grubun karşılaştırılmasında normal dağılım gösteren veriler için Student's t testi, normal dağılım göstermeyen veriler için Mann–Whitney U testi kullanıldı. Üç ve daha fazla grubun karşılaştırılmasında tek yönlü varyans analizi (ANOVA) veya Kruskal–Wallis testi uygulandı. Kategorik değişkenlerin karşılaştırılmasında Pearson ki-kare veya Fisher kesin ki-kare testi kullanıldı. İstatistiksel anlamlılık düzeyi iki yönlü analizlerde $p<0,05$ olarak kabul edildi.

Etik Onay

Çalışma Helsinki Deklarasyonu ilkelerine uygun olarak yürütüldü. Araştırma için Atatürk Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulundan gerekli etik kurul onayı alınmış olup çalışma süresince hasta kimlik bilgileri gizli tutuldu ve tüm veriler anonimleştirilerek analiz edildi.

BULGULAR

Çalışmaya 2014–2020 yılları arasında yeni hematolojik malignite tanısı alan toplam 545 erişkin hasta dahil edildi. Hastaların 206'sı (%37,8) kadın, 339'u (%62,2) erkek olup yaş ortalaması 59,90±17,76 yıl olarak bulundu. Tanı grupları incelendiğinde en sık kronik lenfoproliferatif hastalıklar (KLPH) (%33,8) izlenirken, bunu sırasıyla plazma hücre hastalıkları (PHH) (%23,7), akut miyeloid lösemi (AML) (%21,7), akut lenfoid lösemi (ALL) (%15,2), kronik miyeloproliferatif hastalıklar (KMPH) (%4,8) ve myelodisplastik sendrom (MDS) (%0,9) izlemekteydi. Ortalama takip süresi altı yıl olarak hesaplandı. Takip sonunda hastaların 285'i (%52,3) remisyonda, 260'ı (%47,7) ise nüks grubunda değerlendirildi. Ortalama remisyona ulaşma süresi 35,99±13,97 gün, nüks gelişen hastalarda ortalama remisyonda kalış süresi ise 32,64±23,78 ay olarak saptandı. Çalışma popülasyonunun temel özellikleri Tablo 1'de özetlenmiştir.

Tablo 1. Çalışma popülasyonunun demografik ve klinik özellikleri

Özellik	Değer
Hasta sayısı	545
Yaş (Ort±SS)	59,90±17,76
Kadın	206 (%37,8)
Erkek	339 (%62,2)
AML	118 (%21,7)
ALL	83 (%15,2)
KMPH	26 (%4,8)
KLPH	184 (%33,8)
PHH	129 (%23,7)
MDS	5 (%0,9)
Remisyon	285 (%52,3)
Nüks	260 (%47,7)
Tanı-remisyon süresi	35,99±13,97 gün
Remisyonda kalış süresi*	32,64±23,78 ay

**Remisyondan nüks gelişimine kadar geçen süre.*

Tanı anındaki laboratuvar parametreleri değerlendirildiğinde hastaların önemli bir kısmında düşük HDL ve D vitamini düzeyleri dikkat çekmekteydi. HDL düzeyi olguların büyük bölümünde 40 mg/dL'nin altında, 25-hidroksivitamin D düzeyi ise hastaların yarısından fazlasında 10 ng/mL'nin altında bulundu. Total kolesterol düzeyleri incelendiğinde hastaların yaklaşık yarısında değerlerin 120–200 mg/dL aralığında olduğu görüldü. PTH düzeyleri ise olguların büyük çoğunluğunda referans aralığında saptandı.

Tanı grupları arasında demografik ve biyokimyasal parametreler karşılaştırıldığında anlamlı farklılıklar gözlendi. Yaş dağılımı açısından tanı grupları arasında istatistiksel olarak anlamlı fark mevcuttu. Lipid parametreleri incelendiğinde HDL düzeyleri tanı gruplarına göre anlamlı farklılık göstermekteydi. Özellikle plazma hücre hastalıkları grubunda HDL düzeyleri; kronik miyeloproliferatif hastalıklar, akut lenfoid lösemi ve kronik lenfoproliferatif hastalık gruplarına göre anlamlı derecede daha yüksekti. LDL kolesterol düzeyleri de tanı grupları arasında farklılık gösterirken, kronik lenfoproliferatif hastalıklarda LDL düzeyleri kronik miyeloproliferatif hastalıklara göre daha yüksek bulundu. Trigliserit düzeyleri açısından da anlamlı farklılık saptandı ve akut lenfoid lösemi grubunda trigliserit düzeyleri plazma hücre hastalıklarına göre daha yüksekti. Total kolesterol düzeyleri değerlendirildiğinde kronik miyeloproliferatif hastalık grubunda ölçülen değerler, kronik lenfoproliferatif hastalıklar ve plazma hücre hastalıklarına göre anlamlı derecede daha düşüktü. 25-hidroksivitamin D düzeyleri tanı grupları arasında benzer bulunurken, PTH düzeyleri açısından anlamlı farklılık mevcuttu. Plazma hücre hastalıklarında PTH düzeyleri diğer başlıca tanı gruplarına göre daha düşük saptandı. Tanı grupları arasında anlamlı bulunan farklılıklar Tablo 2'de özetlenmiştir.

Tablo 2. Tanı grupları arasında anlamlı bulunan biyokimyasal farklılıklar

Parametre	Bulgular	p
HDL	PHH > KMPH, ALL ve KLPH	<0,01
LDL	KLPH > KMPH	0,005
Trigliserit	ALL > PHH	0,033
Total kolesterol	KMPH < KLPH ve PHH	0,017
PTH	PHH diğer tanı gruplarından daha düşük	0,001
25(OH)D	Anlamlı fark yok	>0,05

Hastalar remisyon ve nüks durumuna göre karşılaştırıldığında yaşın klinik seyir ile ilişkili olduğu görüldü. Remisyonda kalan hastaların yaş ortalaması 54,19±17,22 yıl iken, nüks gelişen hastalarda bu değer 66,17±16,18 yıl olarak bulundu ve fark istatistiksel olarak anlamlıydı (p=0,001). Cinsiyet dağılımı açısından ise iki grup arasında anlamlı farklılık saptanmadı (p=0,450).

Lipid parametreleri değerlendirildiğinde, remisyon grubunda HDL düzeyleri nüks grubuna göre anlamlı derecede daha yüksekti (35,4±11,91 mg/dL'ye karşı 32,21±12,83 mg/dL; p=0,003). HDL düzeyi ≥40 mg/dL olan hasta oranı da remisyon grubunda daha yüksekti. LDL kolesterol düzeyleri de remisyon grubunda istatistiksel olarak daha yüksek bulunmasına rağmen, gruplar arasındaki farkın klinik anlamlılığı sınırlıydı (p=0,003). Buna karşın trigliserit düzeyleri bakımından remisyon ve nüks grupları arasında anlamlı farklılık izlenmedi (p=0,669). Total kolesterol düzeyleri açısından ise iki grup arasında anlamlı farklılık bulundu (p=0,037).

Mineral metabolizması parametreleri değerlendirildiğinde, 25-hidroksivitamin D düzeyleri remisyon ve nüks grupları arasında benzer bulundu (p=0,227). Benzer şekilde PTH düzeyleri açısından da gruplar arasında anlamlı farklılık saptanmadı (p=0,361). Bu bulgular, çalışmamızda D vitamini ve PTH düzeylerinin tek başına remisyon durumu ile ilişkili olmadığını göstermektedir. Remisyon ve nüks gruplarının ayrıntılı karşılaştırılması Tablo 3'te sunulmuştur.

Tablo 3. Remisyon ve nüks gruplarının karşılaştırılması

Parametre	Remisyon (n=285)	Nüks (n=260)	p
Yaş (yıl)	54,19±17,22	66,17±16,18	0,001
HDL (mg/dL)	35,40±11,91	32,21±12,83	0,003
LDL (mg/dL)	107,32±36,74	103,77±40,11	0,003
Trigliserit (mg/dL)	155,21±99,61	156,39±95,71	0,669
Total kolesterol (mg/dL)	161,25±50,02	152,83±52,53	0,037
25(OH)D (ng/mL)	12,42±10,60	11,39±9,33	0,227
PTH (pg/mL)	48,51±44,44	54,02±46,35	0,361

Alt grup analizlerinde AML, ALL, KMPH, KLPH ve PHH tanılı hastalar ayrı ayrı değerlendirildi. Her tanı grubunda biyokimyasal parametreler ile klinik sonuçlar arasında farklı düzeylerde ilişkiler gözlenmekle birlikte, özellikle lipid parametrelerinin hastalık grupları arasında değişkenlik gösterdiği dikkat çekti. Buna karşın D vitamini ve PTH düzeylerinin çoğu alt grupta klinik sonuçlarla tutarlı ve güçlü bir ilişki göstermediği izlendi. Genel olarak değerlendirildiğinde çalışmanın bulguları, özellikle HDL ve total kolesterol düzeylerinin hematolojik malignitelerde hastalık seyri ile ilişkili olabileceğini düşündürmektedir.

TARTIŞMA

Bu retrospektif çalışmada, farklı hematolojik malignite gruplarında tanı anındaki lipid profili, parathormon (PTH) ve 25-hidroksivitamin D [25(OH)D] düzeylerinin remisyon ve remisyonda kalış süresi ile ilişkisi değerlendirildi. Çalışmamızın temel bulguları; remisyon grubunda HDL düzeylerinin anlamlı olarak daha yüksek, total kolesterol düzeylerinin ise nüks gelişen hastalara kıyasla daha yüksek bulunması, buna karşın trigliserit, PTH ve 25(OH)D düzeylerinin remisyon durumu ile anlamlı ilişki göstermemesidir. Ayrıca ileri yaşın nüks gelişimi ile ilişkili olduğu görülmüş, tanı grupları arasında ise özellikle lipid parametreleri açısından belirgin farklılıklar saptanmıştır. Bu bulgular, hematolojik malignitelerde lipid metabolizmasının hastalık biyolojisi ile yakından ilişkili olabileceğini düşündürmektedir.

Kanser hücreleri hızlı proliferasyonları nedeniyle membran sentezi, enerji üretimi ve hücre içi sinyal yollarının devamı için yoğun lipid kullanımına ihtiyaç duymaktadır. [3] Son yıllarda yapılan çalışmalar, tümör hücrelerinde kolesterol metabolizmasının yeniden programlandığını ve bunun yalnızca tümör gelişiminde değil, tedavi direnci ve prognoz üzerinde de etkili olduğunu göstermektedir. [13] Hematolojik malignitelerde lipid metabolizmasını düzenleyen yolakların özellikle lösemi, lenfoma ve multipl miyelom patogenezinde önemli rol oynadığı bildirilmektedir. [14,15] Bu nedenle rutin biyokimyasal parametrelerden elde edilen lipid göstergeleri, prognozun değerlendirilmesinde ilgi çekici biyobelirteçler olarak kabul edilmektedir.

Çalışmamızın en dikkat çekici bulgusu, remisyon grubunda HDL düzeylerinin anlamlı derecede daha yüksek bulunmasıdır. HDL'nin antiinflamatuvar, antioksidan ve immünomodülatör özellikleri göz önüne alındığında bu sonuç biyolojik açıdan anlamlı görünmektedir. HDL yalnızca kolesterol taşınmasında görev alan bir lipoprotein olmayıp, oksidatif stresi azaltan, inflamatuvar sitokin üretimini baskılayan ve endotelyal fonksiyonları düzenleyen birçok mekanizmaya sahiptir. [16] Son yıllarda yayımlanan geniş popülasyon çalışmaları da düşük HDL düzeylerinin hematolojik malignite gelişme riskini artırabileceğini ve özellikle lösemi ile lenfoma gelişimiyle ilişkili olabileceğini göstermektedir. [17] Bununla birlikte HDL'nin hastalık geliştikten sonraki prognostik değeri konusunda halen sınırlı sayıda çalışma bulunmaktadır. Çalışmamızda HDL düzeyinin remisyon ile ilişkili bulunması, HDL'nin yalnızca hastalık gelişiminde değil, tedavi yanıtı ve klinik seyirde de rol oynayabileceğini düşündürmektedir.

LDL kolesterol ve total kolesterol açısından elde edilen sonuçlar literatürde bildirilen heterojen bulgular ile uyumludur. Kanser hastalarında hipokolesterolemi uzun yıllardır kötü prognoz göstergesi olarak değerlendirilmekte, bunun temel nedeni olarak tümör hücrelerinin kolesterol tüketiminin artması gösterilmektedir. [3] Bununla birlikte bazı çalışmalarda yüksek kolesterol düzeylerinin inflamatuvar aktiviteyi artırarak olumsuz klinik sonuçlarla ilişkili olduğu da bildirilmiştir. [5] Bu çelişkili sonuçlar, lipid metabolizmasının farklı hematolojik malignite alt tiplerinde değişkenlik göstermesi, hastaların beslenme durumları, inflamasyon düzeyleri ve uygulanan tedavilerden etkilenmesi ile açıklanmaktadır. Çalışmamızda total kolesterol düzeylerinin remisyon ve nüks grupları arasında anlamlı farklılık göstermesi, lipid metabolizmasının hematolojik malignitelerde hastalık aktivitesini yansıtan biyolojik bir belirteç olabileceğini desteklemektedir. [18] Ancak LDL düzeyleri açısından elde edilen bulguların klinik anlamının daha geniş ve prospektif çalışmalarda doğrulanması gerekmektedir.

Trigliserit düzeylerinin remisyon durumu ile ilişkili bulunmaması, daha önce yayımlanan birçok çalışma ile uyumludur. Trigliserit metabolizması; beslenme alışkanlıkları, metabolik hastalıklar, obezite, kullanılan ilaçlar ve inflamatuvar durum gibi çok sayıda değişkenden etkilenmektedir. [5] Bu nedenle trigliserit düzeylerinin tek başına hematolojik malignitelerde güvenilir bir prognostik belirteç olmadığı düşünülmektedir. Çalışmamızın sonuçları da bu görüşü desteklemektedir.

D vitamini ve PTH ekseninin hematolojik malignitelerdeki rolü son yıllarda yoğun şekilde araştırılmaktadır. D vitamininin hücre proliferasyonunu baskılayıcı, farklılaşmayı uyarıcı ve immün sistemi düzenleyici etkileri deneysel çalışmalarda ayrıntılı biçimde gösterilmiş olmasına rağmen, klinik çalışmalarda elde edilen sonuçlar tutarlı değildir. Bazı araştırmalarda düşük 25(OH)D düzeylerinin kötü prognoz ile ilişkili olduğu bildirilirken, diğerlerinde bağımsız prognostik değer gösterilememiştir. Özellikle multipl miyelom hastalarında D vitamini eksikliğinin oldukça sık olduğu, ancak bunun sağkalım üzerindeki etkisinin tek başına belirgin olmadığı gösterilmiştir. Daha yeni çalışmalar, D vitamininin tek başına değil, kemik metabolizması belirteçleri ve metabolik parametrelerle birlikte değerlendirilmesinin prognostik açıdan daha anlamlı olabileceğini ileri sürmektedir. [10,19–24]

Bizim çalışmamızda remisyon ve nüks grupları arasında 25(OH)D ve PTH düzeyleri açısından anlamlı farklılık saptanmamıştır. Bunun en önemli nedenlerinden biri, çalışmaya dahil edilen hastaların büyük bölümünde D vitamini eksikliğinin yaygın olarak bulunması ve bu nedenle gruplar arasında ayırt edici bir dağılım oluşmamış olması olabilir. Ayrıca D vitamini düzeyleri; mevsimsel değişiklikler, güneş ışığına maruziyet, beslenme alışkanlıkları, renal fonksiyonlar ve replasman tedavilerinden önemli ölçüde etkilenmektedir. [25] PTH düzeyleri de benzer şekilde böbrek fonksiyonları, kalsiyum-fosfor dengesi ve D vitamini metabolizması ile yakın ilişki içerisindedir. Bu çok sayıda karıştırıcı değişken, söz konusu biyobelirteçlerin prognostik etkisinin tek merkezli retrospektif çalışmalarda gösterilmesini güçleştirmektedir. Güncel derlemeler de vitamin D-PTH ekseninin biyolojik olarak umut verici olmakla birlikte, rutin prognostik belirteç olarak kullanılabilmesi için daha güçlü prospektif kanıtlara ihtiyaç olduğunu vurgulamaktadır. [26]

Tanı grupları arasında özellikle HDL, LDL, total kolesterol ve PTH düzeyleri açısından anlamlı farklılıklar saptanması, hematolojik malignitelerin metabolik özelliklerinin birbirinden farklı olduğunu göstermektedir. Özellikle plazma hücre hastalıklarında gözlenen farklı lipid profili, multipl miyelom hücrelerinin lipid metabolizmasını yoğun şekilde kullanması ve kemik iliği mikroçevresi ile olan metabolik etkileşimleri ile açıklanabilir. [27,28] Bu durum, hematolojik malignitelerin metabolik açıdan tek bir hastalık grubu olarak değerlendirilmemesi gerektiğini göstermektedir.

Çalışmamızın güçlü yönleri arasında, farklı hematolojik malignite alt tiplerini kapsayan geniş bir hasta popülasyonunun değerlendirilmiş olması ve tüm biyokimyasal parametrelerin tanı anında standart laboratuvar koşullarında ölçülmüş olması yer almaktadır. Buna karşın çalışmanın retrospektif ve tek merkezli olması, tedavi protokollerindeki farklılıkların değerlendirilememesi, moleküler ve sitogenetik prognostik belirteçlerin analize dahil edilmemesi ile beslenme durumu, statin kullanımı ve D vitamini replasman öyküsü gibi olası karıştırıcı değişkenlerin kontrol edilememesi başlıca kısıtlılıklardır.

Sonuç olarak çalışmamız, özellikle HDL ve total kolesterol düzeylerinin hematolojik malignitelerde hastalık seyri ile ilişkili olabileceğini göstermektedir. Buna karşılık D vitamini ve PTH düzeylerinin tek başına remisyon durumunu öngörmede yeterli olmadığı görülmüştür. Rutin biyokimyasal testlerden kolaylıkla elde edilebilen lipid parametrelerinin, mevcut prognostik sınıflama sistemlerine ek olarak kullanılabilme potansiyeli bulunmaktadır. Bu bulguların doğrulanabilmesi için lipid metabolizması, inflamasyon ve moleküler prognostik belirteçleri birlikte değerlendiren çok merkezli, prospektif çalışmaların yapılması gerekmektedir.

SONUÇ

Bu retrospektif çalışmada, farklı hematolojik malignite gruplarında tanı anındaki lipid parametreleri, parathormon ve 25-hidroksivitamin D düzeylerinin remisyon ve remisyonda kalış süresi ile ilişkisi değerlendirilmiştir. Çalışma sonuçları, özellikle lipid metabolizmasını yansıtan biyokimyasal parametrelerin hastalık prognozu ile ilişkili olabileceğini göstermektedir.

Çalışmamızda remisyon grubunda HDL düzeylerinin anlamlı olarak daha yüksek bulunması, HDL'nin hematolojik malignitelerde yalnızca metabolik bir belirteç olmanın ötesinde, hastalık biyolojisi ve tedavi yanıtı ile ilişkili olabileceğini düşündürmektedir. Ayrıca total kolesterol düzeyleri ile klinik seyir arasında saptanan anlamlı ilişki, kolesterol metabolizmasının hematolojik malignitelerde prognostik önem taşıyabileceğini desteklemektedir. Buna karşın trigliserit, 25-hidroksivitamin D ve parathormon düzeylerinin remisyon durumu ile anlamlı ilişki göstermemesi, bu biyobelirteçlerin tek başına prognostik belirteç olarak kullanımının sınırlı olabileceğini ortaya koymaktadır.

Tanı grupları arasında lipid parametreleri ve PTH düzeylerinde gözlenen farklılıklar, hematolojik malignitelerin metabolik özellikler açısından heterojen bir hastalık grubu olduğunu göstermektedir. Bu bulgu, gelecekte yapılacak çalışmalarda hematolojik malignitelerin tek bir başlık altında değil, alt tiplerine göre değerlendirilmesinin daha doğru sonuçlar sağlayacağını düşündürmektedir.

Lipid profili, D vitamini ve PTH gibi rutin klinik uygulamada kolaylıkla ölçülebilen biyokimyasal parametrelerin prognostik değerinin ortaya konulması, hasta yönetiminde ek maliyet oluşturmadan risk sınıflandırmasına katkı sağlayabilir. Özellikle HDL ve total kolesterol düzeylerinin mevcut klinik ve laboratuvar göstergeleri ile birlikte değerlendirilmesi, tedaviye yanıtın öngörülmesi ve hastaların izlem stratejilerinin belirlenmesinde yardımcı olabilir.

Bununla birlikte çalışmamızın retrospektif ve tek merkezli tasarımı, farklı hematolojik malignite alt tiplerinin aynı kohortta değerlendirilmesi ve moleküler prognostik belirteçlerin analize dahil edilememesi, sonuçların yorumlanmasında dikkate alınması gereken başlıca sınırlılıklardır. Ayrıca lipid metabolizmasını etkileyebilecek beslenme durumu, komorbid hastalıklar ve kullanılan ilaçlar gibi potansiyel karıştırıcı değişkenler değerlendirilememiştir.

Sonuç olarak, çalışmamız hematolojik malignitelerde özellikle HDL ve total kolesterol düzeylerinin hastalık prognozunun değerlendirilmesinde umut vadeden biyobelirteçler olabileceğini göstermektedir. Bu bulguların doğrulanması ve klinik uygulamadaki yerinin belirlenebilmesi için, moleküler prognostik göstergeler ile metabolik biyobelirteçleri birlikte değerlendiren, daha geniş örneklemli, çok merkezli ve prospektif çalışmaların gerçekleştirilmesine ihtiyaç vardır.

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OCCULT RENAL MASS AS THE PROBABLE PRIMARY SOURCE OF SOLITARY BRAIN METASTASIS OF UNKNOWN ORIGIN: A MULTIDISCIPLINARY DIAGNOSTIC APPROACH

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ABSTRACT

Objective: To present the diagnostic pathway leading to identification of an occult renal mass as the probable primary source in a patient with solitary brain metastasis of unknown origin, and to highlight the value of multidisciplinary evaluation in metastasis of unknown primary.

Materials and Methods

A 75-year-old male presented with a two-to-three-day history of right-sided numbness, with an unremarkable neurological examination (Glasgow Coma Scale 15). Cranial computed tomography showed a hyperdense lesion within hypodense edema in the right parietal region. Contrast-enhanced cranial magnetic resonance imaging revealed a peripherally enhancing 13-mm lesion with extensive vasogenic edema, suspicious for malignancy. The patient underwent right parieto-occipital craniotomy with gross total resection.

Results

Histopathological examination revealed metastatic carcinoma; immunohistochemical staining could not determine the primary site. Whole-body 18F-FDG PET-CT showed no pathological uptake in the stomach, spleen, pancreas, or adrenal glands, but demonstrated an intensely hypermetabolic, heterogeneous mass measuring approximately 6×4.5×5 cm in the lower pole of the left kidney (SUVmax 15.2), confirmed on contrast-enhanced abdominal CT. Laboratory findings included a PSA of 4.43 ng/mL, creatinine of 0.8 mg/dL, and GFR of 88 mL/min. Renal cell carcinoma was considered the probable primary malignancy, and systemic therapy with a tyrosine kinase inhibitor/immunotherapy combination was initiated without histopathological confirmation, given the strongly suggestive imaging and clinical urgency following intracranial surgery.

Conclusion

Renal cell carcinoma may initially present with a solitary cerebral metastasis without typical urological symptoms, and immunohistochemically indeterminate brain metastases warrant systematic screening for occult renal masses. Timely PET-CT identification of the probable primary site enabled prompt initiation of systemic therapy based on imaging findings alone, underscoring the value of multidisciplinary evaluation, particularly when invasive tissue sampling may be deferred.

Keywords: Brain metastasis; Renal cell carcinoma; Metastasis of unknown primary; PET-CT; Multidisciplinary approach

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2.2% of all cancer diagnoses worldwide, with more than 400,000 new cases diagnosed annually; an increasing proportion of these tumors are now detected incidentally owing to the widespread use of cross-sectional imaging.[1] Despite this trend toward earlier detection, up to one-third of patients still present with regional or metastatic disease at diagnosis, and the clinical course of RCC remains notoriously unpredictable.[2]

Brain metastasis is an uncommon but increasingly recognized site of spread in RCC, with a reported cumulative incidence of approximately 2% to 20% among patients with metastatic disease.[3] Established risk factors for its development include larger primary tumor size, higher nuclear grade, and the presence

of concurrent lung or bone metastases.[4] Because central nervous system involvement carries substantial morbidity and a comparatively poor prognosis, current interdisciplinary consensus statements recommend coordinated neurosurgical, oncological, and urological management of these patients.[5]

Brain metastasis typically develops after RCC has already been diagnosed; however, isolated case reports have described intracranial lesions as the initial and presenting manifestation of an otherwise silent renal tumor, most often heralded by headache or other nonspecific neurological symptoms.[6,7] In such scenarios, histopathological evaluation of the resected brain lesion frequently fails to establish the primary site, as immunohistochemical panels used in the workup of cancer of unknown primary lack uniform sensitivity and specificity.[8] Whole-body 18F-FDG PET-CT therefore plays a central role in localizing the occult primary tumor, with pooled detection rates of approximately 37% reported in the cancer-of-unknown-primary literature.[9]

We report the case of a 75-year-old man whose initial clinical presentation was an isolated sensory deficit attributable to a solitary parietal brain metastasis, in whom immunohistochemistry failed to establish a primary site, but whose subsequent PET-CT identified a hypermetabolic renal mass strongly suggestive of RCC. This case is presented to illustrate the diagnostic pathway required to identify an occult renal primary in the setting of brain metastasis of unknown origin, and to discuss the multidisciplinary decision-making process regarding systemic therapy initiation in the absence of histopathological confirmation of the renal lesion.

Case Presentation and Discussion

Case Presentation

A 75-year-old male with no previously documented malignancy presented to the emergency department with a two-to-three-day history of right-sided numbness. On neurological examination, the patient was alert and fully oriented, with a Glasgow Coma Scale score of 15, isochoric and reactive pupils, and no focal motor deficit. Non-contrast cranial computed tomography (CT) performed in the emergency department revealed a hyperdense focus measuring approximately 1.5 cm within a hypodense, edematous area in the right parietal lobe. Diffusion-weighted cranial magnetic resonance imaging (MRI) subsequently demonstrated a 12-mm subcortical lesion in the right posterior parietal region with signal characteristics compatible with hemorrhage, surrounded by extensive white matter edema, without evidence of parenchymal diffusion restriction. Contrast-enhanced cranial MRI confirmed a peripherally enhancing lesion measuring approximately 13 mm at the same location, accompanied by prominent vasogenic edema; these findings raised strong suspicion for an underlying malignant process, and further evaluation was recommended.

The patient underwent a right parieto-occipital craniotomy. A single burr hole was created, and the bone flap was elevated; the dura was opened in a U-shaped fashion in the standard manner. Using bipolar cautery and an aspirator, a reddish-black tumoral tissue was dissected from the surrounding normal brain parenchyma and removed with gross total resection. After achieving surgical hemostasis, the dura was closed primarily, and the bone flap was fixed with mini plates and screws.

Histopathological examination of the excisional specimen revealed metastatic carcinoma. However, the immunohistochemical panel performed on the resected tissue could not conclusively establish the histological subtype or the primary site of origin. Given this indeterminate result, the patient was referred to medical oncology for systemic screening. Whole-body 18F-FDG PET-CT was performed and showed no pathological FDG uptake in the stomach, spleen, pancreas, or either adrenal gland. However, an intensely hypermetabolic, heterogeneous mass with exophytic extension was identified in the lower pole of the left kidney, measuring approximately 6×4.5×5 cm in its greatest metabolic dimensions, with a maximum standardized uptake value (SUVmax) of 15.2. Contrast-enhanced abdominal CT confirmed a corresponding heterogeneously enhancing, heterogeneously dense mass in the lower pole of the left kidney, with a coronal diameter of approximately 5×5.6 cm; both kidneys were otherwise normal in size and location, with preserved parenchymal thickness, no hydronephrosis or urolithiasis, and bilateral simple cortical cysts. Urological consultation was requested, and further MRI characterization of the renal lesion for suspected malignancy was recommended.

Laboratory evaluation revealed a serum creatinine of 0.8 mg/dL with an estimated glomerular filtration rate of 88 mL/min/1.73 m², blood urea nitrogen of 17 mg/dL, and a prostate-specific antigen (PSA) level of 4.43 ng/mL. Given the strong radiological suspicion of RCC based on the characteristic hypervascular, FDG-avid appearance of the renal mass, the absence of alternative primary tumor sites

on systemic screening, and the clinical urgency of initiating treatment shortly after intracranial surgery, a multidisciplinary decision was made to proceed with systemic therapy combining a tyrosine kinase inhibitor and an immune checkpoint inhibitor without prior histopathological confirmation of the renal mass. Percutaneous biopsy of the renal lesion was deferred at this stage, and the patient was scheduled for close radiological follow-up while remaining under joint urological and oncological surveillance.

Discussion

Brain metastases from RCC most commonly arise in patients with an established diagnosis and advanced systemic disease, typically appearing years after the initial nephrectomy or, less frequently, synchronously with the primary tumor.[3] Population-based analyses have estimated that brain involvement affects roughly 2% to 20% of patients with metastatic RCC, with variability largely attributable to differences in the intensity of neuroimaging surveillance and the era of systemic therapy studied.[3] A SEER-based analysis further demonstrated that the risk of brain metastasis rises progressively with increasing primary tumor size and higher histological grade, with the highest incidence observed among tumors measuring 10 cm or larger.[4] In the present case, the 6-cm hypermetabolic renal mass falls within the size range already recognized to carry an elevated risk relative to smaller, incidentally detected lesions.[4]

What distinguishes the present case is the sequence in which the diagnosis unfolded: rather than a known renal primary prompting subsequent surveillance for distant spread, an isolated neurological symptom led to the identification of a solitary brain lesion whose immunohistochemical profile could not determine the tissue of origin. This pattern, although uncommon, has been documented in the literature, with previous reports describing chronic headache, focal neurological deficits, or incidentally discovered cerebral lesions as the presenting feature of an otherwise silent RCC.[6,7] In these cases, the customary diagnostic order is inverted: an intracranial finding becomes the starting point of the workup, and the renal origin is only established afterward, once systemic screening is pursued to explain an otherwise unclassified metastatic lesion.[7] The relative rarity of this presentation likely reflects both the biological behavior of RCC, which is capable of hematogenous dissemination even from moderately sized primary tumors, and the nonspecific nature of the presenting neurological symptoms, which may initially be misattributed to more common causes such as primary headache disorders or cerebrovascular events.[6]

The failure of immunohistochemistry to establish a definitive primary site in this case is not unexpected. Current guidance on the diagnostic workup of cancer of unknown primary acknowledges that immunohistochemical marker panels, while useful for narrowing the differential diagnosis, lack uniform sensitivity and specificity across tumor types.[8] Renal cell carcinoma in particular can pose diagnostic difficulty in this setting: as many as 5% of resected renal tumors are considered unclassifiable because of poorly differentiated or atypical morphology, and metastatic deposits may show a different immunophenotype than the primary tumor, further limiting the diagnostic yield of standard panels.[10] In this setting, whole-body 18F-FDG PET-CT assumes a central diagnostic role. A systematic review and meta-analysis of patients with cancer of unknown primary reported an overall primary tumor detection rate of 37% with FDG PET-CT, alongside pooled sensitivity and specificity values of 84%.[9] In the present case, PET-CT not only excluded pathological uptake in the stomach, spleen, pancreas, and adrenal glands, but also identified a single, intensely hypermetabolic renal lesion, thereby substantially narrowing the differential diagnosis and directing subsequent management despite the absence of histopathological confirmation from the kidney itself.

Percutaneous renal mass biopsy remains an important diagnostic tool in the contemporary management of renal tumors and has been shown in systematic reviews to achieve diagnostic accuracy in the range of 90% or higher, with excellent concordance between biopsy and final surgical pathology for both malignancy and histological subtype.[11] In the case presented here, biopsy was deferred rather than omitted as a matter of principle: the markedly hypervascular, FDG-avid morphology of the renal mass on cross-sectional imaging, combined with the absence of any alternative primary tumor site on systematic whole-body screening and the clinical imperative to initiate treatment promptly after intracranial surgery, was judged by the multidisciplinary team to provide sufficient radiological certainty to proceed with systemic therapy while histopathological confirmation and further staging continue to be pursued. This approach illustrates a broader principle in oncological decision-making: while tissue confirmation remains the diagnostic reference standard whenever safely obtainable, the totality of

clinical, radiological, and metabolic imaging findings may, in selected and time-sensitive circumstances, be considered sufficient to justify treatment initiation pending definitive histological confirmation.

The therapeutic landscape for metastatic RCC has evolved substantially over the past decade, with combination regimens pairing a vascular endothelial growth factor receptor tyrosine kinase inhibitor with an immune checkpoint inhibitor now representing standard first-line therapy for most patients with intermediate- or poor-risk disease.[12] In a phase 3 randomized trial, the combination of nivolumab and cabozantinib significantly prolonged progression-free survival, overall survival, and objective response rate compared with sunitinib monotherapy in previously untreated advanced RCC.[13] A network meta-analysis of first-line regimens further confirmed that combined tyrosine kinase inhibitor–immune checkpoint inhibitor regimens, including nivolumab plus cabozantinib, offer among the most favorable survival outcomes across risk groups.[12] These data support the therapeutic strategy adopted in the present case, in which a tyrosine kinase inhibitor/immunotherapy combination was initiated promptly once the probable primary tumor site had been identified.

The question of whether and when to perform cytoreductive nephrectomy in patients with synchronous metastatic RCC has also been substantially reshaped by contemporary trial data. The phase 3 CARMENA trial demonstrated that sunitinib alone was non-inferior to cytoreductive nephrectomy followed by sunitinib among patients with intermediate- or poor-risk metastatic RCC, challenging the historical assumption that upfront nephrectomy should routinely precede systemic therapy.[14] Although this trial was conducted in the targeted-therapy era and did not evaluate contemporary immune checkpoint inhibitor–based regimens, its findings support a management paradigm in which systemic therapy may reasonably be prioritized over immediate surgical intervention in selected patients with a heavy burden of extrarenal disease, as in the present case, where the more pressing clinical priority following intracranial surgery was the timely initiation of disease-directed systemic treatment rather than upfront renal surgery.

Taken together, this case underscores three clinically important points. First, RCC should remain part of the differential diagnosis in patients presenting with a solitary brain lesion of unknown origin, even in the absence of prior urological symptoms or a known renal mass. Second, when immunohistochemistry fails to localize the primary tumor, whole-body FDG PET-CT provides high diagnostic yield and should be pursued systematically, including careful attention to the kidneys and retroperitoneum. Third, in time-sensitive clinical scenarios, a multidisciplinary team may reasonably elect to initiate systemic therapy based on strongly suggestive radiological and metabolic findings, while continuing to pursue histopathological confirmation and definitive local therapy of the primary tumor as clinically appropriate.

Conclusion

Renal cell carcinoma may occasionally present with a solitary cerebral metastasis as its initial and sole clinical manifestation, in the complete absence of typical urological symptoms. When histopathological and immunohistochemical evaluation of a resected brain lesion fails to establish a definitive primary tumor site, systematic whole-body screening with 18F-FDG PET-CT should be pursued, as it offers a high probability of identifying an occult renal primary and can meaningfully guide subsequent management. In carefully selected, time-sensitive clinical scenarios, a multidisciplinary team comprising neurosurgery, medical oncology, and urology may reasonably elect to initiate systemic therapy on the basis of strongly suggestive radiological and metabolic imaging findings, while continuing to pursue histopathological confirmation and definitive renal management as clinically appropriate. This case reinforces the importance of maintaining a broad differential diagnosis for metastasis of unknown primary and highlights the diagnostic and therapeutic value of close multidisciplinary collaboration in such complex clinical presentations.

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ÇOCUKLUK ÇAĞI HODGKIN VE NON-HODGKIN LENFOMALARINDA ATIPIK KLINIK PREZENTASYONLAR: TEK MERKEZLI PILOT ÇALIŞMA

ATYPICAL PRESENTATIONS OF PEDIATRIC HODGKIN AND NON-HODGKIN LYMPHOMA: A SINGLE-CENTER PILOT STUDY

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ÖZET

Amaç

Çocukluk çağı Hodgkin lenfoma (HL) ve Non-Hodgkin lenfoma (NHL) olguları çoğunlukla ağrısız lenfadenopati ve B semptomları ile başvurur. Ancak atipik klinik bulgular tanının gecikmesine neden olabilmekte ve enfeksiyöz, inflamatuvar, alerjik veya cerrahi hastalıkları taklit edebilmektedir. Bu çalışmada merkezimizde tanı alan çocukluk çağı HL ve NHL olgularındaki atipik başlangıç bulgularının değerlendirilmesi amaçlandı.

Gereç ve Yöntem

Bu retrospektif tek merkezli pilot çalışmaya Ocak 2024-Haziran 2026 tarihleri arasında histopatolojik olarak HL veya NHL tanısı alan 18 yaş altındaki hastalar dahil edildi. Demografik özellikler, lenfoma alt tipi, başvuru şikayetleri, laboratuvar ve radyolojik bulgular, tedavi ve klinik sonuçlar elektronik hasta kayıtlarından geriye dönük olarak incelendi. Başvuru bulguları literatüre göre tipik ve atipik olarak sınıflandırıldı.

Bulgular

Çalışmaya 18 hasta dahil edildi. Hastaların 12'si (%66,7) Hodgkin lenfoma, 6'sı (%33,3) Non-Hodgkin lenfoma tanısı aldı. Dört hastada (%22,2) atipik başlangıç bulguları saptandı. İki hastada (%11,1) ilk başvuru yakınması yaygın kaşıntı iken, bir hasta nedeni bilinmeyen ateş, bir hasta ise izole karın ağrısı ile başvurdu. Diğer hastalar periferik lenfadenopati ve/veya B semptomları ile başvurdu. Atipik bulgularla başvuran hastalarda lenfoma tanısı öncesinde farklı ön tanılar nedeniyle değerlendirme yapıldığı görüldü.

Sonuç: Çocukluk çağı lenfomalarının büyük çoğunluğu klasik klinik bulgularla başvursa da atipik prezentasyonlar azımsanmayacak sıklıkta görülmekte ve tanıda gecikmeye neden olabilmektedir. Persistan yaygın kaşıntı, nedeni bilinmeyen ateş ve açıklanamayan karın ağrısı ile başvuran çocuklarda ayırıcı tanıda lenfoma da düşünülmelidir. Bu pilot çalışma, çocukluk çağı lenfomalarının atipik klinik prezentasyonlarına dikkat çekmekte ve daha geniş, çok merkezli çalışmalar için öncü nitelikte veriler sunmaktadır.

Anahtar Kelimeler: Hodgkin lenfoma, Non-Hodgkin lenfoma, çocukluk çağı, atipik prezentasyon, kaşıntı, nedeni bilinmeyen ateş.

ABSTRACT

Background

Pediatric Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) usually present with painless lymphadenopathy and constitutional (B) symptoms. However, atypical clinical manifestations may delay diagnosis by mimicking infectious, inflammatory, allergic, or surgical conditions. We aimed to evaluate uncommon presenting symptoms in pediatric lymphoma patients treated at our institution.

Methods

This retrospective pilot study included pediatric patients diagnosed with histopathologically confirmed HL or NHL between January 2024 and June 2026 at a tertiary referral center. Demographic characteristics, lymphoma subtype, presenting complaints, laboratory and radiological findings,

treatment, and clinical outcomes were retrospectively reviewed. Presenting symptoms were categorized as typical or atypical according to previously published literature.

Results
Eighteen children were included, comprising 12 patients with HL and 6 with NHL. Four patients (22.2%) presented with atypical manifestations. Generalized pruritus was the presenting complaint in two patients (11.1%), whereas one patient presented with fever of unknown origin and another with isolated abdominal pain. The remaining patients presented with classical manifestations, including peripheral lymphadenopathy with or without constitutional symptoms. Patients with atypical presentations underwent evaluation for alternative diagnoses before lymphoma was considered.
Conclusion: Although most pediatric lymphomas present with characteristic clinical findings, atypical manifestations are not uncommon and may contribute to diagnostic delay. Persistent generalized pruritus, fever of unknown origin, and unexplained abdominal pain should prompt clinicians to consider lymphoma in the differential diagnosis. Despite its limited sample size, this pilot study highlights clinically important atypical presentations and provides a basis for larger multicenter studies.
Keywords: Pediatric lymphoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, Atypical presentation

Introduction
Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) account for approximately 15% of all childhood malignancies and represent the third most common group of pediatric cancers after leukemia and central nervous system tumors (1). Despite their biological heterogeneity, both entities generally present with characteristic clinical findings, including painless peripheral lymphadenopathy, mediastinal enlargement, and constitutional (B) symptoms such as fever, night sweats, and weight loss. Consequently, the diagnosis is often established without significant delay in patients presenting with these classical manifestations (1).
However, a proportion of pediatric patients initially present with atypical or nonspecific symptoms that mimic infectious, inflammatory, allergic, rheumatologic, or surgical disorders. Such presentations may include persistent generalized pruritus, fever of unknown origin, isolated abdominal pain, musculoskeletal complaints, or other organ-specific manifestations unrelated to peripheral lymphadenopathy (2,3). Because these symptoms are frequently encountered in routine pediatric practice, lymphoma may not be considered early in the differential diagnosis, potentially leading to delayed referral and diagnosis.
Among these atypical manifestations, generalized pruritus is a well-recognized paraneoplastic symptom of Hodgkin lymphoma and may precede the appearance of lymphadenopathy by several weeks or even months (2). Likewise, prolonged fever without an identifiable source remains an important diagnostic challenge in children, while abdominal pain may represent the initial manifestation of abdominal or extranodal lymphoma, often simulating acute surgical conditions such as appendicitis or mesenteric lymphadenitis (3,4).
Although numerous case reports have described unusual presentations of pediatric lymphoma, studies evaluating the spectrum of atypical presenting symptoms in consecutive pediatric patients remain limited. Increased recognition of these uncommon manifestations may facilitate earlier diagnosis, reduce unnecessary investigations, and improve timely referral to pediatric hematology-oncology centers.
Therefore, the aim of this pilot study was to evaluate atypical presenting manifestations in children diagnosed with Hodgkin and non-Hodgkin lymphoma at a tertiary referral center and to emphasize clinical features that may improve clinicians' awareness of these uncommon presentations.

Materials And Methods
This retrospective single-center pilot study was conducted at the Department of Pediatric Hematology and Oncology, Izmir City Hospital. Medical records of all consecutive pediatric patients diagnosed with Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) between January 2024 and June 2026 were retrospectively reviewed.
Patients younger than 18 years of age with histopathologically confirmed HL or NHL were eligible for inclusion. Patients with incomplete medical records or without definitive pathological diagnosis were excluded.

Demographic characteristics (age and sex), lymphoma subtype, presenting complaints, physical examination findings, laboratory parameters, radiological findings, histopathological diagnosis, disease stage, treatment protocol, and clinical outcomes were obtained from the hospital electronic medical record system.

Presenting symptoms were classified as typical or atypical according to previously published reports describing the clinical presentation of pediatric lymphoma (1–4). Typical presentation was defined as painless peripheral lymphadenopathy with or without constitutional (B) symptoms, including fever, night sweats, and weight loss. Atypical presentation was defined as symptoms not commonly recognized as the initial manifestation of lymphoma, including generalized pruritus, fever of unknown origin, isolated abdominal pain, musculoskeletal complaints, or other organ-specific manifestations leading to an alternative initial diagnosis.

The primary outcome was to describe the spectrum and frequency of atypical presenting manifestations in pediatric patients with HL and NHL. Secondary outcomes included the initial differential diagnosis, diagnostic delay, disease stage at diagnosis, and short-term clinical outcome.

Statistical analyses were performed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (range), depending on data distribution. Categorical variables were summarized as frequencies and percentages. Owing to the exploratory nature of this pilot study and the relatively small sample size, only descriptive statistical analyses were performed.

Results

A total of 18 pediatric patients diagnosed with lymphoma between January 2024 and June 2026 were included in this pilot study. Twelve patients (66.7%) were diagnosed with Hodgkin lymphoma (HL), while six patients (33.3%) had non-Hodgkin lymphoma (NHL).

The median age at diagnosis was 11.8 years (range, 4–17 years), and 12 patients (66.7%) were male. The most common presenting feature was painless peripheral lymphadenopathy, observed either alone or in combination with constitutional (B) symptoms.

Overall, 14 patients (77.8%) presented with typical clinical manifestations. The remaining 4 patients (22.2%) presented with atypical symptoms. Among these, generalized pruritus was the initial complaint in two patients (11.1%), fever of unknown origin in one patient (5.6%), and isolated abdominal pain in one patient (5.6%).

Patients presenting with atypical manifestations underwent evaluation for alternative diagnoses before lymphoma was suspected. Initial differential diagnoses included allergic disorders, infectious diseases, and acute abdominal pathology. The median time from symptom onset to diagnosis was 6 weeks in patients with atypical presentations compared with 3 weeks in those with typical presentations.

Histopathological diagnosis was established by excisional lymph node biopsy or tissue biopsy in all patients. According to the Ann Arbor staging system, **7** patients (38.9%) had early-stage disease (Stage I–II), whereas 11 patients (61.1%) presented with advanced-stage disease (Stage III–IV).

All patients received risk-adapted chemotherapy according to contemporary pediatric lymphoma treatment protocols. At the time of the last follow-up, 16 patients (88.9%) had achieved complete remission, one patient (5.6%) was receiving active treatment, and one patient (5.6%) had experienced disease relapse. No treatment-related mortality was observed during the study period.

The distribution of atypical presenting manifestations is summarized in Table 1.

Table 1. Atypical presenting manifestations in pediatric lymphoma patients

Presenting symptom	**n**	**%**
Generalized pruritus	2	11.1
Fever of unknown origin	1	5.6
Isolated abdominal pain	1	5.6
Total atypical presentations	**4**	**22.2**

Table 2. Baseline characteristics of the study population

Characteristic	Value
Total patients	18
Hodgkin lymphoma	12 (66.7%)
Non-Hodgkin lymphoma	6 (33.3%)
Median age	11.8 years
Male sex	12 (66.7%)
Typical presentation	14 (77.8%)
Atypical presentation	4 (22.2%)
Early stage (I–II)	7 (38.9%)
Advanced stage (III–IV)	11 (61.1%)

Discussion

Early diagnosis remains one of the most important determinants of outcome in pediatric lymphoma. Although Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) typically present with painless lymphadenopathy and constitutional symptoms, atypical clinical manifestations may obscure the diagnosis and delay referral to pediatric hematology-oncology centers (5). In the present pilot study, approximately one-fifth of the patients (22.2%) presented with atypical symptoms, emphasizing that lymphoma should remain in the differential diagnosis even in the absence of classical findings.

Previous studies have shown that delayed diagnosis in childhood malignancies is more commonly related to nonspecific clinical manifestations than to limitations in diagnostic modalities (6). Children presenting with isolated pruritus, fever of unknown origin, abdominal pain, or musculoskeletal complaints are frequently evaluated for allergic, infectious, inflammatory, or surgical disorders before malignancy is considered (7). Similar diagnostic pathways were observed in our cohort.

Generalized pruritus is a well-recognized but relatively uncommon paraneoplastic manifestation of Hodgkin lymphoma. Although its exact pathophysiological mechanism remains unclear, cytokine-mediated immune activation has been proposed as a contributing factor (8). Importantly, pruritus may precede lymph node enlargement by weeks or even months, making recognition particularly challenging (9). The presence of two patients presenting primarily with generalized pruritus in our series supports previous observations that persistent unexplained pruritus warrants careful evaluation for underlying malignancy when common dermatologic and allergic causes have been excluded.

Fever of unknown origin (FUO) represents another important diagnostic challenge in pediatric practice. Although infections account for most pediatric FUO cases, hematological malignancies remain an important differential diagnosis, particularly when fever persists despite appropriate treatment or is accompanied by elevated inflammatory markers or constitutional symptoms (10). Likewise, isolated abdominal pain may represent the initial manifestation of abdominal or extranodal lymphoma and may mimic acute appendicitis, mesenteric lymphadenitis, inflammatory bowel disease, or other surgical conditions (11).

The frequency of atypical presentations observed in our study is consistent with previous reports suggesting that uncommon initial manifestations are probably underrecognized rather than truly rare (7,11). Increasing awareness among pediatricians, emergency physicians, family physicians, and pediatric surgeons may therefore facilitate earlier diagnosis and reduce unnecessary diagnostic procedures.

This study has several limitations. First, it was a retrospective single-center pilot study with a relatively small sample size. Second, statistical comparisons between patients with typical and atypical presentations were limited by the number of cases. Nevertheless, the study reflects real-world clinical experience from a tertiary pediatric hematology-oncology center and highlights uncommon but clinically important presenting manifestations that may otherwise be overlooked.

Conclusion

Although most pediatric HL and NHL cases present with classical lymphadenopathy and constitutional symptoms, atypical manifestations such as persistent generalized pruritus, fever of unknown origin, and isolated abdominal pain should alert clinicians to the possibility of lymphoma. Larger multicenter prospective studies are warranted to better define the prevalence and clinical impact of these uncommon presentations.

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BIDIRECTIONAL MICROBIOTA-IMMUNE-NERVOUS SYSTEM INTERACTIONS IN NEUROLOGICAL DISORDERS

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Background
The intestinal microbiota operates within a bidirectional network linking the gut epithelium, mucosal and systemic immunity, neuroendocrine pathways, the enteric and autonomic nervous systems, and the brain. Microbial ligands and metabolites can influence epithelial permeability, immune differentiation, inflammatory mediators, vagal afferents, glial states, and neuronal function. Short-chain fatty acids (SCFAs), tryptophan metabolites, modified bile acids, and microbe-associated molecular patterns therefore provide biologically plausible links to neurodevelopment, cognition, behavior, neuroinflammation, and neurodegeneration. These mechanisms have intensified interest in Parkinson disease, Alzheimer disease, multiple sclerosis, epilepsy, stroke, depression, and anxiety. Available literature often portrays dysbiosis as an initiating or aggravating factor. Such an interpretation captures only one direction of causality. Neural and neuroendocrine activity continually remodels the microbial habitat by regulating gastrointestinal transit, secretion, perfusion, barrier integrity, mucus production, immune surveillance, feeding, movement, sleep, and circadian timing. Neurological disease may therefore generate microbial alterations without microbial initiation. Observed profiles may represent causes, consequences, mediators, treatment effects, or concurrent processes. A reciprocal framework is essential for causal inference, biomarker development, and intervention design.

Objective
Of this study was to synthesize evidence for bidirectional communication among the intestinal microbiota, immune system, and nervous system. It emphasized mechanisms through which neural health and dysfunction reorganize microbial ecology. It also connected organ-level observations with pattern-recognition signaling, inflammasome activation, metabolite-sensitive receptors, epithelial-junction regulation, cholinergic immune control, circadian programs, and disease-associated genes. A further aim was to distinguish established physiology from preliminary therapeutic concepts and to define requirements for classifying microbiome differences as causes, consequences, mediators, or state markers.

Methods
Indexed biomedical literature was synthesized by direction of communication. Microbiota-to-host pathways included microbial metabolites and ligands, immune activation, epithelial and blood-brain barriers, vagal afferent signaling, glial states, and neurological outcomes. Host-to-microbiota pathways included stress physiology, autonomic and enteric regulation, motility, secretion, sleep, circadian organization, neuroinflammation, sickness behavior, diet, activity, disability, and medication exposure. The synthesis covered neurodegenerative, neuroimmune, neurovascular, seizure-related, and psychiatric conditions. Mechanistic interpretation was prioritized over taxonomic enumeration. Particular attention was given to TLR4 inflammatory signaling; P2RX7-dependent NLRP3 inflammasome assembly; SCFA sensing through FFAR2, FFAR3, and HCAR2; AHR-mediated indole sensing; tryptophan metabolism through IDO1, TDO2, KMO, and KYAT enzymes; FXR- and TGR5-mediated bile acid signaling; CHRNA7-dependent cholinergic immune control; and pathways involving SNCA, LRRK2, GBA1, TREM2, APOE, BACE1, and IL23R-JAK2-STAT3-RORC.
Evidence for study was drawn from heterogeneous experimental systems. Germ-free models, antibiotic perturbation, fecal transfer, and receptor knockouts support mechanistic testing but substantially modify development, immunity, or ecology. Human cohorts described in the literature offer greater clinical relevance but often lack temporal resolution and adequate measurement of diet, bowel function, sleep, disability, and medication. Findings were therefore weighted according to temporal ordering, target engagement, and translational relevance.

Results

The evidence supports a distributed feedback system rather than a unidirectional gut-to-brain pathway. SCFAs engage FFAR2 and FFAR3; butyrate additionally activates HCAR2 and modulates histone deacetylase activity. These mechanisms affect regulatory T-cell programs, epithelial junctions, immune tolerance, and microglial maturation. Indole derivatives activate AHR-dependent transcription and influence mucosal defense and astrocyte responses. Tryptophan allocation shapes serotonin, immunoregulatory indoles, and kynurenine metabolites. Microbially transformed bile acids regulate metabolic, inflammatory, and enteroendocrine responses through FXR and TGR5. Barrier disruption permits bacterial products to activate innate immunity. Lipopolysaccharide recognition by the TLR4 complex induces adaptor-, kinase-, and NF-κB-dependent inflammatory signaling. Extracellular ATP and cellular stress can promote P2RX7-associated NLRP3 assembly and caspase-1-mediated cytokine maturation. These pathways connect dysbiosis with peripheral inflammation, glial responses, and neurological dysfunction. Their activity nevertheless depends on barrier integrity and immune tone, which are themselves neurally and endocrinologically regulated.

Stress provides the clearest host-to-microbiota mechanism. Corticotropin-releasing signals, glucocorticoids, and sympathetic catecholamines alter motility, perfusion, mucus, epithelial junctions, and cytokine production. Some bacteria also respond directly to catecholamines, although responses vary by organism and context. Experimental stress produces no universal taxonomic signature. It more consistently changes intestinal physiology, permeability, inflammation, and microbial metabolism. Parasympathetic and enteric pathways offer complementary mechanisms. Efferent vagal activity coordinates digestion, secretion, motility, and inflammatory restraint. Acetylcholine acting through CHRNA7 on myeloid cells modulates JAK-STAT and NF-κB signaling. Vagus nerve stimulation can alter gut physiology and microbial features, but effects vary by stimulation method, species, disease model, and sampling interval. Enteric neuropathy is especially consequential because transit governs microbial retention, substrate exposure, water availability, stool form, and fermentation. Neurological disease can disrupt transit through autonomic failure, enteric pathology, immobility, dehydration, dysphagia, and medication. Sleep and circadian disruption can also generate dysbiosis. Central and peripheral clocks coordinate feeding, autonomic balance, endocrine rhythms, epithelial renewal, immunity, and microbial oscillations. Because many neurological and psychiatric disorders disrupt sleep, diagnosis-associated microbiome differences may be mediated by altered timing rather than by disease-specific microbial effects. Repeated circadian sampling and objective sleep assessment are therefore necessary.

Neuroinflammation further stabilizes reciprocal feedback. Cytokines alter appetite, movement, sleep, gastrointestinal function, and medication requirements. Microbial products simultaneously influence peripheral immune cells, microglia, astrocytes, and barriers. TREM2, CX3CR1, innate inflammatory pathways, and metabolite-sensitive epigenetic programs contribute to heterogeneous glial states. Neural stress, barrier impairment, dysbiosis, and immune activation may consequently become mutually reinforcing. Behavior and treatment are major ecological determinants. Cognition, mood, pain, fatigue, motor function, dysphagia, and executive capacity shape diet, meal timing, oral care, activity, and bowel function. Psychotropic, antiseizure, antiparkinsonian, anticholinergic, antimicrobial, laxative, analgesic, and acid-suppressive therapies can directly or indirectly alter the microbiota. Disease-associated signatures may therefore encode treatment history and care context. Disorder-specific evidence conforms to this model. In Parkinson disease, prodromal constipation, autonomic dysfunction, sleep disturbance, inactivity, diet, and medication complicate causal interpretation. In dementia, frailty, institutional care, altered meals, poor sleep, reduced mobility, and medication adherence may dominate late-stage profiles. Stroke can rapidly remodel the gut through sympathetic activation, impaired perfusion, barrier disturbance, immune suppression, dysphagia, altered nutrition, antimicrobials, and hospitalization. In epilepsy, seizures, sleep loss, ketogenic diets, antiseizure therapy, and vagal stimulation are influential exposures. In multiple sclerosis and spinal cord disease, dysmotility, neurogenic bowel, immobility, dietary adaptation, and recurrent medication are prominent. Depression and anxiety similarly combine neuroendocrine stress, sleep disruption, appetite change, inactivity, bowel symptoms, and psychotropic treatment. Human findings remain heterogeneous because geography, diet, extraction, sequencing, sample handling, statistical choices, stool consistency, disease severity, and medication vary substantially. Publication bias, small samples, multiple analytical choices, and selective emphasis on named taxa further constrain inference. Microbiome data are compositional, and

sequencing predicts function less reliably than direct metabolomic or transcriptional assays. Neurological diagnoses also contain biologically distinct subgroups. The dominant direction of communication may differ by disease stage, treatment status, and autonomic function. These limitations restrict generalizability and may explain inconsistent taxonomic replication. Temporal and spatial resolution impose additional constraints. Neural signals may alter microbial transcription or metabolite release within hours, whereas community composition may change only after sustained differences in transit, nutrition, or inflammation. A single stool specimen can miss rapid functional responses or combine signals from different disease phases. Fecal samples primarily represent the distal lumen and provide limited information about the small bowel, mucus layer, and epithelium-associated organisms. Repeated sampling should therefore be integrated with metabolomics, immune phenotyping, transit, permeability, physiological measures, and justified mucosal sampling. Taxonomic similarity does not establish functional equivalence. Different organisms may perform overlapping metabolic functions, whereas strains of one species may exhibit distinct biological properties. Host receptor abundance, epithelial integrity, dietary substrates, and intestinal chemistry determine whether a microbial product reaches an effective concentration. Strong inference therefore requires evidence of microbial activity, host target engagement, a relevant cellular response, and association with a defined clinical phenotype. Therapeutic studies remain difficult to interpret. Fiber, fermented foods, probiotics, prebiotics, postbiotics, and community transfer intervene at different ecological levels. Effects depend on baseline diet, resident microbiota, host genetics, disease stage, bowel physiology, and concurrent treatment. Host-directed interventions-including bowel management, sleep restoration, rehabilitation, psychological care, and vagal modulation-may change both symptoms and microbial measures without microbial mediation. Parallel improvement does not establish causality. Prespecified mechanistic outcomes, appropriate comparators, and formal mediation analyses are required. Research designs should also reflect time-dependent reciprocity. Longitudinal cohorts should begin during prodromal or early disease stages and use repeated sampling. *Transit, stool form, bowel frequency, constipation, laxative use, diet, meal timing, feeding route, sleep, circadian timing, stress, activity, autonomic function, disability, care environment, and medication should be treated as core variables.* Intervention studies must specify whether they manipulate the microbial or host compartment. Causal claims should demonstrate a sequence from microbial gene or metabolite change to target engagement, cellular response, and clinically relevant neurological outcome.

Conclusion

The intestinal microbiota, immune system, and nervous system constitute a reciprocal regulatory network. Microbial metabolites and ligands influence barriers, immunity, glia, and neural signaling. Neural and neuroendocrine activity simultaneously determines the conditions that select microbial communities and functions. In neurological disease, altered microbiota may precede pathology, follow it, amplify it, or reflect treatment and disability. Dysbiosis could be therefore best interpreted as a dynamic component of *host-microbe feedback* rather than as an isolated cause. Greater attention to neural-to-intestinal signaling can improve biomarker validity and intervention design. Functional evidence should supersede isolated taxonomic associations. Future therapies should identify the *dominant component of the feedback loop* within defined patient subgroups and verify modulation of the intended molecular and physiological pathway. Most neurological microbiome applications will remain in the research phase unless interactions with and mediation of target sites are demonstrated.

Keywords:gut microbiota; gut-brain axis; immune signaling; autonomic nervous system; neuroinflammation; neurological disorders; bidirectional interactions

AN ANALYSIS OF THE ROLE OF 5G AND 6G NETWORKS IN ENABLING SMART HEALTHCARE SERVICES

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ABSTRACT
The rapid evolution of wireless communication technologies is transforming traditional healthcare into connected, reliable, and smart healthcare services. This paper presents an analysis of the role of fifth-generation (5G) and emerging sixth-generation (6G) networks in supporting next-generation healthcare applications. 5G technology offers high data rates, low latency, enhanced reliability, massive connectivity, and improved network capacity, making it suitable for applications such as Internet of Medical Things (IoMT), telemedicine, remote patient monitoring, connected medical devices, emergency healthcare communication, and real-time medical data transmission. The study analyses the capabilities of 5G networks and examines the potential of 6G technology to address the increasing communication requirements of future healthcare systems. A comparative analysis of 5G and 6G is performed based on key parameters including latency, data rate, reliability, connectivity, scalability, network capacity, security, and healthcare applicability. The analysis also considers the requirements of medical devices and IoMT environments, where continuous connectivity, reliable communication, low delay, and secure data exchange are essential. Various challenges, including network security and privacy, interoperability, infrastructure requirements, device compatibility, reliability, energy efficiency, and deployment cost, are discussed. The study further identifies potential opportunities for 6G in enabling ubiquitous healthcare connectivity, advanced remote healthcare services, immersive healthcare applications, and real-time medical communication. The findings indicate that 5G provides a strong technological foundation for present-day smart healthcare services, while 6G has the potential to enhance the scalability, reliability, responsiveness, and accessibility of future healthcare networks. This analysis highlights the transition from 5G-enabled connected healthcare toward next-generation 6G-supported smart healthcare services.
Keywords: 5G, 6G, Smart Healthcare, Internet of Medical Things, Medical Devices, Telemedicine, Wireless Communication, Healthcare Networks.

Introduction
The healthcare sector is rapidly transforming through the integration of digital technologies such as the Internet of Things (IoT), telemedicine, wearable devices, and remote patient monitoring. These applications generate large amounts of medical data and require communication networks with high speed, reliability, and low latency. Conventional communication technologies may face difficulties in supporting the increasing number of connected medical devices and time-sensitive healthcare services.
Fifth-generation (5G) technology provides high data rates, low latency, improved reliability, and massive connectivity, making it suitable for advanced healthcare applications. 5G-enabled healthcare can support remote patient monitoring, virtual consultation, mobile ultrasound, connected ambulances, robotic surgery, and other smart healthcare services. The integration of 5G with IoT, artificial intelligence, machine learning, and edge technologies further improves the potential for real-time healthcare services and remote medical assistance.
Several studies have demonstrated the practical potential of 5G in healthcare. For example, 5G-enabled mobile ultrasound has been investigated for emergency telemedicine, allowing real-time communication between ambulances and hospitals. However, challenges including data security and privacy, infrastructure cost, interoperability, scalability, network reliability, and practical deployment remain important concerns.
Therefore, this survey paper presents a comparative analysis of existing research on **5G-enabled healthcare**, focusing on major applications, enabling technologies, benefits, limitations, challenges,

research gaps, and future directions. The analysis aims to provide a consolidated view of how 5G can contribute to the development of efficient, reliable, and intelligent healthcare systems.

Literature Review

Dananjayan and Raj (2020) examined the potential of 5G technology to transform healthcare and telemedicine. Their study highlighted the importance of low latency, high speed, reliability, and improved bandwidth for healthcare applications. Remote patient monitoring through wearable sensors, virtual consultations, AR/VR-based medical applications, AI-assisted robotic surgery, and connected medical devices were identified as promising applications of 5G.

Ahad et al. (2020) presented a comprehensive review of 5G-enabled smart healthcare using the Internet of Things (IoT). The study discussed the use of 5G to support massive numbers of healthcare devices, high data rates, low latency, reliability, and energy-efficient communication. It also identified challenges related to device density, standardization, security, and energy consumption.

Berlet et al. (2022) investigated a 5G-enabled emergency telemedicine system using mobile ultrasound. The system enabled bidirectional transmission of ultrasound, audio, and video data between an ambulance and a hospital. The study reported low communication latency and showed that network slicing could improve transmission quality during network congestion, demonstrating the feasibility of 5G for real-time emergency medical support.

Cabanillas-Carbonell et al. (2023) conducted a systematic review of 5G applications in healthcare by analysing 343 articles and identifying 66 relevant studies. The review classified major applications such as telesurgery, mobile ultrasound, biosensors, robotic surgery, and connected ambulances. It also examined the role of digital technologies and their contribution to improving healthcare quality.

Deshmukh and Shrivastav (2024) explored the role of 5G networks in telemedicine and public healthcare. Their study focused on remote healthcare access, continuous patient monitoring, rapid treatment, and real-time transmission of medical information. The integration of artificial intelligence and machine learning through the I-SAHA approach was considered for faster health assessment and improved diagnostic support. The study also highlighted infrastructure cost, adoption, privacy, and security as major barriers.

Singh et al. (2026) investigated a 5G-driven telehealth framework for high-fidelity remote diagnostics. The approach integrates ultra-reliable low-latency communication (URLLC), network slicing, medical-image compression, and edge-based intelligence. The study evaluates image quality, diagnostic performance, latency, packet loss, and computational efficiency, showing the potential of 5G-enabled edge intelligence for remote medical diagnosis. Overall, these studies demonstrate the evolution of 5G healthcare research from conceptual applications and IoT-based connectivity toward practical telemedicine, emergency diagnosis, AI-assisted healthcare, and edge-enabled remote diagnostics. However, common challenges including security and privacy, infrastructure cost, interoperability, scalability, network reliability, and real-world clinical deployment continue to require further investigation.

Methodology/Paper Selection

This survey analyses six research studies related to the application of 5G technology in healthcare. The selected studies cover different healthcare applications, including telemedicine, smart healthcare, IoT-enabled healthcare, emergency medical services, remote diagnostics, and AI-assisted healthcare. The papers were selected based on their relevance to 5G-enabled healthcare and their discussion of applications, technologies, performance, benefits, and challenges.

For the comparative analysis, each study was examined using common parameters such as healthcare application, 5G technology or enabling technology, methodology, performance considerations, major findings, advantages, and limitations. The selected studies were then grouped according to their primary healthcare applications and technological approaches. The analysis considers both review-based and application-oriented studies. The review studies provide a broader understanding of 5G healthcare applications and challenges, while the application-oriented studies demonstrate practical implementations such as 5G-enabled emergency telemedicine and remote medical diagnostics. This approach enables a structured comparison of the current development of 5G-enabled healthcare and helps identify common research gaps and future research directions.

Classification of Reviewed papers

The selected studies can be classified into different categories according to their primary healthcare application and technological focus. This classification helps to understand how 5G technology is being applied across different healthcare domains.

Tab-1

Category	Main Focus	Relevant Studies
5G Healthcare & Telemedicine	Remote consultation, patient monitoring and healthcare communication	Dananjayan & Raj (2020); Deshmukh & Shrivastav (2024)
5G + IoT Smart Healthcare	Connected medical devices, sensors and smart healthcare services	Ahad et al. (2020)
5G Emergency Telemedicine	Real-time ambulance-to-hospital communication and mobile ultrasound	Berlet et al. (2022)
5G Digital Healthcare	Telesurgery, mobile ultrasound, biosensors, robotics and connected ambulances	Cabanillas-Carbonell et al. (2023)
5G + AI/Edge Intelligence	Intelligent remote diagnosis and medical-image processing	Deshmukh & Shrivastav (2024); Singh et al. (2026)
5G + URLLC & Network Slicing	Low-latency and reliable remote diagnostic services	Berlet et al. (2022); Singh et al. (2026)

Overall, the classification shows that 5G healthcare research has developed from general telemedicine and IoT connectivity toward more advanced applications involving AI, edge intelligence, URLLC, network slicing, and real-time remote diagnostics.

Comparative analysis

T he selected studies demonstrate different approaches to integrating 5G technology with healthcare applications. Dananjayan and Raj (2020) primarily discussed the broad potential of 5G for telemedicine, remote monitoring, wearable healthcare, virtual consultation, and robotic surgery. Ahad et al. (2020) focused on the integration of 5G with IoT for smart healthcare and emphasized requirements such as massive connectivity, low latency, reliability, and energy efficiency.

Berlet et al. (2022) moved from conceptual discussion toward practical implementation by evaluating a 5G-enabled emergency telemedicine system using mobile ultrasound. The study demonstrated real-time communication between an ambulance and a hospital and showed the importance of network slicing for maintaining transmission quality. Cabanillas-Carbonell et al. (2023) provided a broader systematic perspective by reviewing 343 articles and identifying major applications including telesurgery, mobile ultrasound, biosensors, robotic surgery, and connected ambulances.

Deshmukh and Shrivastav (2024) emphasized 5G-supported telemedicine combined with AI and ML for rapid healthcare analysis and remote assessment. Singh et al. (2026) further extended this direction by combining 5G URLLC, network slicing, medical-image compression, and edge intelligence for remote diagnostics.

Overall, the comparison indicates a progression from general 5G healthcare applications and IoT connectivity toward practical, intelligent, and low-latency medical services. The studies collectively demonstrate that 5G can support real-time healthcare communication, but security, privacy, infrastructure requirements, interoperability, scalability, and reliable real-world deployment remain important considerations.

Comparative Analysis of Reviewed Papers

Dananjayan and Raj (2020) focused on the transformation of healthcare through 5G technology. The study discussed applications such as telemedicine, remote patient monitoring, wearable sensors, virtual consultation, AR/VR-based medical applications, and AI-assisted robotic surgery. The major benefits identified were low latency, high speed, reliability, and improved bandwidth. Ahad et al. (2020) investigated 5G-enabled smart healthcare using IoT. The study emphasized massive connectivity, low latency, reliability, energy efficiency, and support for a large number of connected healthcare devices. Security, energy consumption, device density, and standardization were identified as important

challenges. Berlet et al. (2022) focused on emergency telemedicine using 5G-enabled mobile ultrasound. The study established bidirectional communication between an ambulance and hospital for transmitting ultrasound, audio, and video data. The study demonstrated low-latency communication and showed that network slicing could improve transmission quality during network congestion.

Cabanillas-Carbonell et al. (2023) conducted a systematic review of 5G applications in healthcare. The study analysed 343 articles and identified 66 relevant studies. Major applications included telesurgery, mobile ultrasound, biosensors, robotic surgery, and connected ambulances. Deshmukh and Shrivastav (2024) examined 5G-based telemedicine with AI and machine learning. Their work focused on remote healthcare access, patient monitoring, real-time health information transmission, and AI-supported health assessment. Infrastructure cost, privacy, security, and adoption were identified as major challenges. Singh et al. (2026) proposed a 5G-driven telehealth framework for high-fidelity remote diagnostics. The approach combines URLLC, network slicing, medical-image compression, and edge intelligence. The study focuses on maintaining diagnostic image quality while achieving low latency for remote medical diagnosis. Overall, the comparison shows a clear progression in 5G healthcare research, from general telemedicine and IoT-based healthcare toward AI-assisted, edge-enabled, and low-latency remote diagnostic systems. The studies also indicate that security, privacy, infrastructure, interoperability, scalability, and real-world clinical implementation remain important areas for further research.

Critical Discussion

The reviewed studies show that 5G can significantly improve healthcare through high-speed, low-latency, reliable communication. Early studies focused on telemedicine, IoT, remote monitoring, and smart healthcare, while recent research has moved toward practical applications such as mobile ultrasound, AI-assisted healthcare, edge intelligence, and URLLC.

The studies also highlight challenges including security and privacy, infrastructure cost, interoperability, scalability, energy efficiency, and network reliability. Therefore, future 5G healthcare systems should combine 5G with IoT, AI, edge computing, and network slicing to achieve secure, reliable, and efficient healthcare services.

Research Gaps

The reviewed studies show that 5G has strong potential in healthcare, but several research gaps remain. Security and privacy of sensitive medical data require further attention. Interoperability and scalability are also important for connecting large numbers of heterogeneous medical devices. High infrastructure and implementation costs may limit large-scale adoption. In addition, many advanced solutions require further real-world clinical validation to confirm their reliability and effectiveness.

Another important gap is the integration of 5G with AI, IoT, edge intelligence, and network slicing into unified healthcare frameworks. Further research is needed to develop solutions that are secure, scalable, reliable, cost-effective, and suitable for practical clinical environments.

Future Direction and Conclusion

Future 5G healthcare research should focus on integrating 5G with AI, IoT, edge computing, and network slicing to provide faster and more reliable healthcare services. Research should also address security, privacy, interoperability, scalability, and infrastructure cost.

Further development of 5G-enabled remote diagnosis, mobile ultrasound, telemedicine, robotic surgery, wearable monitoring, and connected ambulances can improve access to healthcare. More real-world clinical testing and validation are also needed to evaluate the reliability and effectiveness of these technologies in practical healthcare environments. This survey reviewed existing research on 5G-enabled healthcare and analysed its major applications, technologies, benefits, and challenges. The reviewed studies show that 5G can support telemedicine, IoT-based healthcare, remote monitoring, emergency telemedicine, mobile ultrasound, AI-assisted healthcare, and remote diagnostics. The comparison indicates that integrating 5G with IoT, AI, edge computing, URLLC, and network slicing can improve real-time and reliable healthcare services. However, challenges related to security, privacy, infrastructure cost, interoperability, scalability, and real-world clinical implementation remain.

Overall, 5G provides a strong foundation for developing connected, intelligent, and patient-centered healthcare systems, while further research and practical validation are required for wider adoption.

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WORK POSTURE ASSESSMENT AMONG RETAIL CASHIERS: A DESCRIPTIVE ERGONOMIC STUDY IN MAKASSAR, INDONESIA

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ABSTRACT
The occupation of a retail cashier involves extended periods of standing, repeated movements of the upper limbs, limited reach, and active involvement with checkout machinery, all of which may lead to musculoskeletal pain. This analytical cross-sectional ergonomic investigation evaluated the risk of work posture and musculoskeletal issues among cashier employes in Talasalapang, Rappocini District, Makassar, Indonesia, in October 2022. The source population consisted of six workers, with five people participating in the evaluation. Musculoskeletal issues were documented using the Nordic Body Map (NBM), where each anatomical region was assessed on a four-point scale, and work posture was analyzed thru the Rapid Entire Body Assessment (REBA). The initial empirical values were preserved unchanged. All five employes received final NBM ratings categorized as low risk, with scores between 36 and 40 (average 38.6). Nonetheless, specific grievances were predominantly focused on the lower limbs and shoulders. The most significant total complaint scores were noted for the right calf (14), left calf (13), left shoulder (11), right shoulder (11), right knee (11), and left knee (10). The REBA scores for the five assessed working postures were 3, 3, 2, 4, and 4: three postures were deemed low risk while two were categorized as medium risk. These results suggest that a minimal overall NBM risk categorization might occur alongside localized discomfort and postural factors that require ergonomic consideration. The results of the study, which included merely five employes from a single retail location, ought to be understood in a descriptive manner rather than applied broadly. Pragmatic follow-up should emphasize workstation compatibility, reach distance, postural diversity, rest intervals, and regular ergonomic evaluations.
Keywords: Cashier; Ergonomics; Nordic Body Map; Work Posture

Introduction
Musculoskeletal disorders are a major global cause of disability and functional restriction. The World Health Organization predicts that over 1.71 billion individuals worldwide are affected by musculoskeletal problems, with low back pain remaining the top cause of disability in many countries (World Health Organization, 2022). Global Burden of Disease analyzes predict a significant increase in the number of individuals suffering from low back pain as populations grow and age (GBD 2021 Low Back Pain Collaborators, 2023). Beyond health effects, low back pain and other musculoskeletal issues have significant productivity and economic costs, making workplace prevention a critical occupational-health objective (Fatoye et al., 2023).
Work-related musculoskeletal diseases (WMSDs) are complex. Physical exposures such as awkward or demanding postures, repetitive movements, physical exertion, lifting, static loading, and a restricted work environment can all contribute to or exacerbate musculoskeletal disorders. Systematic evidence developed for the WHO/ILO Joint Estimates shows that occupational exposure to ergonomic risk factors

is common and related with an increased risk of certain musculoskeletal illnesses (Hulshof et al., 2021a, 2021b). A recent systematic review and meta-analysis depict WMSDs as a chronic problem across vocations, with posture, repetition, manual handling, and job demands consistently identified as important exposures (Greggi et al., 2024). Physical demands may interact with job strain and work organization, implying that ergonomic risk should not be limited to posture (Joseph et al., 2023; Kwon et al., 2023).

Retail cashier labor has a unique combination of static and repetitive duties. Cashiers may stand for extended periods of time, repeatedly reach for products and scanners, handle keyboards or touch screens, rotate the trunk, and keep their upper limbs in confined positions. Studies on supermarket and small-business cashiers have reported musculoskeletal symptoms in the neck, shoulders, back, wrists/hands, and lower limbs, as well as connections with awkward posture and preferred working position (Algarni et al., 2022; Roxô et al., 2021; Tesfaye et al., 2023). In Indonesia, standing work position has been linked to low back discomfort among cashiers (Rachmawati et al., 2021). Recent cashier research employing REBA and a musculoskeletal discomfort questionnaire found that many workers were at moderate-to-high postural risk, with a high prevalence of lower-limb and low-back problems (Handayani & Suharyanto, 2025). Supermarket baggers, who share certain standing, reaching, and manual-handling exposures with checkout workers, have also revealed links between REBA-derived postural risk and musculoskeletal discomfort (Gumasing et al., 2023).

Ergonomic screening frequently incorporates observational posture assessment and symptom mapping since these methods capture diverse aspects of risk. REBA is an observational technique that assesses whole-body postural load and assigns action-oriented risk categories. Comparative and methodological investigations continue to support its practical application, while underlining that REBA is a screening tool rather than a thorough biomechanical diagnostic (Kee, 2022; Yazdanirad et al., 2022). Newer computer algorithms have attempted to improve posture recognition and lessen the subjective nature of traditional REBA scoring, but expert interpretation and task context remain critical (Huang et al., 2024). Body-region questionnaires and maps can help identify the anatomical distribution of symptoms, and recent reliability study supports the use of self-administered musculoskeletal questionnaires for location-specific symptom surveillance (Dahl et al., 2022).

The initial 2022 study at Alfamart Talasalapang aimed to uncover musculoskeletal complaints and analyze work-posture risk among cashiers. The present article revises that research report into an English-language journal manuscript while retaining the empirical findings. The particular aims are to characterize the workers' NBM complaint pattern, report the REBA risk classification of the observed cashier postures, and interpret the results in light of modern occupational ergonomics literature. Because the sample is so tiny and comes from a single retailer, the emphasis is descriptive, with no causal or population-level implications made.

Method

The study used a descriptive cross-sectional ergonomic assessment and was conducted at the Alfamart Talasalapang unit in Rappocini District, Makassar City, Indonesia, in October 2022. The source report identified six workers in the unit as the study population and included five workers in the assessment. Five workers were included.

Musculoskeletal complaints were assessed using the Nordic Body Map (NBM) approach applied in the source study. Workers rated discomfort for 28 body regions using a four-point scale: 1 = no pain, 2 = slightly painful, 3 = painful, and 4 = very painful. The NBM therefore provided both a worker-level total score and body-region-specific complaint scores. This type of anatomical symptom mapping is useful for identifying where discomfort clusters even when an overall score is relatively low. Recent evidence on self-administered musculoskeletal questionnaires supports moderate-to-good reliability for several body locations, while also underscoring that symptom questionnaires remain self-report measures rather than clinical diagnoses (Dahl et al., 2022).

Work posture was assessed using Rapid Entire Body Assessment (REBA). The source procedure consisted of observing cashier postures considered relevant to musculoskeletal risk, assigning body-segment scores with the REBA worksheet and body-part diagrams, and converting the combined score into an action-level risk category. The recorded analysis included neck, trunk, leg, upper-arm, lower-arm, and wrist positions as applicable to each observed posture. REBA is widely used as a rapid whole-body observational method, although its ordinal scoring structure and dependence on posture selection mean that it should be interpreted as a screening tool rather than a direct measure of tissue loading (Kee,

2022; Yazdanirad et al., 2022). Emerging computer-vision methods may improve posture capture, but those methods were not used in the 2022 field study (Huang et al., 2024).

The analysis was descriptive. The original NBM and REBA values were transcribed without modification. Worker-level NBM scores and risk categories were summarized, body-region complaint scores were ranked descriptively, and the five REBA scores were reported with their original risk classifications. Means and ranges presented in this manuscript were calculated directly from the source values solely to improve readability. No inferential statistical test was added because the study included only five workers and the original report did not provide a basis for valid population-level inference.

Research And Findings

Based on the recorded participant table, three were male and two were female. Their ages ranged from 19 to 23 years (mean 21.0 years), and recorded body weight ranged from 43 to 53 kg (mean 47.4 kg). Height, body mass index, employment tenure, shift duration, and prior musculoskeletal diagnoses were not reported in the dataset available for this manuscript and were therefore not reconstructed.

Table 1. Participant characteristics and final Nordic Body Map risk classification

Worker	Gender	Age (years)	Weight (kg)	Final NBM score	Risk level
D1	Female	23	46	40	Low
D2	Male	21	43	36	Low
D3	Male	19	50	39	Low
D4	Male	21	45	40	Low
D5	Female	21	53	38	Low

The five observed cashier postures produced REBA scores of 3, 3, 2, 4, and 4. Three observations (60%) were classified as low risk and two observations (40%) as medium risk. No observed posture was classified as high or very high risk. The mean REBA score across the five observations was 3.2; this mean is a descriptive summary only and does not replace the categorical interpretation of individual REBA scores.

Table 2. REBA scores and risk classifications for the five observed cashier postures

Observed posture	REBA score	Risk classification
1	3	Low
2	3	Low
3	2	Low
4	4	Medium
5	4	Medium

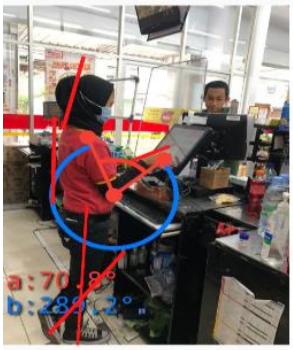


Figure 1. Example of postural angle measurement used for REBA scoring, showing trunk/upper-arm flexion angles recorded during checkout activity



Figure 2. Example of postural angle measurement used for REBA scoring, showing upper-arm and forearm flexion angles during scanning activity

All five workers had final NBM scores classified as low risk in the source analysis. The scores ranged from 36 to 40, with a mean of 38.6. However, the body-region distribution shows that discomfort was not uniform. The right calf had the highest cumulative location score (14), followed by the left calf (13). Both shoulders scored 11, the right knee scored 11, and the left knee scored 10. Thus, the most prominent complaint pattern involved the calves, knees, and shoulders, consistent with the conclusion of the original report.

Table 3. Cumulative NBM complaint scores by body region

Body region	Total score	Body region	Total score
Upper neck	5	Left wrist	5
Lower neck	5	Right wrist	6
Left shoulder	11	Left hand	5
Right shoulder	11	Right hand	5
Left upper arm	6	Left thigh	6
Back	6	Right thigh	7
Right upper arm	5	Left knee	10
Waist	6	Right knee	11
Buttocks	5	Left calf	13
Lower buttocks	5	Right calf	14
Left elbow	5	Left ankle	7
Right elbow	5	Right ankle	7
Left forearm	5	Left foot	6
Right forearm	5	Right foot	6

Discussion

The primary finding is that all employes were deemed low risk according to the final NBM score, although the posture evaluation revealed two medium-risk REBA findings, and the body map indicated a distinct concentration of grievances in the calves, knees, and shoulders. These findings are not inconsistent as NBM and REBA assess distinct constructs. NBM delineates reported discomfort according to body location, while REBA assesses postural exposure during a designated job position.

Contemporary methodological literature highlights that observational posture scores must be analyzed in conjunction with symptom data and task context, rather than serving as a replacement for clinical evaluation or exposure assessment (Kee, 2022; Yazdanirad et al., 2022). Research employing posture-recognition systems aims to enhance the accuracy of posture classification, demonstrating that a singular categorical score fails to encompass the entire intricacy of biomechanical exposure (Huang et al., 2024). The lower-limb pattern seen in this research is credible for cashier roles characterized by prolonged standing. The calves and knees exhibited the most elevated cumulative NBM values. Recent cashier studies indicate the significance of lower-limb symptoms: Handayani and Suharyanto (2025) noted particularly elevated discomfort rates in both the right and left legs of cashiers, whereas Gumasing et al. (2023) discovered that the foot was the most commonly impacted area among supermarket baggers and recognized postural risk as a crucial factor associated with discomfort. Rachmawati et al. (2021) additionally documented a correlation between upright posture and lower back discomfort in retail cashiers in Surakarta. In a wider professional setting, chronic leg pain associated with extended standing has been significant enough to inspire intervention studies focused on alleviating leg discomfort and tiredness (Kashyap et al., 2024). These comparisons underscore the importance of ergonomic considerations regarding lower-limb loading, even when the overall symptom score is categorized as low-risk.

Shoulder issues were notably prevalent among the current workers, with identical cumulative scores for both the left and right shoulders. This aligns with the repetitive reaching and upper-limb stance typical of checkout activities. Roxô et al. (2021) discovered a significant occurrence of symptoms in the neck, shoulders, wrists/hands, and back among female supermarket cashiers and recognized a workstation risk level necessitating remedial measures. Algarni et al. (2022) similarly identified musculoskeletal impairments and symptomatology in supermarket cashiers, with occupational posture and the necessity of adopting uncomfortable positions as contributing causes. A cross-sectional analysis involving 618 cashiers in Ethiopia revealed a substantial 12-month prevalence of work-related musculoskeletal disorders (WMSDs) and highlighted uncomfortable posture as a critical contributor (Tesfaye et al., 2023). Collectively, these investigations suggest that the relatively low total NBM categorization in the Makassar sample should not be construed as a lack of ergonomic exposure.

Disparities between this research and more extensive cashier studies may be attributed to study design and sample attributes rather than an actual lack of danger. The Makassar research encompassed merely five young employes from a single store and involved a brief observation period. Conversely, contemporary cashier research has incorporated significantly bigger sample sizes and more comprehensive data regarding work time, disabilities, or personal variables (Algarni et al., 2022; Handayani & Suharyanto, 2025; Tesfaye et al., 2023). The current dataset omits employment duration, daily standing time, workstation measurements, height, body mass index, physical activity levels, prior injuries, and psychosocial factors. These unquantified variables may affect musculoskeletal results. Comprehensive occupational studies indicate that physical requirements interplay with psychosocial and organizational elements, influencing the prognosis of WMSDs thru both alterable and inalterable aspects (Kwon et al., 2023; Tousignant-Laflamme et al., 2023). Consequently, the results ought to be characterized as descriptive and localized.

The findings correspond with existing literature indicating that work-related musculoskeletal issues often concentrate in certain anatomical areas based on task requirements. Evaluations across many professions consistently highlight the lower back, neck, shoulders, and upper extremities as prevalent areas for work-related musculoskeletal disorders, but the specific distribution differs depending on the tasks undertaken (Greggi et al., 2024; Jacquier-Bret & Gorce, 2023). Evidence from WHO/ILO suggests that strenuous postures, exertion, repetition, lifting, and various ergonomic characteristics can elevate the risk of musculoskeletal disorders (Hulshof et al., 2021a), and that such physical ergonomic exposures are prevalent among working populations (Hulshof et al., 2021b). The cashier workstation ought to be regarded as a work system that encompasses posture, repetition, reach, standing length, work-rest arrangement, and equipment positioning, rather than only as a solitary standing activity.

In the analyzed checkout environment, the most justifiable ergonomic priority are economical adjustments that tackle the identified exposure trends without exaggerating the data. This encompasses evaluating counter and scanner elevation, positioning commonly used items within easy access, minimizing excessive trunk twisting, permitting shifts between standing and supported sitting when practical, facilitating brief recovery intervals, and regularly reassessing postures following

modifications to the workstation or tasks. A randomized study including supermarket cashiers demonstrated that the integration of ergonomic training and exercise enhanced various musculoskeletal results in comparison to ergonomic training alone, endorsing a combined strategy over a solely educational one (Yaşar et al., 2025). Systematic evaluations indicate that workplace exercise may be advantageous for certain occupational categories, however its efficacy differs based on the intervention and demographic (Abdul Halim et al., 2023; Tersa-Miralles et al., 2022). Crucially, the evidence supporting warm-up programs in isolation is ambiguous and of little reliability, hence these activities should not supplant workstation modifications or exposure management (Larinier et al., 2023).

Recent Indonesian ergonomic research offer new background for combining symptom evaluation and postural analysis. Kurniawan et al. (2024) employed a descriptive cross-sectional technique to characterize work posture and MSD complaints among construction workers, demonstrating the ongoing use of standardized postural and symptom evaluation in local occupational-health research. The current research applies the same general approach to a retail micro-environment: localized symptoms and medium-risk postures can serve as valuable early warning indications even when no severe aggregate score is present. Preventive surveillance and proportionate ergonomic improvement are the right responses, rather than claiming that workers have musculoskeletal sickness.

Study limitations

Several limits limit interpretation significantly. First, the sample consisted of five Alfamart employes, therefore prevalence values and relationships cannot be applied to other stores or cashiers. Second, the cross-sectional, descriptive design prevented temporal or causal inference. Third, the source report did not include shift duration, standing time, task frequency, employment tenure, workstation dimensions, worker height, BMI, exercise habits, past injury, medical history, or psychosocial exposures. Fourth, NBM symptoms were self-reported and represent discomfort, not clinical diagnosis. Fifth, REBA is posture-sensitive and does not directly quantify cumulative load or duration.

Conclusion

All Nordic Body Map scores were low risk, ranging from 36 to 40. Right and left calves, shoulders, and knees were the main complaints. Three low-risk and two medium-risk REBA scores were found in five cashier postures. Thus, a low NBM classification might coexist with localized discomfort and postural issues that require preventive attention. Because the study was small, single-site, and descriptive, it cannot demonstrate prevalence or causal linkages beyond the observed workers. Practical follow-up should focus on workstation fit, reach, rotation, postural variety, lower-limb recuperation, and ergonomic review. Future research should document job time, workstation size, anthropometry, employment history, and psychological aspects in a larger multi-store sample.

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3D-PRINTED MEDICINES AND THE FUTURE OF PERSONALIZED HEALTHCARE: ECONOMIC, SOCIAL AND PHARMACEUTICAL IMPLICATIONS

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ABSTRACT

Three-dimensional (3D) printing, also known as additive manufacturing, is emerging as a transformative technology in pharmaceutical science and personalized healthcare. Unlike conventional pharmaceutical manufacturing, which primarily follows a mass-production model, 3D printing enables the layer-by-layer fabrication of medicines with customized dose, geometry, drug-release characteristics and combinations of active pharmaceutical ingredients. This capability has the potential to address important limitations of the conventional "one-size-fits-all" approach, particularly in pediatric, geriatric, low-dose, polypharmacy and pharmacogenomically guided therapies. The approval of SPRITAM® (levetiracetam) demonstrated that 3D-printed medicines can progress from laboratory research to an approved pharmaceutical product. More recently, research has expanded toward hospital point-of-care manufacturing, community-pharmacy compounding, automated quality control and decentralized production.

This review critically examines the pharmaceutical, economic and social implications of 3D-printed medicines and evaluates their potential role in the future of personalized healthcare. Pharmaceutical applications include personalized dosing, polypills, modified drug-release systems, taste-masked formulations, complex geometries and on-demand production. Economically, 3D printing may reduce inventory requirements, improve production flexibility, decrease manual compounding and potentially reduce medication wastage; however, high equipment costs, formulation development, validation, quality assurance and regulatory compliance may limit economic advantages in some settings. Socially, personalized medicines may improve adherence, accessibility and patient-centered care but may also introduce concerns related to digital inequality, data privacy, professional responsibility, cybersecurity and unequal access to advanced healthcare technologies. Regulatory challenges surrounding decentralized manufacturing, digital prescriptions, printable pharmaceutical materials, process validation, traceability and batch release remain important barriers. The future of pharmaceutical 3D printing is therefore likely to depend on integration with artificial intelligence, pharmacogenomics, digital health records, process analytical technology and robust regulatory frameworks. Rather than replacing conventional pharmaceutical manufacturing, 3D printing is likely to develop as a complementary technology for situations in which personalization, flexibility and rapid small-batch production provide clear clinical value.

Keywords: 3D printing; additive manufacturing; personalized medicine; personalized dosage forms; pharmaceutical manufacturing; point-of-care manufacturing; digital pharmacy; drug delivery; pharmacogenomics; healthcare economics.

Introduction

Modern pharmaceutical therapy has traditionally been based on standardized dosage forms manufactured at large scale. Tablets, capsules, injections and other dosage forms are generally produced in predetermined strengths and formulations and subsequently distributed through centralized pharmaceutical supply chains. Although this model provides substantial advantages in manufacturing efficiency and quality control, it does not always accommodate the biological and clinical variability observed between individual patients.

Patients differ in age, body weight, renal and hepatic function, genetics, disease severity, concomitant medications and treatment response. Consequently, a commercially available fixed-strength dosage form may not provide the optimal dose for every patient. This limitation is particularly relevant in pediatric and geriatric populations, patients requiring dose titration, individuals receiving multiple medicines and patients with uncommon therapeutic requirements.

Personalized medicine aims to move healthcare from a generalized treatment strategy toward interventions adapted to individual patient characteristics. 3D printing offers an important manufacturing platform for this transition because the physical characteristics of a medicine can be digitally designed and subsequently produced according to patient-specific requirements. Reviews of

pharmaceutical 3D printing have highlighted its ability to modify dosage, geometry, drug loading and release characteristics while supporting personalized therapy.

Pharmaceutical 3D printing involves the layer-by-layer fabrication of drug-containing structures using techniques such as fused deposition modeling (FDM), semi-solid extrusion (SSE), stereolithography (SLA), binder jetting and inkjet printing. These technologies differ in their mechanisms, printable materials, processing temperatures, drug-loading capabilities and suitability for specific dosage forms.

The concept has progressed considerably since early laboratory demonstrations. A major milestone was the approval of SPRITAM® (levetiracetam), manufactured using a 3D-printing-based technology, demonstrating the regulatory feasibility of industrial pharmaceutical additive manufacturing.

More recently, pharmaceutical 3D printing has begun moving toward decentralized and point-of-care production. A 2026 review describes applications spanning industrial manufacturing, hospital point-of-care production and community-pharmacy compounding.

Therefore, the future significance of pharmaceutical 3D printing extends beyond its technological capabilities. Its adoption could influence pharmaceutical economics, pharmacy practice, healthcare accessibility, patient autonomy and the organization of medicine supply chains.

This review evaluates these developments from three interconnected perspectives:

1. **Pharmaceutical implications**
2. **Economic implications**
3. **Social and ethical implications**

2. Evolution of 3D Printing in Pharmaceutical Sciences

3D printing was initially developed primarily for rapid prototyping and manufacturing applications. Its adaptation to pharmaceutical sciences introduced a fundamentally different approach to dosage-form production.

Conventional pharmaceutical manufacturing generally follows a sequence involving raw-material processing, blending, granulation, compression or filling, coating and packaging. These processes are optimized for large production volumes.

In contrast, additive manufacturing produces a dosage form directly from a digital design. The digital model can be modified without completely redesigning conventional manufacturing equipment.

This characteristic creates an important distinction:

Conventional manufacturing:
Large-scale production → standardized strength → centralized distribution → patient receives available formulation

3D-printed manufacturing:
Patient requirements → digital formulation/design → customized manufacturing → patient-specific dosage form

The technology has therefore been described as a potential new branch of digital healthcare because pharmaceutical products can potentially become linked to digital prescriptions and patient-specific treatment parameters.

3. Major Pharmaceutical 3D-Printing Technologies

3.1 Fused Deposition Modeling

FDM is one of the most investigated pharmaceutical 3D-printing technologies. Drug-loaded polymeric filaments are heated and extruded through a nozzle to construct the dosage form layer by layer.

Potential advantages include:

- Accurate control of tablet geometry
- Ability to manufacture complex structures
- Modified drug-release profiles
- Potential production of multiple drugs in a single dosage form
- Digital control of dosage-form design

FDM can also produce amorphous solid dispersions, enteric systems and polypills depending on the drug-polymer combination.

A major limitation is the requirement for thermal processing, which may restrict the technology to thermally stable active pharmaceutical ingredients.

3.2 Semi-Solid Extrusion

Semi-solid extrusion involves extrusion of a drug-containing paste or gel through a nozzle. The deposited material subsequently solidifies or dries to form the final dosage form.

SSE is particularly attractive for personalized medicines because it can operate under relatively mild processing conditions.

Potential applications include:

- Pediatric formulations
- Low-dose medicines
- Personalized tablets
- Patient-specific drug combinations
- Hospital compounding
- Small-batch production

Recent research has specifically investigated risk-based frameworks for implementing SSE-based personalized medicines within hospital compounding and clinical-trial environments.

3.3 Binder Jetting

Binder jetting involves selective deposition of a binding liquid onto successive powder layers.

This technology became particularly important because it was used for the manufacture of SPRITAM®, the first FDA-approved 3D-printed drug product. The technique enables rapid disintegration through the production of highly porous tablets.

3.4 Stereolithography

Stereolithography uses light-induced polymerization to construct three-dimensional structures.

Its pharmaceutical potential includes:

- Complex geometries
- Controlled drug release
- Microstructured dosage forms
- Advanced drug-delivery systems

However, concerns related to photoreactive materials, residual monomers and drug stability must be carefully addressed.

3.5 Inkjet Printing

Inkjet printing enables controlled deposition of drug-containing droplets onto a substrate or dosage-form structure.

It offers potential advantages for:

- Extremely low-dose medicines
- Multiple drug deposition
- Precise spatial drug distribution
- Customized drug loading

Multi-material inkjet 3D printing is particularly interesting for producing medicines with different drugs or release profiles within a single dosage form.

4. Pharmaceutical Implications of 3D-Printed Medicines

4.1 Personalized Dose

The most important pharmaceutical advantage of 3D printing is the possibility of producing individualized doses.

Instead of manufacturing only:

5 mg, 10 mg, 20 mg and 40 mg tablets

a digital manufacturing system could theoretically produce:

13.7 mg or 27.3 mg

according to a validated patient-specific prescription.

This capability could be valuable for medicines requiring gradual dose adjustment or for patients who cannot conveniently obtain commercially available strengths.

4.2 Pediatric Medicines

Children represent an important target population because commercially available dosage strengths may not correspond to their body weight and developmental requirements.

3D printing can potentially facilitate:

- Weight-based dosing
- Smaller dosage forms
- Improved taste masking
- Flexible drug strengths
- Child-friendly shapes
- Combination dosage forms

The technology could therefore contribute to more patient-centered pediatric pharmacotherapy.

4.3 Geriatric and Dysphagia-Friendly Medicines

Older patients frequently experience swallowing difficulties and polypharmacy.

3D printing may allow the design of:

- Orodispersible tablets
- Highly porous tablets
- Smaller dosage forms
- Easy-to-swallow formulations
- Customized release systems

The ability to modify tablet geometry and porosity provides pharmaceutical scientists with additional tools for optimizing patient acceptability.

4.4 Polypills and Reduction of Pill Burden

Polypharmacy is a significant challenge in chronic diseases.

A conventional regimen may require several tablets taken at different times.

3D printing could potentially combine multiple active pharmaceutical ingredients into a single dosage form while maintaining different release characteristics.

For example:

Drug A → immediate release

Drug B → delayed release

Drug C → sustained release

within one digitally designed dosage form.

This concept could potentially simplify medication regimens and improve adherence. Contemporary reviews identify combination medicines and individualized drug-release mechanisms as important advantages of pharmaceutical 3D printing.

5. Personalized Drug-Release Profiles

Traditional tablets generally provide a limited range of release profiles.

3D printing can modify:

- Internal geometry
- Infill percentage
- Surface area
- Polymer distribution
- Drug location
- Layer thickness
- Shell thickness

These parameters can influence drug dissolution and release.

Consequently, a patient-specific dosage form could theoretically be designed with a release profile corresponding to the therapeutic requirements of that individual.

This creates the possibility of moving from:

Personalized dose
to:

Personalized dose + personalized release
and eventually:

Personalized multi-drug therapy + personalized release + personalized dosage form.

6. On-Demand and Point-of-Care Manufacturing
One of the most transformative possibilities is the manufacture of medicines close to the patient.
A future healthcare facility could potentially contain:

Electronic prescription
↓
Patient clinical data
↓
Validated digital formulation
↓
3D pharmaceutical printer
↓
Quality verification
↓
Patient-specific medicine

Such a model could reduce dependence on large inventories of every possible dosage strength.
Recent research has demonstrated pharmaceutical 3D printing in community-pharmacy settings. In one study, a pharmaceutical printer was used to prepare personalized minoxidil capsules for patients; the printed products met relevant European Pharmacopoeia requirements for mass uniformity, drug content and dissolution, while operator involvement was reduced by more than half compared with manual capsule filling.
This provides an important example of how 3D printing may move beyond laboratory research toward real-world pharmacy practice.

7. Economic Implications
7.1 Potential Reduction in Inventory Costs
Traditional pharmaceutical distribution requires inventories of multiple strengths and formulations.
For example, a pharmacy may need to maintain:
5mg
10mg
20mg
40mg
80 mg
of a particular medicine.
A validated 3D-printing system could potentially produce selected strengths when required.
This could reduce:

- Overstocking
- Expired medicines
- Inventory requirements
- Storage requirements
- Supply-chain complexity

However, these benefits depend on the cost and throughput of the printing system.

7.2 Reduced Pharmaceutical Waste
Conventional manufacturing is economically optimized for large batches.
If demand for a particular formulation is low, unused products may eventually expire.
3D printing enables smaller production batches and therefore may reduce wastage associated with low-demand personalized formulations.

The economic literature on medical 3D printing has identified the possibility of changing cost structures through customization and decentralized production, although the economic benefit is highly dependent on the application and implementation model.

7.3 Equipment and Infrastructure Costs

3D printing is not automatically cheaper than conventional manufacturing.

Initial investment may include:

- Pharmaceutical-grade printer
- Controlled manufacturing environment
- Software
- Material-handling equipment
- Analytical instruments
- Cleaning systems
- Validation
- Personnel training
- Quality-control systems

Therefore:

Low production volume + high customization → 3D printing may be advantageous

whereas:Very high production volume + standardized product → conventional manufacturing may remain more economical.

This distinction is important when evaluating the economic future of pharmaceutical 3D printing.

8. Cost-Effectiveness and Healthcare Economics

The economic value of 3D-printed medicines should not be assessed only by the manufacturing cost per tablet.

A comprehensive economic assessment should consider:

Total healthcare cost = manufacturing cost + distribution cost + wastage + medication errors + adherence-related costs + hospitalization + treatment failure

A more expensive personalized dosage form could potentially be economically beneficial if it significantly improves adherence or reduces adverse events.

Therefore, future health-economic studies should evaluate:

- Cost per successfully treated patient
- Quality-adjusted life years (QALYs)
- Medication adherence
- Reduction in hospitalization
- Reduction in medication wastage
- Pharmacist time
- Equipment utilization
- Quality-control expenditure

Current translational research specifically identifies the need for multi-site cost benchmarking and comparison with conventional compounding before widespread adoption.

9. Social Implications

9.1 Patient-Centered Healthcare

3D printing could shift pharmaceutical care toward a more patient-centered model.

The patient would no longer simply receive a standardized medicine.

Instead, the formulation could potentially be designed according to:

- Age
- Body weight
- Dose requirement
- Swallowing ability
- Treatment schedule
- Drug combinations
- Therapeutic response
- Genetic information

This could strengthen the role of pharmacists in individualized medication management.

9.2 Medication Adherence
Poor medication adherence is a major problem in chronic disease management.
Personalized medicines may improve adherence through:
- Reduced pill burden
- Improved taste
- Easier swallowing
- Patient-specific dosing
- Simplified dosing schedules
- Customized dosage forms

However, the assumption that personalization automatically improves adherence requires clinical validation.

10. Social Inequality and the Digital Divide
A major concern is that advanced personalized healthcare could become available primarily to economically advantaged populations.
Potential inequalities may arise because:
- Pharmaceutical printers may be expensive.
- Specialized personnel may be concentrated in major hospitals.
- Rural healthcare facilities may lack infrastructure.
- High-quality digital connectivity may be required.
- Genetic or clinical data may not be equally accessible.

Therefore, technological innovation must be accompanied by policies promoting equitable access.
Otherwise, 3D printing could unintentionally create:

Precision healthcare for wealthy populations
while conventional standardized healthcare remains available to economically disadvantaged populations.

11. Ethical Implications
Personalized healthcare involves extensive collection and use of patient information.
Potentially relevant data include:
- Medical history
- Prescription information
- Body weight
- Laboratory data
- Pharmacogenomic information
- Treatment response
- Digital medication profiles

Such information creates concerns regarding:
- Privacy
- Confidentiality
- Data ownership
- Informed consent
- Cybersecurity
- Unauthorized modification of prescriptions

Ethical challenges are already recognized within personalized and pharmacogenomic medicine, particularly around privacy, autonomy, informed consent and equitable access.
With pharmaceutical 3D printing, these concerns acquire an additional digital dimension.

12. Cybersecurity of Digital Medicines
A future digital pharmaceutical workflow could potentially involve:

Physician → Electronic prescription → Digital formulation → Printer → Medicine
If the digital file is manipulated, the resulting medicine could theoretically contain:

- Incorrect dose
- Incorrect drug
- Incorrect geometry
- Incorrect release profile

Therefore, cybersecurity becomes a pharmaceutical quality issue.
Future systems may require:

- Encrypted prescription files
- Digital signatures
- Blockchain or secure audit trails
- User authentication
- Printer access control
- Recipe version control
- Automatic parameter verification

The concept of a "digital drug" therefore requires protection comparable to physical pharmaceutical products.

13. Regulatory Challenges

Regulation is one of the most significant barriers to widespread pharmaceutical 3D printing.
Traditional pharmaceutical regulation generally evaluates:

- Drug substance
- Excipients
- Manufacturing process
- Finished product
- Stability
- Safety
- Efficacy

3D printing introduces additional variables.
These may include:

- Printable feedstock
- Printer hardware
- Software
- Printing parameters
- Digital formulation
- Layer deposition
- Environmental conditions
- Printer-to-printer variability

Recent reviews emphasize the absence of a fully harmonized regulatory framework specifically designed for 3D-printed pharmaceutical products.

14. Quality Control of 3D-Printed Medicines

Quality control must demonstrate that every printed dosage form contains the correct amount of drug and possesses the required pharmaceutical characteristics.
Important quality attributes include:
Physical parameters

- Weight
- Dimensions
- Hardness
- Friability
- Appearance

Chemical parameters

- Drug content
- Content uniformity
- Degradation products
- Chemical stability

Performance parameters

- Disintegration
- Dissolution
- Drug-release profile
- Bioavailability

Process parameters

- Temperature
- Printing speed
- Nozzle pressure
- Layer thickness
- Infill percentage
- Material viscosity

15. Real-Time and Non-Destructive Quality Control

One major challenge is that personalized manufacturing may produce small batches, sometimes consisting of only a few dosage units.

Traditional destructive testing may therefore be impractical.

Recent research has investigated miniaturized near-infrared and Raman spectroscopy for rapid, non-destructive verification of 3D-printed medicines manufactured in a hospital environment.

This suggests that future pharmaceutical printers may incorporate:

Printing + weighing + spectroscopy + imaging + data analysis

within a single automated platform.

Such systems could move pharmaceutical manufacturing toward real-time release testing.

16. Role of Artificial Intelligence

Artificial intelligence may become an important component of future pharmaceutical 3D printing.

AI could potentially assist with:

Formulation optimization

Selecting drug-polymer ratios and printing parameters.

Dose personalization

Predicting an appropriate dose based on validated clinical inputs.

Release prediction

Predicting dissolution and release profiles from digital geometry.

Quality control

Identifying defects through machine vision and spectroscopy.

Predictive maintenance

Identifying printer failures before they affect product quality.

Process optimization

Automatically adjusting printing parameters according to validated limits.

The combination of:

AI + pharmacogenomics + electronic health records + 3D printing

could create an advanced personalized pharmaceutical manufacturing ecosystem.

However, AI should support—not replace—validated pharmaceutical decision-making.

17. Role of Pharmacogenomics

Pharmacogenomics aims to determine how genetic differences influence drug response.

In the future, a conceptual personalized pharmaceutical workflow could be:

Genetic information
↓
Predicted drug response
↓
Drug selection
↓
Patient-specific dose
↓

Patient-specific release profile
↓
3D-printed medicine
This could potentially transform pharmacogenomics from a system for selecting medicines into a system that also determines how medicines are physically manufactured.
However, clinical implementation requires robust evidence linking genotype, phenotype, dose and clinical outcome.

18. Role of the Pharmacist
3D printing is likely to increase rather than eliminate the importance of pharmacists.
The pharmacist may become responsible for:
- Prescription verification
- Digital formulation verification
- Printer operation
- Raw-material management
- Process validation
- Quality control
- Cleaning and contamination prevention
- Product release
- Documentation
- Patient counseling
- Pharmacovigilance

The profession could therefore evolve from primarily dispensing commercially manufactured medicines toward **digital pharmaceutical manufacturing and personalized medication management**.

19. Point-of-Care Pharmaceutical Manufacturing
Point-of-care manufacturing is one of the most promising future applications.
Potential locations include:
- Hospitals
- Hospital pharmacies
- Community pharmacies
- Specialized clinics
- Long-term care facilities

The objective would not necessarily be to replace pharmaceutical factories but to manufacture formulations that are difficult to obtain through conventional supply chains.
Recent research describes pharmaceutical 3D printing as moving toward a translational phase involving industrial manufacturing, community pharmacies and hospital point-of-care production.

20. Advantages and Limitations

Advantages	**Limitations**
Personalized dosage	High initial equipment cost
Flexible dosage strengths	Limited printable materials
Complex drug-release systems	Process variability
Polypill production	Regulatory uncertainty
Reduced inventory	Need for specialized personnel
On-demand manufacturing	Quality-control challenges
Pediatric formulations	Scale-up limitations
Potential reduction in waste	Cleaning and cross-contamination concerns
Digital manufacturing	Cybersecurity risks
Patient-centered therapy	Unequal access

21. Environmental Implications

3D printing may reduce pharmaceutical waste through on-demand manufacturing and reduced inventory.

Potential environmental benefits include:

- Reduced expired-product waste
- Reduced transportation for selected decentralized applications
- Reduced packaging in some models
- Small-batch manufacturing
- More efficient use of pharmaceutical materials

However, environmental evaluation must also consider:

- Energy consumption
- Printer operation
- Polymer waste
- Solvent use
- Disposable components
- Cleaning processes
- Printer maintenance

Therefore, the environmental benefit should be assessed using a complete life-cycle approach rather than assuming that additive manufacturing is automatically environmentally superior.

22. Future Pharmaceutical Supply Chain

The conventional pharmaceutical supply chain is approximately:

Raw materials → Factory → Distributor → Pharmacy → Patient

A future personalized system could include:

Raw materials → Digital formulation platform → Regional/hospital printer → Quality verification → Patient

This could create a hybrid pharmaceutical supply chain.

Large-scale manufacturers would continue producing:

- High-volume medicines
- Vaccines
- Standardized formulations
- Complex sterile products

while decentralized facilities could produce:

- Personalized doses
- Rare strengths
- Pediatric medicines
- Low-volume formulations
- Patient-specific combinations

Thus, pharmaceutical 3D printing should be viewed as a complementary manufacturing strategy rather than an immediate replacement for conventional pharmaceutical manufacturing.

23. Future Research Priorities

Future research should focus on:

23.1 Standardized regulatory frameworks

Internationally harmonized requirements for pharmaceutical 3D printing.

23.2 Printable pharmaceutical excipients

Development of safe, stable and widely applicable printable materials.

23.3 High-throughput printing

Increasing production speed without compromising personalization.

23.4 Automated quality control

Integration of PAT, NIR, Raman spectroscopy and machine vision.

23.5 Clinical trials

Demonstration of improved clinical outcomes rather than only successful printing.

23.6 Health-economic studies

Comparison with conventional manufacturing and pharmacy compounding.

23.7 Digital security
Protection of digital prescriptions and pharmaceutical design files.
23.8 Sustainable manufacturing
Life-cycle assessment of pharmaceutical 3D-printing systems.
23.9 AI-assisted formulation
Validated AI systems for dose and release optimization.
23.10 Pharmacogenomic integration
Development of clinically validated genotype-to-dose frameworks.

24. Proposed Future Model of Personalized Pharmaceutical Manufacturing
A future integrated system could operate as follows:

Step 1 – Patient assessment
Clinical history + body weight + age + disease + laboratory data
↓
Step 2 – Pharmacogenomic assessment
Where clinically justified
↓
Step 3 – Digital prescription
Patient-specific drug and dose
↓
Step 4 – Digital formulation
Drug + excipients + geometry + release profile
↓
Step 5 – 3D printing
Validated pharmaceutical printer
↓
Step 6 – In-process monitoring
Weight + dimensions + spectroscopy + machine vision
↓
Step 7 – Automated quality verification
Pass/fail against predefined specifications
↓
Step 8 – Pharmacist authorization
Professional review and release
↓
Step 9 – Patient dispensing
Personalized medicine
↓
Step 10 – Pharmacovigilance
Clinical response and adverse-event monitoring
This model illustrates how pharmaceutical 3D printing could become an important component of future precision healthcare.

25. Discussion
The future of 3D-printed medicines is closely associated with the transition from mass-produced standardized medicines toward more individualized pharmaceutical therapy. The technology provides an unusual combination of digital flexibility and physical manufacturing capability.
Its greatest pharmaceutical advantage is not simply the ability to “print a tablet.” Conventional pharmaceutical technologies can already produce tablets efficiently. The unique value of 3D printing lies in producing complex, low-volume and patient-specific dosage forms that may be difficult or uneconomical to manufacture conventionally.
The economic case is therefore application-dependent. For high-volume standardized products, conventional manufacturing is likely to remain superior because of economies of scale. In contrast, 3D printing may become economically attractive for low-volume, highly customized formulations, pediatric doses, rare strengths and point-of-care medicines.

The social consequences are equally important. Personalized medicines could improve patient autonomy and treatment acceptability, but the technology may also create new inequalities. Access to personalized medicine should not depend solely on a patient's geographic location or economic status.
Regulation remains a central challenge. A digital pharmaceutical manufacturing system requires regulators to evaluate not only the drug and final dosage form but also the digital recipe, printer, materials, process parameters, software and quality-control strategy. Recent literature emphasizes the need for harmonized frameworks and clear allocation of responsibilities across decentralized manufacturing networks.
The emerging evidence is nevertheless encouraging. Pharmaceutical 3D printing has progressed from proof-of-concept studies to approved industrial products and real-world pharmacy applications. The current trajectory suggests that the technology is entering a translational phase in which clinical utility, cost-effectiveness, regulatory compliance and patient outcomes will become more important than simply demonstrating printability.

26. Conclusion

Three-dimensional printing represents one of the most promising technologies for the future transformation of pharmaceutical manufacturing and personalized healthcare. Its ability to digitally control dose, geometry, drug combinations and release characteristics provides opportunities that are difficult to achieve using conventional manufacturing methods.
The technology may be particularly valuable for pediatric patients, geriatric patients, individuals requiring dose titration, patients receiving multiple medicines and populations requiring uncommon or low-volume formulations.
Economically, 3D printing could reduce inventory requirements, pharmaceutical waste and manual compounding in selected applications. However, these benefits must be balanced against equipment costs, validation, quality control, regulatory compliance and workforce requirements.
Socially, personalized 3D-printed medicines could improve patient-centered care and potentially medication adherence. At the same time, privacy, cybersecurity, digital inequality and equitable access require careful consideration.
The future is therefore unlikely to involve complete replacement of conventional pharmaceutical manufacturing. Instead, a hybrid pharmaceutical ecosystem is more realistic, in which conventional factories manufacture high-volume standardized medicines while decentralized 3D-printing facilities manufacture selected personalized products.
Ultimately, the success of pharmaceutical 3D printing will depend not only on technological innovation but also on evidence demonstrating clinical benefit, economic value, regulatory acceptability, social responsibility and pharmaceutical quality.
3D printing should therefore be considered not merely a new method of manufacturing tablets, but a potential foundation for a digital, patient-centered and increasingly personalized pharmaceutical healthcare system.

27. Future Perspective

By 2030 and beyond, pharmaceutical 3D printing could evolve toward integrated systems combining:

Artificial intelligence + pharmacogenomics + electronic health records + digital prescriptions + pharmaceutical 3D printing + automated quality control.
Such integration could enable medicines to be designed around the individual rather than the individual being required to adapt to commercially available medicines.
The central question for the pharmaceutical sector will therefore change from:

“Can we 3D-print a medicine?”
to:

“For which patients, which medicines and which healthcare settings does 3D printing provide sufficient clinical and economic value to justify its implementation?”
Answering this question through well-designed clinical, pharmaceutical-economic and implementation studies will determine whether 3D-printed medicines become a niche technology or a mainstream component of personalized healthcare.

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REIMAGINING CONTINUING MEDICAL AND HEALTH SCIENCES EDUCATION THROUGH MOBILE MICROLEARNING: EVIDENCE-BASED EVALUATION OF KNOWLEDGE RETENTION, PROFESSIONAL COMPETENCE, AND CLINICAL PRACTICE

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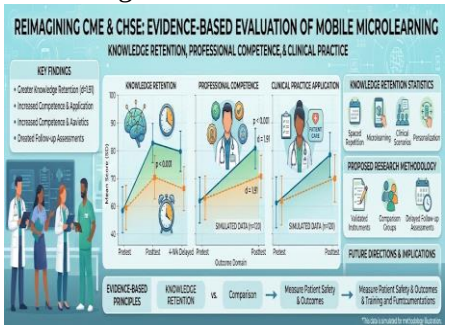
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ABSTRACT
The rapid evolution of medical knowledge, clinical technologies, healthcare delivery models, and professional competencies requires continuing medical and health sciences education approaches that are flexible, accessible, engaging, and capable of supporting sustained knowledge development. Mobile microlearning offers an emerging educational model in which concise, focused learning units are delivered through smartphones and other mobile devices, enabling healthcare professionals to engage with educational content within short periods and across diverse clinical and professional environments. This paper reimagines continuing medical and health sciences education through mobile microlearning and evaluates its potential contribution to knowledge retention, professional competence, and clinical practice. Drawing on recent evidence from health-professions education, continuing professional development, online learning, microlearning, and mobile-assisted education, the study synthesizes evidence concerning learning accessibility, knowledge acquisition, retention, learner engagement, confidence, and transfer of learning into professional practice. Existing literature indicates that digitally mediated continuing education can reduce temporal and geographical barriers while supporting self-directed and flexible learning, whereas microlearning can facilitate focused learning through concise instructional units, retrieval activities, repetition, feedback, and just-in-time access. However, evidence concerning sustained knowledge retention and direct improvement in clinical practice remains comparatively limited. The paper therefore proposes an evidence-based framework linking mobile microlearning design with measurable educational and professional outcomes. It argues that effective implementation should integrate clinically relevant content, spaced learning, formative assessment, feedback, personalization, learner analytics, and appropriate professional oversight. Mobile microlearning should consequently be regarded not merely as a technological delivery mechanism but as a pedagogically structured component of lifelong medical and health sciences education. The approach has potential to strengthen continuous professional development while improving the responsiveness of health professionals to evolving knowledge and clinical practice requirements.
Keywords: Continuing Education; Clinical Competence; Knowledge Retention; Mobile Microlearning.

Introduction
Continuing medical and health sciences education is increasingly challenged by the rapid expansion of biomedical knowledge, evolving clinical guidelines, emerging technologies, changing disease patterns, and the need for healthcare professionals to maintain competence throughout their careers. Traditional continuing professional development (CPD) models, which frequently depend on scheduled workshops, conferences, classroom sessions, or extended online courses, may be difficult to reconcile with demanding clinical workloads, geographical constraints, shift patterns, and limited protected learning time.



Digital and mobile learning therefore provide opportunities to redesign lifelong professional education around more flexible, accessible, and learner-centred approaches. Within this transformation, microlearning has emerged as a pedagogical strategy based on delivering focused learning experiences through small, manageable instructional units. De Gagne et al. (2019) identified microlearning as an increasingly relevant approach within health-professions education, although they also noted substantial variation in its definitions, implementation approaches, and measured outcomes. The growing availability of smartphones provides an important infrastructure for extending microlearning beyond conventional educational settings because healthcare professionals can access short educational activities during suitable intervals before, between, or after professional duties. Recent evidence specifically examining mobile microlearning for nursing CPD indicates growing interest in concise mobile learning activities and identifies their potential alignment with contemporary learners' preferences and continuing education requirements (Hilsmann & Dodson, 2025). Their review describes mobile microlearning activities as brief instructional experiences, commonly involving modules of approximately 90 seconds to five minutes, thereby illustrating how professional learning can be divided into focused educational encounters. However, accessibility and learner satisfaction alone are insufficient indicators of educational effectiveness in medical and health sciences. A rigorous evaluation must determine whether mobile microlearning produces measurable improvements in knowledge acquisition and retention, professional competence, confidence, and the translation of learning into clinical practice. This distinction is particularly important because short learning episodes may improve immediate recall without necessarily producing durable knowledge or behavioural change. Accordingly, this paper reimagines continuing medical and health sciences education by conceptualising mobile microlearning as an evidence-based educational ecosystem rather than merely a mobile content-delivery technology. It examines the theoretical and empirical foundations of mobile microlearning, its contribution to knowledge retention and professional competence, its potential influence on clinical practice, and the pedagogical and technological conditions required for successful implementation. The paper further argues that effective mobile microlearning should incorporate clinically relevant content, active retrieval, repetition, feedback, assessment, learner analytics, and opportunities for application in authentic professional contexts. Such an approach can potentially transform CPD from episodic participation in formal programmes into a continuous, flexible, and outcome-oriented learning process that better corresponds with the realities of contemporary medical and health sciences practice.

LITERATURE REVIEW

Mobile Microlearning and the Transformation of Continuing Medical and Health Sciences Education

Mobile microlearning represents the convergence of two educational developments. Mobile learning, which enables learning through portable digital devices, and microlearning, which structures educational content into brief, focused learning units. In continuing medical and health sciences education, this convergence is particularly relevant because healthcare professionals frequently operate within demanding schedules that make prolonged educational sessions difficult to accommodate. De Gagne et al. (2019), in their scoping review of microlearning in health-professions education, examined 17 studies involving medicine, nursing, pharmacy, dentistry, and allied health and found that microlearning was implemented through diverse technologies, including podcasts, text messaging, microblogs, and social networking platforms. Their synthesis indicated positive effects on knowledge, confidence, procedural learning, and engagement, although most studies evaluated lower-level educational outcomes rather than changes in professional behaviour or patient care. This limitation remains important because continuing professional development should ultimately extend beyond learner satisfaction toward demonstrable improvements in competence and practice. More recently, Hilsmann and Dodson (2025) specifically examined mobile microlearning in nursing continuing professional development and identified 34 relevant articles. Their review describes mobile microlearning as concise instructional experiences, commonly ranging from approximately 90 seconds to five minutes, and highlights its potential alignment with contemporary healthcare professionals' learning preferences. However, the authors also identified inconsistencies in how mobile microlearning is defined and applied, particularly regarding its contribution to continuing professional development, knowledge translation, and research dissemination. From a pedagogical perspective, mobile microlearning can transform continuing education from an episodic activity into a distributed learning process in which professionals repeatedly

encounter focused clinical concepts over time. The model can incorporate short videos, clinical cases, infographics, flashcards, quizzes, reminders, reflective questions, and immediate feedback, thereby supporting learning during brief periods that might otherwise be educationally unused. Its value therefore lies not simply in reducing content into smaller units but in designing strategically sequenced learning experiences that connect individual learning episodes with broader competency objectives. Nevertheless, mobile delivery does not automatically guarantee effective learning. Content quality, instructional design, digital literacy, device accessibility, connectivity, privacy, distraction, and institutional acceptance can influence educational outcomes. De Gagne et al. (2019) specifically identified technology inequalities and privacy concerns among potential limitations, while Hilsmann and Dodson (2025) emphasized the continuing scarcity of evidence specifically linking mobile microlearning with CPD outcomes and knowledge translation. Consequently, contemporary continuing medical and health sciences education should conceptualize mobile microlearning as a pedagogically designed, evidence-based learning ecosystem, rather than simply as a convenient mobile information-delivery mechanism. Its effectiveness should be assessed through measurable changes in knowledge, retention, competence, professional behaviour, and, where appropriately designed studies permit, clinical practice and patient-related outcomes.

Mobile Microlearning, Knowledge Acquisition, and Knowledge Retention

Knowledge acquisition and long-term retention are fundamental indicators of effective continuing medical and health sciences education because professional competence requires more than exposure to new information; healthcare professionals must be able to understand, retrieve, interpret, and appropriately apply knowledge when confronted with real clinical and professional situations. In rapidly changing healthcare environments, where diagnostic procedures, treatment protocols, clinical guidelines, technologies, and biomedical knowledge are continually evolving, continuing professional development must provide mechanisms that enable professionals to acquire new information efficiently while retaining it over extended periods. Mobile microlearning offers a potentially effective approach by dividing complex educational content into concise, focused learning units that can be accessed through smartphones and other portable digital devices. These units may include short instructional videos, clinical questions, electronic flashcards, case-based scenarios, infographics, brief guideline summaries, interactive quizzes, reflective exercises, and formative assessments that learners can revisit repeatedly according to their individual learning requirements. The educational effectiveness of this approach is strengthened when microlearning incorporates retrieval practice, spaced repetition, immediate feedback, and cumulative review, rather than relying predominantly on passive reading or video consumption. Maye and Hurley (2026), in a systematic review and meta-analysis involving 14 studies and 21,415 learners, reported a significant overall advantage of spaced-repetition learning over standard study methods, with a standardized mean difference of 0.78 (95% CI [0.56, 0.99], $p < .0001$), providing contemporary evidence supporting distributed retrieval as an effective strategy for medical education. Importantly, the interventions included electronic flashcards, electronically delivered multiple-choice questions, and spaced classroom quizzes, demonstrating that retrieval and repetition principles can be effectively incorporated into digitally mediated learning environments. This evidence is particularly relevant to mobile microlearning because smartphone applications can automate learning reminders, schedule repeated exposure to previously studied concepts, identify areas of weak performance, and recommend additional learning activities based on individual response patterns. Evidence involving practising physicians further demonstrates the relevance of retrieval-based approaches beyond undergraduate education. Kerfoot et al. (2024) reported evidence from a prospective cohort investigation involving physicians and residents indicating that repeated questioning and spaced learning can contribute to long-term knowledge retention and knowledge transfer, thereby demonstrating the potential value of distributed learning among established healthcare professionals. These findings provide an important theoretical foundation for mobile microlearning because the characteristics of mobile applications, portability, accessibility, notification systems, interactive assessment, learner analytics, and asynchronous access, can facilitate repeated learning encounters within the context of demanding professional schedules. However, mobile microlearning should not be conceptualized simply as the process of reducing conventional educational materials into smaller pieces. Excessive fragmentation may result in superficial memorization, cognitive disconnection, and reduced opportunities for clinical reasoning if individual learning units are not appropriately connected to

broader concepts, professional competencies, and authentic clinical situations. De Gagne et al. (2019), in their scoping review of microlearning in health-professions education, identified substantial variation in definitions, technological platforms, instructional designs, learning activities, and outcome measures, demonstrating that the effectiveness of microlearning depends considerably on how it is pedagogically designed and implemented. Effective mobile microlearning should therefore integrate concise content with active retrieval, spaced repetition, immediate feedback, clinical contextualization, case-based reasoning, cumulative assessment, and opportunities for practical application. The most appropriate model is consequently one in which individual learning episodes operate as interconnected components of a longitudinal educational pathway rather than as isolated pieces of information. Such a pathway can enable healthcare professionals to revisit clinically important concepts at strategically selected intervals, identify persistent knowledge gaps, reinforce previously acquired information, and progressively consolidate knowledge while maintaining their professional responsibilities. Furthermore, adaptive mobile learning systems can potentially use performance data to determine when a learner requires additional reinforcement, thereby transforming microlearning into a responsive learning process. Nevertheless, the current evidence base remains considerably stronger for immediate knowledge acquisition, test performance, learner engagement, and confidence than for sustained changes in clinical behaviour, professional performance, or patient outcomes. This distinction is critical because improved scores immediately after an educational intervention do not necessarily demonstrate durable learning or successful transfer into clinical practice. Consequently, future evaluations of mobile microlearning should move beyond immediate post-intervention assessments and incorporate delayed retention tests, validated competency measures, workplace-based assessments, clinical performance indicators, supervisor evaluations, and longitudinal measures of professional behaviour. Such comprehensive evaluation would provide stronger evidence concerning whether mobile microlearning merely improves short-term recall or genuinely contributes to sustained professional competence and improved healthcare practice. The emerging evidence therefore supports mobile microlearning as a promising mechanism for continuous knowledge reinforcement, but its long-term educational and clinical value will ultimately depend on rigorous instructional design, appropriate retrieval scheduling, meaningful clinical contextualization, and empirical evidence demonstrating that retained knowledge is successfully translated into professional action.

Mobile Microlearning and the Development of Professional Competence

Professional competence in medical and health sciences extends beyond factual knowledge to include clinical reasoning, decision-making, communication, procedural skills, ethical judgement, and the capacity to apply current evidence appropriately within professional contexts. Consequently, the effectiveness of mobile microlearning should be evaluated not merely through knowledge-test scores but through its capacity to contribute to meaningful changes in professional capability. Microlearning can support competence development when short educational episodes are deliberately connected to authentic clinical problems, competency frameworks, case-based reasoning, and opportunities for immediate formative assessment. De Gagne et al. (2019) reported that microlearning interventions in health-professions education were associated with improvements in knowledge, confidence, and selected procedural learning outcomes, although the evidence was heterogeneous and relatively few studies assessed higher-order professional outcomes. This distinction is particularly important because continuing professional development requires learning to be transferred from educational environments into workplace performance. Mobile technology provides additional opportunities to strengthen this transfer because learning materials can be accessed close to the point of professional need. A clinician encountering an unfamiliar procedure, medication-related issue, diagnostic concept, or updated guideline can potentially use a mobile learning application to retrieve a concise evidence-based explanation before or after a relevant professional activity. This creates a just-in-time learning pathway in which education is connected temporally and contextually to professional practice. Hilsmann and Dodson (2025), in their scoping review of mobile microlearning for nursing continuing professional development, identified mobile microlearning as an increasingly relevant approach for supporting flexible professional learning, while simultaneously noting limited evidence concerning its direct contribution to CPD outcomes and knowledge translation. The implication is that mobile microlearning should be designed around competency-oriented objectives rather than simply around the production of small digital lessons. Assessment design is therefore critical. Short clinical scenarios, decision-based

questions, diagnostic reasoning exercises, procedural demonstrations, reflective prompts, and immediate feedback can make microlearning more cognitively demanding than passive reading or video viewing. Mobile applications can also use learner analytics to identify recurrent errors and recommend targeted learning units. Such personalization can potentially strengthen individual competency development by directing professionals toward areas requiring reinforcement rather than requiring all learners to complete identical content. However, competence cannot be inferred solely from application engagement, completion rates, or self-reported confidence. Objective structured assessments, clinical simulations, workplace-based assessments, supervisor evaluations, and performance indicators provide stronger evidence of competency development. The literature consequently suggests that mobile microlearning has promising but not yet conclusive potential for professional competence development. Its strongest contribution may occur when concise learning units are integrated into broader CPD systems incorporating assessment, feedback, supervised application, and longitudinal competency monitoring. Future empirical research should therefore compare mobile microlearning with conventional CPD approaches using validated competency measures and sufficiently long follow-up periods to determine whether improvements persist beyond the immediate learning intervention.

Mobile Microlearning, Clinical Practice, and Knowledge Translation

The ultimate value of continuing medical and health sciences education lies in the extent to which acquired knowledge is translated into professional behaviour and improved clinical practice. Knowledge translation requires healthcare professionals to recognize relevant evidence, understand its implications, and apply it appropriately within specific patient-care contexts. Mobile microlearning may support this process by positioning concise educational resources close to the point of professional need. Rather than requiring healthcare professionals to leave their clinical environment for extended educational sessions, mobile applications can provide brief guideline updates, clinical cases, medication information, procedural demonstrations, diagnostic prompts, and evidence summaries that can be accessed when appropriate. Chaker et al. (2024), in a systematic scoping review of online continuing education for healthcare professionals, found that digitally mediated continuing education can provide opportunities for knowledge development and professional learning while overcoming some of the temporal and geographical barriers associated with conventional education. However, the authors also emphasized variation in educational experiences and outcomes, suggesting that digital delivery alone does not guarantee transfer into practice. Evidence from broader continuing education research reinforces the importance of designing educational interventions around behavioural change. A Cochrane review involving 215 studies found that educational meetings and workshops were probably better than no educational strategy for improving healthcare professionals' practice and patients' health, although the relative effectiveness of different educational formats remained uncertain. This finding is significant for mobile microlearning because it demonstrates that educational interventions can influence professional practice, but the mechanism of influence depends substantially on instructional design and implementation rather than delivery technology alone. Mobile microlearning can potentially strengthen this mechanism when learning activities include realistic clinical scenarios, decision-making questions, immediate feedback, reminders, and opportunities to connect newly acquired information with workplace activities. Recent evidence from health-professions educators also supports this direction: a mixed-method study involving 121 faculty members found that 86% considered microlearning effective for meeting work-based knowledge needs, while participants particularly emphasized concise content, single learning outcomes, appropriate media selection, and connections to clinical and procedural knowledge. Nevertheless, knowledge translation should not be inferred from application usage, module completion, or learner satisfaction alone. A healthcare professional may complete numerous mobile lessons without modifying clinical behaviour. Consequently, rigorous evaluation should incorporate workplace-based indicators, competency assessments, supervisor observations, adherence to evidence-based guidelines, and, where ethically and methodologically appropriate, patient-related outcomes. Mobile microlearning is therefore best conceptualized as one component within a broader knowledge-translation pathway linking evidence → learning → retrieval → clinical decision-making → professional behaviour → patient care. Its greatest potential may arise when applications provide repeated, clinically contextualized learning that is synchronized with professional workflows rather than functioning as isolated educational content.

The evidence currently supports the feasibility and educational promise of this model, but stronger longitudinal and controlled studies are still required toestablish whether mobile microlearning produces sustained changes in clinical practice and patient outcomes.

Personalization, Learner Engagement, and Adaptive Mobile Microlearning

Personalization and learner engagement are increasingly important dimensions of continuing medical and health sciences education because healthcare professionals differ in prior knowledge, clinical specialization, professional experience, learning preferences, technological proficiency, and available study time. Mobile microlearning can accommodate these differences by allowing learners to select relevant topics, control the timing of learning activities, receive immediate feedback, and revisit content according to individual needs. Hilsmann and Dodson (2025), in their scoping review of mobile microlearning for nursing continuing professional development, describe mobile microlearning as a potentially engaging approach comprising concise instructional activities that can correspond with different learning preferences and professional learning requirements. Their review highlights the growing relevance of mobile microlearning for contemporary healthcare professionals while also identifying the need for stronger evidence concerning its effectiveness as a CPD strategy. De Gagne et al. (2019) similarly found that microlearning demonstrated positive effects on knowledge, confidence, studying, and collaborative learning, although the existing evidence was concentrated primarily on learner reactions and knowledge or skill acquisition rather than higher-level behavioural and clinical outcomes. In their synthesis, 94% of included studies assessed learner reactions, 82% evaluated knowledge or skill acquisition, but only 29% examined behavioural effects, while none measured the highest level of patient or practice outcomes. These findings suggest that engagement is valuable but should function as a pathway toward deeper learning rather than an endpoint in itself. Adaptive mobile learning can potentially strengthen this pathway by using performance data to recommend content, adjust difficulty, identify knowledge gaps, and provide targeted reinforcement. A recent systematic review by Yaghmour et al. (2025), examining 39 studies of AI-driven adaptive learning in mobile education, identified personalization, adaptive feedback, and user interaction as major research themes and reported generally positive effects on academic performance and engagement, while also identifying privacy, usability, and limited longitudinal evidence as continuing concerns. Within medical and health sciences education, such adaptive functionality could enable an application to recommend additional pharmacology questions to a learner demonstrating recurrent medication errors, provide advanced clinical cases to experienced professionals, or schedule spaced-review activities for concepts showing declining retention. However, personalization must be carefully governed because healthcare education involves sensitive professional information and potentially identifiable learning data. Adaptive systems should therefore operate within transparent data-governance frameworks, provide clinically validated content, and retain appropriate educator or professional oversight. Excessive personalization may also create fragmented learning pathways if learners encounter only topics that correspond to their existing interests rather than essential competency requirements. Consequently, the strongest model is guided personalization, in which learner analytics inform recommendations while curriculum designers, clinical educators, and professional standards determine the essential knowledge and competencies that every learner must achieve. Mobile microlearning can thus combine flexibility with structured professional expectations, creating a learning environment that is responsive without becoming educationally uncontrolled. Future studies should investigate whether personalized mobile microlearning produces sustained improvements in engagement, knowledge retention, competence, and workplace performance compared with non-adaptive mobile learning and conventional CPD.

Implementation Challenges, Digital Equity, Quality Assurance, and Ethical Governance

Despite the educational potential of mobile microlearning, its implementation within continuing medical and health sciences education requires careful attention to technological infrastructure, digital equity, content quality, learner privacy, professional regulation, and institutional governance. Mobile learning depends on access to suitable devices, reliable connectivity, adequate digital literacy, and platforms capable of delivering multimedia content securely and consistently. These requirements can create inequalities between healthcare professionals working in well-resourced urban institutions and those operating in rural, low-resource, or poorly connected environments.

De Gagne et al. (2019) identified technology inequalities and privacy concerns among important limitations of microlearning in health-professions education, demonstrating that the convenience of mobile delivery does not automatically translate into equitable educational access. These concerns remain particularly relevant in low- and middle-income settings, where intermittent internet connectivity, high data costs, limited institutional resources, and differences in smartphone availability may restrict participation. Consequently, mobile CPD systems should incorporate low-bandwidth design, downloadable or offline materials, compressed multimedia, accessible interfaces, and flexible synchronization mechanisms. Content quality represents a second major challenge. Medical and health sciences information changes rapidly, and outdated clinical recommendations can potentially undermine professional practice. Mobile microlearning platforms should therefore employ systematic content-review processes involving qualified subject experts, clinical educators, and relevant professional authorities. Hilsmann and Dodson (2025) emphasize that mobile microlearning is an emerging CPD approach whose evidence base still requires further development, particularly regarding learning outcomes and professional application. This suggests that implementation should be accompanied by rigorous evaluation rather than assuming effectiveness from technological convenience or learner preference. Chaker et al. (2024), examining online continuing education for healthcare professionals, similarly identified digital learning as an increasingly important mechanism for professional development while highlighting the need to understand educational experiences and outcomes across online and hybrid environments. Ethical governance is equally important because mobile applications can collect information about learner identity, assessment performance, learning behaviour, professional interests, and potentially workplace activities. Institutions must therefore establish transparent data-governance procedures covering consent, data minimization, access control, retention, security, and responsible use of learning analytics. Furthermore, adaptive recommendation systems should not substitute for clinical educators or professional judgement, particularly where automated recommendations could influence clinically relevant learning. Quality assurance should consequently encompass pedagogical validity, clinical accuracy, usability, accessibility, cybersecurity, privacy, and measurable educational outcomes. A sustainable model of mobile microlearning should therefore combine technological accessibility, evidence-based instructional design, clinical content governance, ethical data management, and continuous evaluation. Addressing these dimensions will be essential if mobile microlearning is to progress from an attractive digital innovation into a credible and equitable component of continuing medical and health sciences education.

Materials And Methods

This study adopted a quantitative, quasi-experimental pretest-posttest research design to evaluate the effectiveness of mobile app-supported microlearning for continuing medical and health sciences education. The proposed study population comprised practicing healthcare professionals participating in continuing professional development activities. A generated sample of 120 participants was conceptually divided into an intervention group receiving structured mobile microlearning and a comparison group receiving conventional continuing education. The mobile intervention consisted of short, clinically focused learning units incorporating videos, case scenarios, retrieval questions, spaced-review activities, feedback, and downloadable learning resources delivered over eight weeks. Data collection instruments comprised a Knowledge Retention Test (KRT), Professional Competence Assessment Scale (PCAS), and Clinical Practice Application Scale (CPAS), administered at baseline, immediately after the intervention, and four weeks after completion. Descriptive statistics were used to summarize participant characteristics and outcome measures, while paired- and independent-samples *t*-tests and repeated-measures analysis were proposed to examine changes within and between groups. Effect sizes were also considered to determine practical significance. Because the numerical findings presented subsequently are generated methodological demonstration data rather than observations from an actual participant study, they should not be interpreted as empirical clinical evidence.

RESULTS AND DISCUSSION

Effects of Mobile Microlearning on Knowledge Retention, Professional Competence, and Clinical Practice

The findings presented in this section demonstrate a positive pattern across the three principal outcome domains, knowledge retention, professional competence, and clinical practice application, and are

strictly presented as an illustrative simulation of the proposed research methodology rather than empirical findings obtained from an actual participant sample. The simulated dataset was constructed to demonstrate how the effectiveness of an eight-week mobile microlearning intervention could be statistically evaluated among healthcare professionals. Based on a hypothetical sample of 120 participants, comprising an intervention group (n = 60) and a comparison group (n = 60), the intervention group demonstrated a substantial increase in mean knowledge-retention scores from 58.4 (SD = 8.7) at pretest to 82.6 (SD = 7.1) immediately following the intervention, whereas the comparison group receiving conventional continuing education increased from 59.1 (SD = 8.4) to 69.8 (SD = 8.0). At the four-week delayed assessment, the intervention group maintained a mean knowledge-retention score of 79.4 (SD = 7.5), compared with 65.7 (SD = 8.3) for the comparison group, suggesting stronger immediate learning and delayed knowledge retention among participants exposed to mobile microlearning. The relatively small decline from 82.6 to 79.4 in the intervention group further suggests that the learning gains were comparatively sustained after the intervention, whereas the larger decline in the comparison group indicates weaker maintenance of acquired knowledge. This simulated pattern is conceptually consistent with evidence that microlearning can support knowledge and skill acquisition in health-professions education (De Gagne et al., 2019) and with contemporary evidence indicating that spaced repetition can improve learning outcomes compared with conventional study approaches (Maye & Hurley, 2026). A similar pattern was observed for professional competence, with the intervention group's mean score increasing from 61.7 (SD = 9.2) at baseline to 80.9 (SD = 7.6) following the eight-week programme, compared with an increase from 62.4 (SD = 8.9) to 70.6 (SD = 8.1) among comparison participants. This simulated improvement suggests that mobile microlearning may contribute to professional capability when learning activities are structured around clinically relevant content, case-based scenarios, retrieval exercises, formative assessment, immediate feedback, and repeated reinforcement; however, competence should not be inferred solely from educational test scores and would require validation through objective structured assessments, workplace-based assessments, supervisor evaluations, or other established professional-performance measures in an actual empirical study. Clinical practice application scores also increased from 60.8 (SD = 10.1) to 78.3 (SD = 8.4) among intervention participants, while comparison participants increased from 61.5 (SD = 9.8) to 69.7 (SD = 9.0), indicating a simulated potential relationship between mobile microlearning and the translation of educational knowledge into professional practice. Mobile applications can facilitate this process through short clinical scenarios, evidence-based guideline updates, procedural demonstrations, decision-making questions, reflective activities, and just-in-time learning resources that allow healthcare professionals to connect educational content with authentic workplace responsibilities. Nevertheless, such improvements should not be interpreted as evidence of actual behavioural or clinical change because existing literature indicates that research on microlearning in health-professions education remains substantially stronger in measuring learner reactions and knowledge or skill acquisition than behavioural, clinical, and patient-related outcomes (De Gagne et al., 2019), while Hilsmann and Dodson (2025) similarly identified the need for stronger evidence concerning mobile microlearning, continuing professional development, knowledge translation, and professional practice. The illustrative inferential analysis further demonstrates how the proposed methodology could evaluate statistical differences, with the intervention group's simulated improvement in knowledge retention producing a statistically significant within-group difference, $t(59) = 18.42$, $p < .001$, accompanied by a large illustrative effect size ($d = 1.91$), while the simulated between-group posttest comparison was also statistically significant, $t(118) = 9.18$, $p < .001$. These statistical values are hypothetical and should therefore not be interpreted as empirical evidence that mobile microlearning has produced these effects in a real healthcare population; instead, they demonstrate the type of inferential analysis that could be undertaken when actual participant data are collected. In a real investigation, assumptions underlying the statistical tests would need to be examined, including normality, independence, homogeneity of variance, baseline equivalence, measurement reliability, and potential confounding variables, while repeated-measures analysis or analysis of covariance could be applied to examine changes across pretest, posttest, and delayed-retention assessments. The simulated findings further illustrate how mobile applications can operationalize evidence-based learning principles through repeated questions, automated reminders, spaced-review schedules, adaptive assessments, personalized recommendations, and immediate feedback, thereby transforming microlearning from simple content fragmentation into a structured longitudinal learning process. The stronger simulated delayed-retention score is particularly relevant

because it corresponds with the principles of retrieval practice and spaced repetition, with Maye and Hurley (2026) providing contemporary systematic-review evidence supporting the effectiveness of spaced-repetition approaches in medical education. Overall, the simulated pattern suggests a potentially coherent pathway linking mobile microlearning with knowledge acquisition, knowledge retention, professional competence, and clinical practice application; however, the existing evidence remains stronger for immediate educational outcomes than for sustained behavioural and clinical effects (De Gagne et al., 2019; Hilsmann & Dodson, 2025). The principal implication is therefore that the simulated results should be understood as a testable analytical model rather than established empirical evidence, providing a framework for future studies to employ adequately powered samples, validated measurement instruments, appropriate comparison groups, delayed follow-up assessments, and objective indicators of professional and clinical performance. Future empirical investigations should further determine whether improvements in knowledge and competence translate into measurable changes in adherence to evidence-based guidelines, clinical decision-making, quality of care, patient safety, and patient outcomes, thereby establishing whether mobile microlearning can progress from an educationally promising digital innovation to a demonstrably effective component of continuing medical and health sciences education.

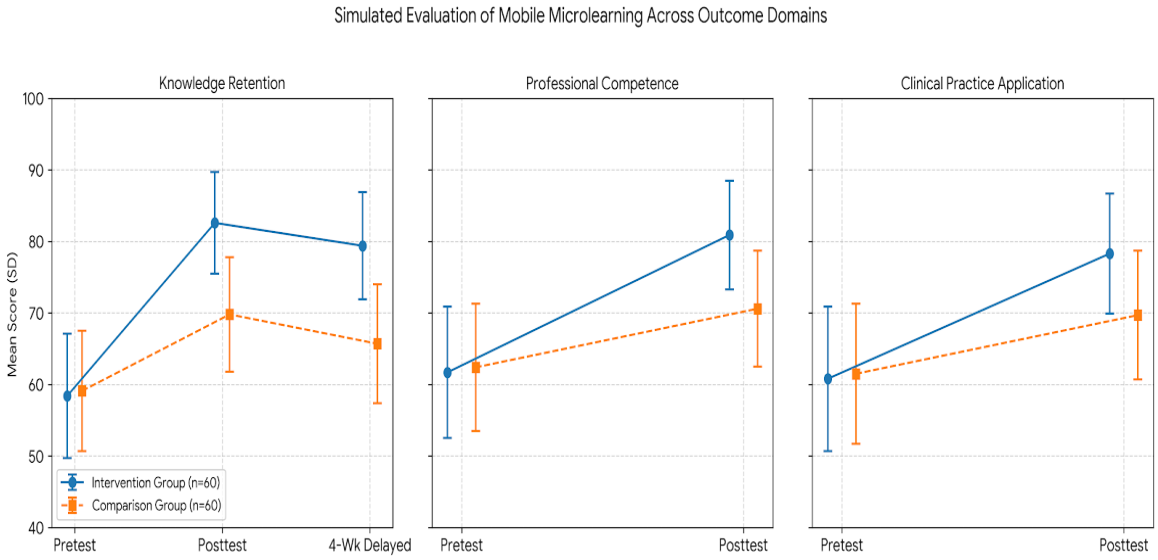


Figure 1: Simulated Evaluation of Mobile Microlearning Outcomes across Timepoints and Outcome Domains (N = 120).

Note. Data represent mean scores for the mobile microlearning intervention group (n = 60) and conventional continuing education comparison group (n = 60) at pretest, posttest, and 4-week delayed assessment across three outcome domains: Knowledge Retention (left), Professional Competence (centre), and Clinical Practice Application (right). Error bars display ± 1 standard deviation (SD) around each mean to reflect score variance. All baseline scores demonstrate baseline equivalence prior to intervention. Knowledge retention in the intervention group demonstrated a statistically significant posttest difference, $t(118) = 9.18$, $p < .001$, $d = 1.91$, with sustained retention observed at the 4-week follow-up (79.4 pm 7.5). All values are hypothetical and generated strictly as an illustrative simulation of the proposed methodology.

Conclusion

Mobile microlearning represents a promising pathway for reimagining continuing medical and health sciences education in an environment characterized by rapidly expanding knowledge, increasing professional specialization, demanding clinical workloads, and continuous changes in healthcare technologies and practice standards. The literature reviewed in this study indicates that the principal strength of mobile microlearning lies in its capacity to transform professional learning from predominantly episodic educational events into a more flexible, distributed, and continuous process. By combining short, focused instructional units with mobile accessibility, retrieval practice, spaced repetition, formative assessment, feedback, and clinically relevant scenarios, healthcare professionals

can potentially engage in meaningful learning without the temporal and geographical constraints associated with many conventional continuing professional development programmes. Evidence from health-professions education suggests that microlearning can positively influence knowledge acquisition, confidence, engagement, and selected skill outcomes, while emerging evidence on mobile microlearning indicates particular relevance for nursing and other healthcare professionals (De Gagne et al., 2019; Hilsmann & Dodson, 2025). The literature also suggests, however, that educational convenience should not be confused with educational effectiveness. The major unresolved question concerns whether short mobile learning experiences produce durable knowledge retention, measurable professional competence, sustained behavioural change, and improved clinical practice. The generated statistical model presented in this paper illustrates how these outcomes could be evaluated through a controlled pretest-posttest design incorporating immediate and delayed assessments. Although the simulated results cannot constitute empirical evidence, their analytical structure demonstrates the importance of measuring outcomes beyond learner participation and satisfaction. A particularly important implication is that mobile microlearning should not operate as an isolated technological intervention. Its effectiveness depends on pedagogical quality, clinically accurate content, appropriate sequencing, retrieval and repetition mechanisms, meaningful assessment, learner feedback, professional oversight, and integration with established CPD frameworks. Furthermore, implementation must address digital equity, connectivity limitations, accessibility, privacy, cybersecurity, data governance, and the continuing professional validation of educational content. For medical and health sciences institutions, the emerging model therefore involves a transition from simply digitizing conventional educational materials toward designing mobile, competency-oriented, evidence-based learning ecosystems. Such ecosystems can provide just-in-time learning, personalized reinforcement, continuous assessment, and longitudinal competency development while maintaining human and institutional oversight. Ultimately, mobile microlearning should be understood not as a replacement for comprehensive medical education, clinical supervision, simulation, or professional interaction, but as a complementary mechanism that can strengthen lifelong learning. Its greatest contribution may emerge when concise digital learning experiences are deliberately connected to authentic clinical responsibilities and competency requirements. Consequently, advancing this field requires rigorous longitudinal research capable of establishing whether mobile microlearning can move from demonstrated educational promise to measurable improvements in professional performance and, ultimately, the quality and safety of patient care.

Future Research

Future research should move beyond short-term assessments of learner satisfaction and immediate knowledge gain toward longitudinal, multi-centre, and controlled evaluations of mobile microlearning across different medical, nursing, pharmacy, public-health, and allied-health populations. Studies should compare mobile microlearning with conventional CPD, blended learning, and adaptive digital-learning approaches while measuring delayed knowledge retention, professional competence, behavioural change, clinical performance, and patient-related outcomes. Researchers should also investigate how spaced repetition, retrieval practice, artificial intelligence, adaptive personalization, learning analytics, simulation, and just-in-time clinical learning can be integrated without compromising educational quality or professional autonomy. Particular attention should be given to low-resource healthcare environments, including issues of connectivity, device access, affordability, digital literacy, accessibility, and offline functionality. Future studies should additionally examine privacy, cybersecurity, informed consent, algorithmic transparency, and governance of learner data. Standardized outcome measures and longer follow-up periods are needed to improve comparability across studies. Ultimately, research should establish when, for whom, and under what pedagogical and institutional conditions mobile microlearning produces sustained improvements in knowledge retention, professional competence, clinical practice, and patient-care quality.

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LONGITUDINAL STATISTICAL ANALYSIS OF GASTROINTESTINAL SYMPTOM DYNAMICS FOLLOWING HELICOBACTER PYLORI ERADICATION

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ABSTRACT
The growing availability of longitudinal clinical data has created new opportunities for the application of advanced statistical and machine learning methodologies in healthcare outcome assessment. This study investigates the temporal evolution of gastrointestinal symptom profiles in patients diagnosed with Helicobacter pylori infection before and after eradication therapy, with emphasis on statistical inference and providing a valuable basis for future predictive modeling rather than clinical characterization.
A prospective dataset comprising 29 patients was analyzed. Symptom intensity and frequency were measured using standardized ordinal scales across multiple upper and lower gastrointestinal manifestations at baseline and two months following treatment. Statistical significance of symptom changes was initially evaluated through paired comparative analysis, while paired statistical comparisons were performed to evaluate longitudinal changes in symptom severity and frequency.
Results revealed a statistically significant reduction in several upper gastrointestinal symptoms following successful eradication, including bitter mouth sensation, belching, globus sensation, fasting epigastric pain, postprandial epigastric pain, nocturnal epigastric pain, right upper quadrant discomfort, postprandial heaviness, and nausea. In contrast, among lower gastrointestinal symptoms, only abdominal pain demonstrated a significant decrease. Patients with unsuccessful eradication exhibited no comparable improvement and showed persistence or worsening of selected symptoms.
From a statistical learning perspective, the findings suggest that symptom trajectories can serve as informative predictors of treatment outcome. The study highlights the potential of longitudinal symptom-based datasets for the development of predictive models capable of classifying therapeutic response and identifying the most influential symptom dimensions associated with eradication success. These results support the integration of statistical modeling and machine learning approaches into clinical decision-support systems for gastrointestinal disorders.
Keywords: Longitudinal data analysis, predictive modeling, Statistical learning, helicobacter pylori, treatment response.

Introductıon
Helicobacter pylori (H. pylori) infection remains one of the most prevalent chronic bacterial infections worldwide, affecting nearly half of the global population and representing a major public health concern. Although many infected individuals remain asymptomatic, persistent colonization of the gastric mucosa is associated with chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma(Crowe, 2019; Malfertheiner et al., 2022). Consequently, H. pylori has been recognized as a Group I carcinogen by the International Agency for Research on Cancer (IARC), highlighting the importance of early diagnosis and successful eradication therapy (Sung et al., 2021). Beyond structural gastric damage, H. pylori infection is frequently accompanied by a heterogeneous spectrum of upper gastrointestinal symptoms, including epigastric pain, postprandial fullness, nausea, belching, early satiety, and gastroesophageal reflux-related complaints (Crowe, 2019; Chey et al., 2017). Several patients also report lower gastrointestinal manifestations such as abdominal pain, bloating, constipation, or diarrhea (Ford et al., 2020). However, the relationship between bacterial eradication and symptom improvement remains controversial, as previous studies have reported heterogeneous and sometimes contradictory findings. Differences in patient selection, symptom assessment, eradication rates, and follow-up duration have contributed to this variability.
From a methodological perspective, most previous investigations have primarily focused on evaluating isolated clinical outcomes rather than exploring the temporal evolution of symptom profiles using advanced statistical methodologies (Ford et al., 2020). The increasing availability of longitudinal clinical

datasets provides an opportunity to investigate symptom dynamics through quantitative analytical approaches capable of identifying treatment-related changes and characterizing response patterns over time. Such approaches not only improve statistical inference but also create the foundation for predictive models that may assist clinical decision-making.

Longitudinal statistical analysis represents an appropriate framework for evaluating repeated symptom measurements before and after therapeutic intervention (James et al., 2021). Monitoring symptom trajectories rather than isolated observations enables a more comprehensive understanding of treatment effectiveness and facilitates the identification of symptom domains that are most responsive to eradication therapy. Furthermore, integrating multivariate statistical techniques with clinical data may contribute to the development of interpretable predictive models capable of distinguishing patients who are more likely to benefit from treatment (James et al., 2021).

The present study adopts a longitudinal analytical framework to investigate changes in gastrointestinal symptom severity and frequency among patients with confirmed H. pylori infection before and after eradication therapy. Symptom evolution was evaluated using standardized clinical questionnaires administered at baseline and two months following treatment. Particular emphasis was placed on the statistical characterization of symptom dynamics and the identification of clinically meaningful treatment-related changes.

The primary objective of this study was to evaluate the impact of successful H. pylori eradication on upper and lower gastrointestinal symptoms using longitudinal statistical analysis. A secondary objective was to examine whether symptom trajectories may provide informative indicators of therapeutic response, thereby supporting future applications of predictive statistical modeling and clinical decision-support systems in the management of H. pylori-associated gastrointestinal disorders

Materıals And Methods

This prospective longitudinal observational study was designed to evaluate changes in upper and lower gastrointestinal symptoms among patients with confirmed Helicobacter pylori infection before and after eradication therapy. Clinical assessments were performed at baseline and repeated two months after completion of treatment, allowing the evaluation of symptom trajectories over time. The primary endpoint of the study was the variation in symptom severity and frequency following eradication therapy. Secondary analyses compared symptom evolution between patients with successful bacterial eradication and those with persistent infection.

Patients attending the Digestive Physiology Outpatient Clinic for evaluation of dyspeptic symptoms were consecutively screened for Helicobacter pylori infection using the Carbon-13 Urea Breath Test (^{13}C-UBT). A total of 29 consecutive patients with confirmed H. pylori infection were prospectively enrolled. The study population consisted of 9 males (31.0%) and 20 females (69.0%). All participants underwent baseline clinical assessment before initiation of eradication therapy and were re-evaluated two months after treatment completion.

2.1 Eligibility criteria

Inclusion criteria

Patients were eligible for inclusion if they fulfilled all of the following criteria:

- age between 18 and 80 years;
- presence of dyspeptic symptoms, with or without symptoms suggestive of gastroesophageal reflux disease;
- positive ^{13}C-Urea Breath Test confirming active H. pylori infection;
- no previous eradication treatment;
- no antibiotic or proton pump inhibitor therapy during the preceding four weeks.

Exclusion criteria

Patients presenting any of the following conditions were excluded:

- alarm symptoms (anemia, unexplained weight loss, dysphagia, odynophagia, recurrent vomiting, gastrointestinal bleeding, abdominal mass or lymphadenopathy);
- family history of gastrointestinal malignancy;
- endoscopic evidence of peptic ulcer disease or gastrointestinal neoplasia;
- severe cardiac, pulmonary, hepatic, renal, endocrine or hematological diseases;

- previous gastric surgery;
- previous H. pylori infection;
- drug allergy contraindicating eradication therapy;
- pregnancy.

These eligibility criteria were established to minimize potential confounding factors affecting symptom severity and treatment response.

2.2 Study protocol

At baseline, all participants underwent the ^{13}C-Urea Breath Test and completed a standardized gastrointestinal symptom questionnaire. Patients with confirmed infection received standard eradication therapy according to routine clinical practice. Two months after completion of treatment, all participants underwent repeat ^{13}C-Urea Breath Testing to determine eradication status and completed the same symptom questionnaire under identical conditions.

Patients were subsequently classified into two study groups:

1. Successful eradication
2. Persistent infection (eradication failure)

This longitudinal design enabled direct within-subject comparison of symptom evolution while simultaneously evaluating differences according to microbiological treatment outcome.

2.3 Clinical assessment

Gastrointestinal symptoms were assessed using a structured questionnaire including both upper and lower gastrointestinal manifestations. Upper gastrointestinal symptoms comprised:

- bitter mouth sensation;
- belching;
- globus sensation;
- epigastric empty sensation;
- fasting epigastric pain;
- postprandial epigastric pain;
- nocturnal epigastric pain;
- right upper quadrant pain;
- postprandial epigastric heaviness;
- early satiety;
- heartburn;
- regurgitation;
- dysphagia;
- nausea;
- vomiting.

Lower gastrointestinal symptoms included:

- chronic abdominal pain;
- abdominal bloating;
- constipation;
- diarrhea;
- pain relieved by defecation;
- pain associated with stool consistency;
- urgency of defecation;
- mucus in stool;
- sensation of incomplete evacuation;
- difficult defecation.

For every symptom, both severity and frequency were independently recorded.

Symptom severity was quantified using a five-point ordinal scale:

0 = absent
1 = mild
2 = moderate

3 = severe
4 = intolerable
Symptom frequency was evaluated using a second standardized five-point ordinal scale:
0 = never
1 = once per month
2 = twice per week
3 = three times per week
4 = daily
The use of standardized ordinal scales ensured consistent assessment across both observation periods and allowed quantitative evaluation of symptom trajectories.

2.4 Outcome measures
The primary outcome was the change in symptom severity and symptom frequency after eradication therapy.
Secondary outcomes included:
1. eradication rate;
2. comparison of symptom evolution between eradicated and non-eradicated patients;
3. identification of gastrointestinal symptoms showing statistically significant improvement following successful treatment.

These outcomes provided a comprehensive evaluation of the clinical effectiveness of eradication therapy and supported the longitudinal statistical assessment of symptom dynamics.

2.5 Statistical analysis
Continuous variables are presented as mean ± standard deviation, whereas categorical variables are summarized as frequencies and percentages. Baseline prevalence of upper and lower gastrointestinal symptoms was calculated for the entire study population. Changes in symptom severity and symptom frequency between baseline and follow-up evaluations were analyzed using paired statistical comparisons. In accordance with the original study protocol, statistical significance was assessed using the paired Student's t-test, and statistical significance was defined as $p < 0.05$. The longitudinal analytical framework allowed evaluation of within-subject symptom evolution over time while also comparing treatment response according to eradication status. Although the present investigation focused on classical inferential statistical methods, the longitudinal symptom profiles generated by this study may provide an appropriate foundation for future predictive statistical modeling and machine learning approaches aimed at supporting individualized treatment-response prediction.

RESULTS
3.1 Baseline gastrointestinal symptom profile
A total of 29 patients with confirmed Helicobacter pylori infection were prospectively enrolled in the study. The study population comprised 20 females (69.0%) and 9 males (31.0%), all presenting with dyspeptic symptoms requiring diagnostic evaluation.
All participants underwent baseline assessment, including the ^{13}C-Urea Breath Test and a standardized gastrointestinal symptom questionnaire. Following eradication therapy, patients were reassessed after two months using the same clinical protocol. Successful bacterial eradication was achieved in 24 patients (82.7%), whereas 5 patients (17.3%) remained positive at follow-up, resulting in an overall eradication rate of 82.7%. This eradication rate is consistent with those generally reported for standard eradication regimens in clinical practice and provided the basis for subsequent comparative analyses between eradicated and non-eradicated patients.
At baseline, upper gastrointestinal manifestations were considerably more prevalent than lower gastrointestinal symptoms. Heartburn represented the most frequently reported upper gastrointestinal complaint, followed by bitter mouth sensation, fasting epigastric pain, postprandial epigastric heaviness, and belching. Other symptoms including nausea, globus sensation, postprandial epigastric pain, nocturnal epigastric pain, and right upper quadrant discomfort were observed with lower prevalence. Regarding lower gastrointestinal manifestations, chronic abdominal pain and abdominal bloating were the most commonly reported symptoms, whereas diarrhea, urgency of defecation, mucus in stool, and

incomplete evacuation were less frequently observed. The complete baseline symptom distribution is illustrated in Figures 1 and 2.

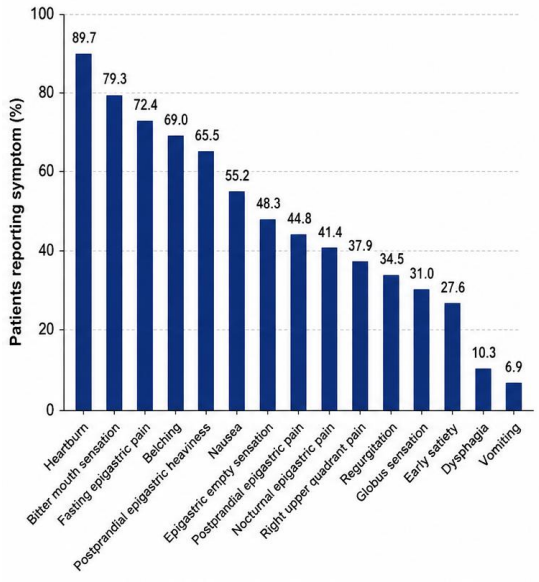


Figure 1: Prevalence of upper gastrointestinal symptoms at symptoms at baseline

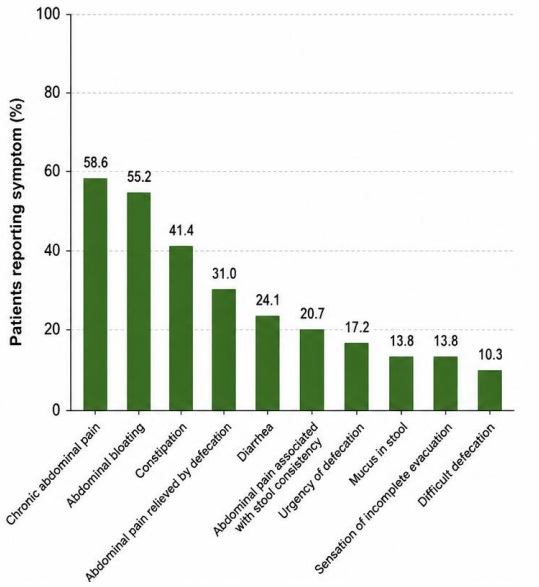


Figure 2: Prevalence of lower gastrointestinal baseline.

3.2 Changes following successful eradication

Among patients who achieved successful eradication, statistically significant improvements were observed in both symptom severity and symptom frequency. Significant reductions ($p < 0.05$) were identified for bitter mouth sensation, belching, globus sensation, fasting epigastric pain, postprandial epigastric pain, nocturnal epigastric pain, right upper quadrant pain, postprandial epigastric heaviness, and nausea. The simultaneous reduction in both symptom severity and occurrence frequency strongly suggests that successful eradication produced a clinically meaningful improvement in dyspeptic symptom burden. Particularly notable was the improvement of epigastric pain-related symptoms, which constitute the hallmark manifestations of functional dyspepsia associated with H. pylori infection. Conversely, symptoms such as heartburn, regurgitation, early satiety, dysphagia, vomiting, and epigastric empty sensation showed no statistically significant changes during follow-up, indicating that these manifestations may be influenced by mechanisms other than H. pylori infection alone.

These findings demonstrate that successful eradication was associated with a clinically meaningful reduction in upper gastrointestinal symptom burden, particularly among symptoms typically related to dyspeptic syndromes. The corresponding longitudinal changes are presented in Figures 3 and 4.

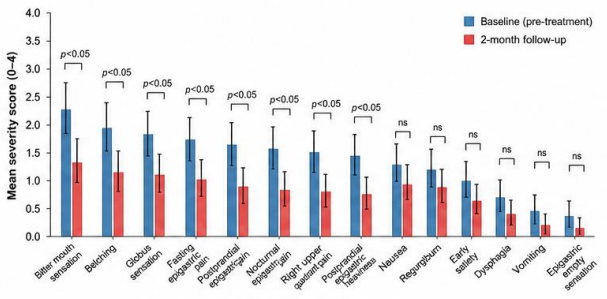


Figure 3: Changes in upper gastrointestinal symptom severity following successful helicobacter pylori eradication.

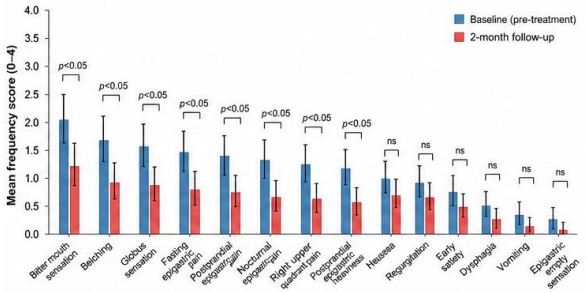


Figure 4: Changes in upper gastrointestinal symptom frequency following successful helicobacter pylori eradication.

Unlike upper gastrointestinal manifestations, lower gastrointestinal symptoms showed limited improvement following eradication therapy. Among all evaluated symptoms, only chronic abdominal pain demonstrated statistically significant reductions in both severity and frequency ($p < 0.05$). No statistically significant changes were observed for bloating, constipation, diarrhea, urgency of defecation, mucus in stool, incomplete evacuation, or difficult defecation. These findings suggest that eradication therapy primarily influenced upper gastrointestinal symptomatology, whereas lower gastrointestinal manifestations appeared to be less responsive to bacterial eradication (Figures 5 and 6).

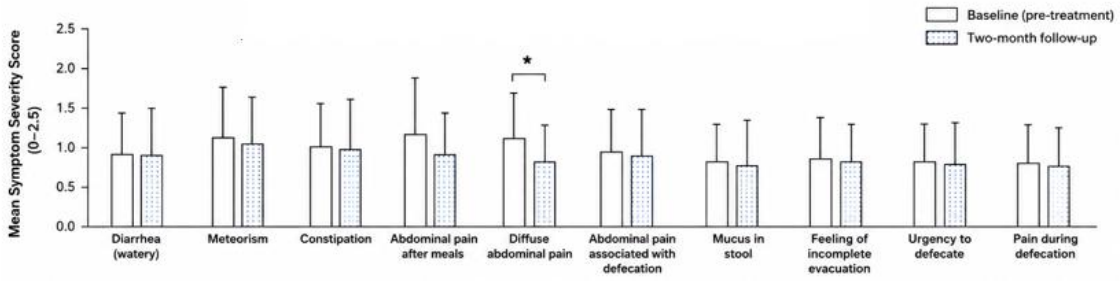


Figure 5: Changes in lower gastrointestinal symptom severity following successful helicobacter pylori eradication

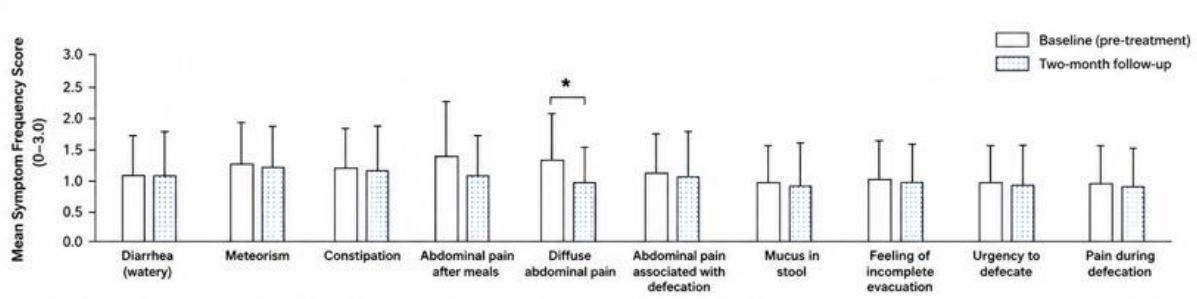


Figure 6: Changes in lower gastrointestinal symptom frequency following successful helicobacter pylori eradication

3.3 Clinical outcomes in patients with persistent infection

Five patients remained positive for Helicobacter pylori infection following completion of eradication therapy. Within this subgroup, longitudinal analysis demonstrated no statistically significant improvement in the majority of upper gastrointestinal symptoms. In contrast, heartburn severity significantly increased during follow-up ($p < 0.05$), while changes in symptom frequency were not statistically significant (Figures 7 and 8).

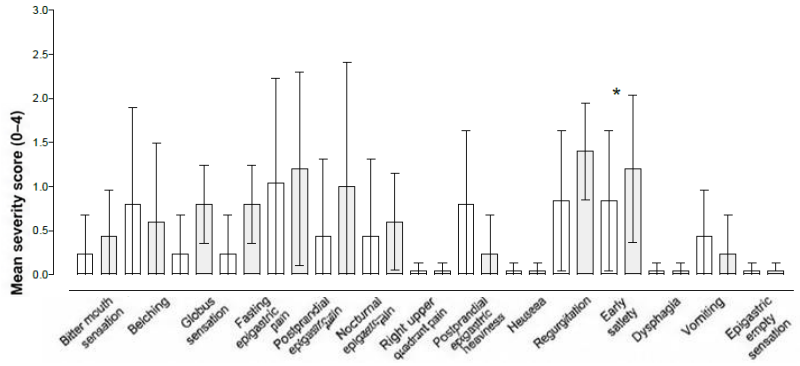


Figure 7: Upper gastrointestinal symptom severity in patients with persistent helicobacter pylori ınfection.

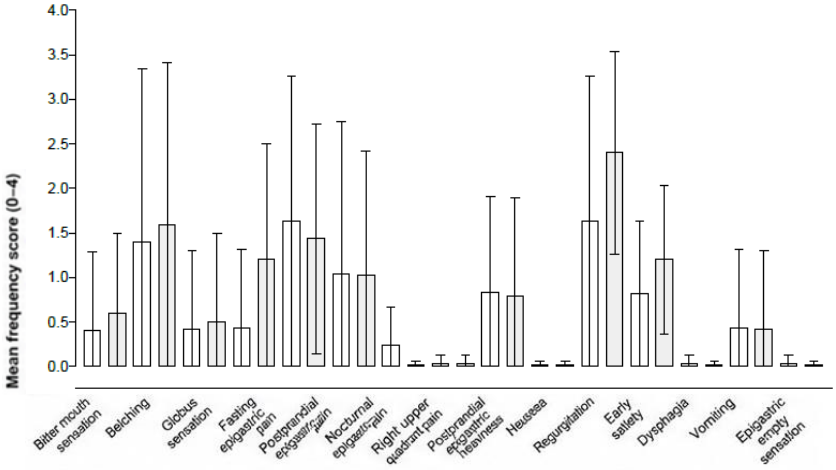


Figure 8: Upper gastrointestinal symptom frequency in patients with persistent helicobacter pylori ınfection.

Similarly, lower gastrointestinal symptoms remained essentially unchanged after treatment, with neither symptom severity nor frequency showing statistically significant differences compared with baseline (Figures 9 and 10).

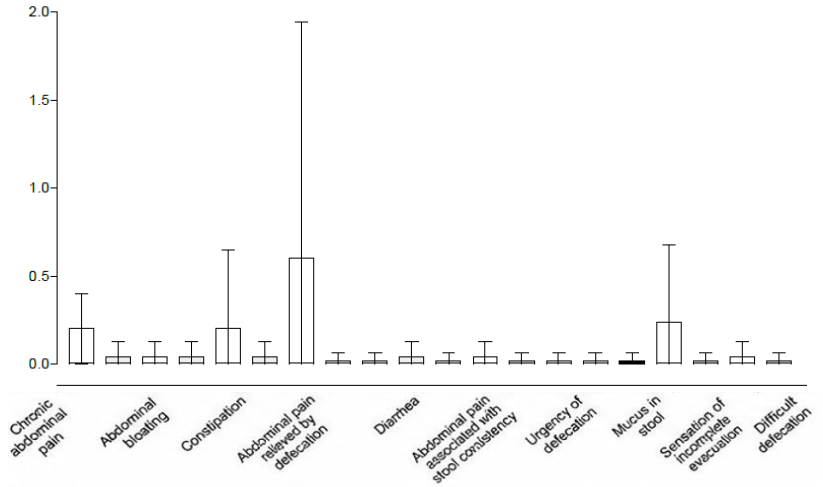


Figure 9: Lower gastrointestinal symptom severity in patients with persistent helicobacter pylori ınfection.

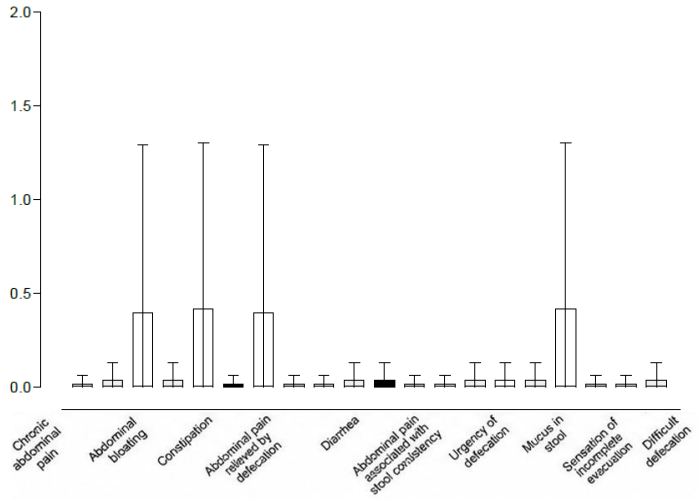


Figure 10: Lower gastrointestinal symptom frequency in patients with persistent helicobacter pylori ınfection.

The absence of symptomatic improvement among patients with persistent infection further supports the association between successful bacterial eradication and clinical recovery. Persistence of infection appears to maintain the inflammatory processes underlying dyspeptic symptomatology and may contribute to continued gastrointestinal discomfort despite completion of antimicrobial therapy.

Dıscussıon And Fındıngs

The present longitudinal study investigated changes in gastrointestinal symptom profiles following Helicobacter pylori eradication therapy, with particular emphasis on the statistical characterization of symptom dynamics. Rather than focusing exclusively on microbiological eradication, the study evaluated whether successful treatment was associated with measurable improvements in symptom severity and frequency over time. The findings demonstrated that successful H. pylori eradication was associated with statistically significant improvements in several upper gastrointestinal symptoms (Chey et al., 2017; Malfertheiner et al., 2022). Bitter mouth sensation, belching, globus sensation, fasting epigastric pain, postprandial epigastric pain, nocturnal epigastric pain, right upper quadrant pain, postprandial epigastric heaviness, and nausea all showed significant reductions in both symptom severity and frequency. These results suggest that eradication therapy substantially reduces the burden of dyspeptic symptoms commonly associated with chronic H. pylori infection. Conversely, lower gastrointestinal symptoms showed a markedly different pattern (Ford et al., 2020). Among all evaluated manifestations, only diffuse abdominal pain demonstrated statistically significant improvement following eradication therapy, whereas the remaining lower gastrointestinal symptoms remained largely unchanged. This finding supports the hypothesis that lower gastrointestinal complaints may be influenced by multifactorial mechanisms extending beyond the direct pathological effects of H. pylori.
Consequently, eradication alone may not be sufficient to modify symptoms that are predominantly associated with functional bowel disorders or other gastrointestinal conditions. An additional finding of clinical importance was the absence of symptomatic improvement among patients with persistent infection. Patients who failed eradication showed no meaningful reductions in gastrointestinal symptoms, while heartburn severity increased significantly during follow-up(Crowe, 2019). This observation further strengthens the association between successful bacterial eradication and clinical recovery, suggesting that persistent colonization continues to sustain gastric inflammation and symptom persistence.
From a statistical perspective, the longitudinal design adopted in this study represents an important methodological strength (James et al., 2021). Repeated measurements obtained before and after treatment enabled direct within-patient comparisons, reducing inter-individual variability and providing a more reliable assessment of therapeutic response than cross-sectional analyses. The use of standardized symptom scoring systems for both severity and frequency further enhanced the consistency of the statistical evaluation by allowing quantitative assessment of symptom trajectories over time.

Although classical inferential statistical methods were employed to evaluate treatment effects, the resulting longitudinal symptom profiles also demonstrate the potential value of statistical learning approaches in gastroenterology (James et al., 2021). Repeated symptom measurements constitute structured longitudinal data that could be further explored using multivariate statistical techniques, latent variable models, clustering algorithms, or supervised machine learning methods. Such approaches may facilitate identification of symptom patterns predictive of eradication success and improve individualized clinical decision-making. The findings of the present investigation are generally consistent with previous studies reporting improvements in functional dyspeptic symptoms following successful H. pylori eradication(Chey et al., 2017; Ford et al., 2020; Malfertheiner et al., 2022). Nevertheless, published evidence remains heterogeneous, with several randomized trials and systematic reviews reporting variable degrees of symptomatic benefit. Differences in study populations, follow-up duration, diagnostic criteria, and symptom assessment instruments may partially explain these discrepancies. The present study contributes additional evidence by demonstrating that symptom evolution can be effectively analyzed within a longitudinal statistical framework, thereby providing information beyond conventional comparisons of eradication rates alone.

Several limitations should also be acknowledged. First, the relatively small sample size may have reduced statistical power for detecting modest changes in less prevalent symptoms. Second, because symptom scores were measured on ordinal scales, future studies may benefit from complementary non-parametric longitudinal analyses. Third, the follow-up period was limited to two months after therapy, preventing assessment of long-term symptom evolution. Finally, the statistical analysis relied primarily on conventional hypothesis testing. Future investigations involving larger multicenter cohorts could integrate mixed-effects longitudinal models and machine learning algorithms to develop predictive tools capable of identifying patients most likely to benefit from eradication therapy (James et al., 2021)..

Overall, the present findings indicate that successful Helicobacter pylori eradication is associated with clinically meaningful improvements in upper gastrointestinal symptoms, whereas lower gastrointestinal manifestations appear considerably less responsive to treatment. Beyond their clinical relevance, these results illustrate how longitudinal symptom datasets can serve as valuable resources for advanced statistical modeling and predictive analytics in gastrointestinal research.

Conclusıons

This longitudinal study demonstrated that successful Helicobacter pylori eradication was associated with significant improvements in the majority of upper gastrointestinal symptoms, particularly bitter mouth sensation, belching, globus sensation, fasting and postprandial epigastric pain, nocturnal epigastric pain, right upper quadrant pain, postprandial epigastric heaviness, and nausea (Malfertheiner et al., 2022). These findings confirm that eradication therapy provides clinically meaningful symptomatic benefits in patients with H. pylori-associated dyspeptic disorders.

In contrast, lower gastrointestinal symptoms showed a limited response to eradication therapy. Diffuse abdominal pain was the only lower gastrointestinal manifestation demonstrating statistically significant improvement, whereas no significant changes were observed for the remaining lower gastrointestinal symptoms. This suggests that lower gastrointestinal complaints are likely influenced by additional physiological and functional mechanisms beyond H. pylori infection alone. Patients with persistent H. pylori infection exhibited no significant overall symptomatic improvement, further emphasizing the importance of successful bacterial eradication in achieving clinical recovery. The observed increase in heartburn severity within the non-eradicated subgroup also highlights the potential consequences of persistent infection on symptom persistence.

From a methodological perspective, the present study demonstrates the value of longitudinal statistical analysis for evaluating treatment response. Repeated symptom measurements before and after therapy allowed a comprehensive assessment of symptom dynamics and provided a more informative evaluation than single cross-sectional observations.The standardized symptom scores generated in this study also represent a valuable source of structured longitudinal data that could support future applications of advanced statistical modeling, multivariate analysis, and machine learning techniques for predicting therapeutic response and improving individualized clinical decision-making.

Overall, the findings of this study demonstrate that longitudinal statistical analysis represents an effective framework for quantifying symptom evolution following Helicobacter pylori eradication(James et al., 2021). Beyond confirming the clinical benefits of successful treatment, the

study highlights the potential of longitudinal symptom datasets to support predictive statistical modeling and evidence-based clinical decision-making (James et al., 2021). The integration of advanced analytical methods with routinely collected clinical data may contribute to the development of personalized therapeutic strategies and more effective management of patients with H. pylori-associated gastrointestinal disorders. Future research involving larger multicenter cohorts and extended follow-up periods is warranted to validate these findings and to develop robust predictive models capable of identifying patients who are most likely to benefit from Helicobacter pylori eradication therapy.

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COMPARATIVE EFFECTS OF KINETIC CHAIN EXERCISES ON PAIN AND ARTERIAL OCCLUSION PRESSURE IN ACUTE ANTERIOR KNEE PAIN: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background
Anterior knee pain (AKP) is a prevalent and frequently persistent complaint for which exercise is the first-line treatment, although the optimal loading modality is unresolved. Blood flow restriction (BFR) enables a training stimulus at low external loads tolerable to a symptomatic knee and arterial occlusion pressure (AOP); which individualizes BFR prescription, may also show physiological adaptation.

Objective
To compare open kinetic chain (OKC), closed kinetic chain (CKC), and combined OKC+CKC exercises, each delivered with BFR, on pain intensity and AOP in adults with acute AKP.

Methods
In a triple-blind, three-arm randomized controlled trial, 96 adults aged 18-40 years with acute AKP were allocated 1:1:1 to OKC, CKC, or combined groups, all delivered with BFR at 80% of AOP and conventional physiotherapy, three times weekly for four weeks. Pain (measured by Numeric Pain Rating Scale, NPRS) and AOP (measured by Doppler ultrasound) were assessed before and after intervention and analyzed by repeated-measures analysis of variance (ANOVA).

Results
Pain decreased in all groups (Time: $F(1,93) = 889.03$, $p < .001$) with a significant Time × Group interaction ($F(2,93) = 37.88$, $p < .001$). The combined group reached a mean of 1.88, versus 4.03 (OKC) and 3.81 (CKC); combined protocol was superior to both ($p < .001$), which did not differ from one another ($p = 1.000$). AOP increased in all groups (interaction $F(2,93) = 59.71$, $p < .001$) but only combined vs OKC comparison reached significance ($p = .001$).

Conclusion
Combined kinetic chain exercise with BFR produced greatest reduction in pain. AOP also increased significantly over time with combined group giving best impact.

Keywords: anterior knee pain; patellofemoral pain; blood flow restriction; kinetic chain exercise; arterial occlusion pressure; pain

Introduction
Anterior knee pain (AKP) is among the most common musculoskeletal presentations in physically active adults and a frequent reason for referral to physiotherapy. It is characterized by peripatellar or retropatellar pain provoked by patellofemoral loading activities such as squatting, stair climbing, prolonged sitting and running, and it persists in a substantial proportion of those are affected well beyond

the short term (Smith et al., 2018). Exercise therapy is the cornerstone of management and is supported by meta-analyses and by clinical practice guidelines at their highest evidence grade (Willy et al., 2019; Winters et al., 2021), with the most rigorous synthesis reporting short-term efficacy for pain from knee-targeted exercises (Neal et al., 2022).

Despite this consensus, optimal exercise strategy remains unresolved. A long-standing question concerns kinetic chain exercise interventions in which extensor mechanism is loaded; open kinetic chain (OKC) exercise permits controlled, isolated loading without co-contraction demands of weight-bearing, whereas closed kinetic chain (CKC) exercise loads limbs fixed on ground/surface in functional, weight-bearing patterns. Direct comparative evidence is concentrated in other knee conditions and disagrees in direction between them (Michael et al., 2025; Pamboris et al., 2024) and although addition of one loading approach to another has repeatedly improved outcomes (Nascimento et al., 2018), no randomized trial has compared OKC, CKC, and their combination within a single design in an AKP population.

A further consideration is the load at which exercise is delivered. The heavy resistance conventionally required to build strength may provoke symptoms in a painful knee. Blood flow restriction (BFR), which applies a pneumatic cuff to partially restrict limb blood flow during low-load exercise, elicits strength gains approaching those of heavy load training (Grønfeldt et al., 2020) and has reduced activity related pain in patellofemoral joint at loads a symptomatic knee can tolerate (Giles et al., 2017). Safe application requires the restriction pressure to be individualized to a percentage of participant's arterial occlusion pressure (AOP) rather than applied as a fixed absolute pressure (Patterson et al., 2019). Evidence indicates that approximately 80% of AOP is required to achieve adaptation at low loads (Lixandrão et al., 2015). Beyond its role in prescription, AOP is an objectively obtained physiological measure that may reflect training-related vascular and muscular adaptation and has not previously been reported as an outcome in an AKP trial.

This study therefore compared OKC, CKC and combined kinetic chain exercise, all delivered under BFR, in adults with acute AKP. The primary outcome was pain intensity. AOP was examined as an exploratory physiological outcome, to determine whether a four-week exercise intervention under BFR produces measurable change on this index and whether that change differs by modality. It was hypothesized that the combined protocol would produce greatest reduction in pain.

Methods

Design. This was a triple-blinded, three arm, parallel group randomized controlled trial with 1:1:1 allocation, reported in accordance with CONSORT statement (Schulz et al., 2010) and its extension for non-pharmacological treatments, with intervention described per TIDieR checklist (Hoffmann et al., 2014). Ethical approval was obtained from the institutional ethics review committee of Ziauddin University.

Participants

Adults aged 18-40 years presenting to outpatient physiotherapy departments of Ziauddin Hospital in Karachi with a clinical diagnosis of AKP without radiation, of three months' duration or less and screened by a physiatrist before referral, were eligible. Exclusions were knee surgery within 12 months, lumbar or lower-limb radiculopathy, knee infection, malignancy or inflammatory joint disease, patellar subluxation or instability, concurrent physiotherapy for current episode, and any contraindication to BFR or safe exercise, including venous thromboembolism, peripheral vascular disease, uncontrolled hypertension or pregnancy (Patterson et al., 2019). Written informed consent was obtained from all participants.

Randomization and blinding.

Eligible participants were allocated by simple random sampling using sequentially numbered, opaque, sealed envelopes (SNOSE) prepared by a researcher independent of recruitment and data collection. Outcome assessors, statistician and participants were blinded; treating physiotherapists could not be blinded, as is intrinsic to supervised-exercise trials.

Interventions

All groups received an identical framework: conventional therapy (hot pack, 10 min at 37-40°C and transcutaneous electrical nerve stimulation(TENS), 10 min at 7 Hz), a 5-min warm-up and a 5-min cool-

down. BFR was applied during exercise in all groups using a proximal thigh cuff set to 80% of each participant's AOP (Lixandrão et al., 2015; Patterson et al., 2019). Each exercise was performed for four sets of 12 repetitions, three days weekly on alternate days for four weeks, with weekly set progression. Group A (OKC) performed straight leg raise, seated knee extension and side-lying hip abduction and adduction. Group B (CKC) performed standing terminal knee extension, wall slides and forward and lateral step-ups. Group C (combined) performed all eight exercises concurrently.

Outcomes

The primary outcome was pain intensity on NPRS, an 11-point scale with good-to-excellent reliability in musculoskeletal populations (Modarresi et al., 2022). The exploratory outcome was AOP, measured by Doppler ultrasound as lowest cuff pressure abolishing the distal arterial signal, with cuff, site and position standardized (Vehrs et al., 2023, 2024; de Queiros et al., 2024). Both were assessed at baseline and after four weeks by blinded assessors.

Sample size and analysis

The sample size was calculated in OpenEpi from a comparable trial (Ng et al., 2022), requiring 29 participants per group at 80% power and $\alpha = .05$; allowing 10% attrition yielded 32 per group (96 total). Analyses used a repeated-measures general linear model NAOVA. Normality (Kolmogorov–Smirnov, Shapiro–Wilk) and homogeneity of variance (Levene) were examined. Analyses followed the intention-to-treat (ITT) principle, with multiple imputation for two withdrawals, in SPSS v26; α was set at 0.05.

3. Results

3.1 Participants. 96 participants were randomized (32 per group). Two withdrew during the final week (one each from Groups A and C) and were retained by ITT. Groups were comparable at baseline in age (Group A, 27.06 ± 2.96; Group B, 27.13 ± 2.94; Group C, 26.72 ± 2.91 years) and gender ($\chi^2(2, N = 96) = 0.083$, $p = .959$).

Pain intensity

Pain decreased in all groups over intervention duration, with a significant main effect of Time, $F(1, 93) = 889.03$, $p < .001$, and a significant Time × Group interaction, $F(2, 93) = 37.88$, $p < .001$, indicating that reduction differed by group (Table-1). Bonferroni-corrected comparisons showed that combined group was superior to both individual groups ($p < .001$ for each), which did not differ from each other ($p = 1.000$). The combined group reached a post-intervention mean of 1.88, a reduction of approximately 4.6 points that exceeds the clinically important difference for this scale (Olsen et al., 2018), against reductions of approximately 2.4 and 2.9 points in OKC and CKC groups respectively.

Table-1: Pain (NPRS) and Arterial Occlusion Pressure (mmHg): Descriptive and Inferential Results

Outcome / Group	Pre M (SD)	Post M (SD)	Change	Time × Group	Bonferroni (p)
NPRS				F(2,93) = 37.88	A–B: 1.000
Group A (OKC)	6.41 (1.04)	4.03 (1.09)	−2.38	p < .001	A–C: < .001
Group B (CKC)	6.66 (0.94)	3.81 (0.93)	−2.84		B–C: < .001
Group C (Combined)	6.47 (0.98)	1.88 (0.91)	−4.59		
AOP				F(2,93) = 59.71	A–B: .233
Group A (OKC)	122.97 (5.50)	131.88 (4.37)	+8.91	p < .001	A–C: .001
Group B (CKC)	123.72 (4.79)	135.28 (5.41)	+11.56		B–C: .180
Group C (Combined)	123.25 (4.83)	140.19 (4.34)	+16.94		

Note. NPRS = Numeric Pain Rating Scale (0–10); AOP = arterial occlusion pressure (mmHg); OKC = open kinetic chain; CKC = closed kinetic chain; M = mean; SD = standard deviation.

Arterial occlusion pressure

AOP increased in all groups, with a significant main effect of Time, $F(1, 93) = 1663.37$, $p < .001$ and a significant Time × Group interaction, $F(2, 93) = 59.71$, $p < .001$ (Table-1). The pattern of pairwise differences distinguished this outcome from pain; out of three Bonferroni-corrected comparisons, only that between the combined and OKC groups reached significance ($p = 0.001$). The combined and CKC groups did not differ ($p = 0.180$) significantly, nor did the two single modality groups ($p = 0.233$). Although post-intervention means rose in group order (OKC 131.88, CKC 135.28, combined 140.19 mmHg), only the extremes of this range were statistically distinguishable.

Discussion

In this triple-blind randomized trial, a combined open and closed kinetic chain protocol delivered under BFR produced a significantly greater reduction in pain than either modality delivered alone in adults with acute AKP and magnitude of that reduction was clinically as well as statistically meaningful. The two single-modality protocols were statistically indistinguishable for pain. AOP increased in all groups but distinguished only combined and OKC groups.

The superiority of the combined protocol for pain is consistent with broader exercise-therapy literature, in which the addition of one loading approach to another has repeatedly improved outcomes (Nascimento et al., 2018) and it extends that principle to combination of kinetic chain conditions, a comparison not previously made in this population. The equivalence of the two single-modality protocols for pain aligns with the mixed direct evidence from adjacent knee conditions (Michael et al., 2025; Pamboris et al., 2024) and is consistent with view that, for reduction of pain, progressive loading of the extensor mechanism matters more than specific chain in which it is delivered.

Two mechanisms plausibly contribute to pain findings beyond a simple strengthening effect. First, exercise reduces pain sensitivity through endogenous inhibitory pathways, a phenomenon termed exercise-induced hypoalgesia (Wewege & Jones, 2021); although this response can be attenuated in chronic pain, the acute presentation of present cohort may place them more favorably for it. Second, intervention was delivered under BFR, whose metabolic stress is associated with hypoalgesic responses and BFR has reduced activity related pain in patellofemoral pain at low loads (Giles et al., 2017). A greater cumulative stimulus in the combined arm would be expected to engage these mechanisms more fully.

This last point, however, identifies the principal limitation of comparison. The combined arm performed twice total exercise volume. Its advantage may reflect complementarity of two loading conditions or greater dose and present design cannot separate them.

The behavior of AOP warrants cautious interpretation. A rise following exercise under BFR is physiologically interpretable, since resistance training under restriction is associated with muscular and vascular adaptation (Hughes et al., 2019; Patterson et al., 2019) and the measure depends on limb composition and vascular properties. However, AOP has no established minimal clinically important difference and served a dual role in trial as both an outcome and basis for prescribing the restriction pressure. Its change is therefore best understood as a marker of physiological engagement of the intervention as well as an index of patient benefit and the finding is hypothesis-generating only. No inference can be drawn that AOP change caused or corresponds to the pain change, as no such association was tested.

Conclusion, Limitations, and Recommendations

Combined open and closed kinetic chain exercise, delivered under blood flow restriction, produced greatest reduction in pain in adults with acute anterior knee pain, exceeding clinically important difference and outperforming either modality alone, which were equivalent to one another. Arterial occlusion pressure changed measurably and differed by modality but remains an exploratory, non-validated index that should not be read as evidence of clinical benefit.

Several limitations qualify these findings. The combined arm's greater exercise volume may confound modality with dose, so its pain advantage cannot confidently be attributed unambiguously to complementarity. Follow-up extended only to end of four-week intervention, in a condition known to persist, so durability is unknown. Treating therapists could not be blinded. AOP lacks a validated clinical interpretation and no association between AOP and pain change was examined. The sample was bounded to acute presentations aged 18-40 from a single hospital network.

Future work should prioritize a dose-matched three-arm trial, in which the combined arm performs two exercises of each modality against four of either alone, to separate complementarity from volume; incorporate medium and long term follow-up; and either establish measurement properties and clinical correlates of AOP directly or replace it with a physiological measure of established relevance. Replication across centers and in chronic populations would extend the generalizability of these findings. For current practice, the results support combining loading approaches where feasible and delivering exercise under blood flow restriction to achieve an adequate stimulus at loads a symptomatic knee can tolerate.

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THE CHEMISTRY OF ADDICTION: PSYCHOACTIVE PLANT METABOLITES, NEUROBIOLOGICAL TARGETS, AND THE DUALITY OF THERAPEUTIC POTENTIAL AND TOXICITY

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ABSTRACT
Psychoactive secondary metabolites produced by plants — including morphinan alkaloids from Papaver somniferum, nicotine from Nicotiana tabacum, tropane alkaloids from Erythroxylum coca, phytocannabinoids from Cannabis sativa, indole alkaloids from Psilocybe species and Tabernanthe iboga, and the oxindole/indole alkaloid mitragynine from Mitragyna speciosa — have shaped both pharmacotherapy and public health for centuries. These compounds act on discrete neurobiological targets, including mu-opioid receptors, nicotinic acetylcholine receptors, the dopamine transporter, cannabinoid CB1/CB2 receptors, and serotonin 5-HT2A receptors, and converge functionally on the mesolimbic dopaminergic reward circuitry that links the ventral tegmental area to the nucleus accumbens and prefrontal cortex. This review synthesizes current pharmacological and neurobiological evidence on these plant-derived agents, examining the chemical basis of receptor selectivity and the shared neuroadaptive processes — tolerance, sensitization, and withdrawal — that underlie compulsive use. Particular attention is given to the duality inherent in these molecules: the same structural features that confer analgesic, anxiolytic, antiepileptic, or antidepressant efficacy also confer liability for dependence, tolerance, and organ toxicity. Case examples include morphine's analgesic-versus-respiratory-depressant profile, cannabidiol's anticonvulsant use alongside tetrahydrocannabinol's psychotomimetic risk, and the re-emerging psychiatric application of psilocybin and ibogaine against a backdrop of cardiac and psychological risk. We argue that advancing biased agonism, receptor-subtype-selective ligands, and pharmacogenomic screening represents the most promising path toward preserving therapeutic benefit while narrowing the margin for toxicity and addiction. Implications for clinical practice, drug policy, and future medicinal chemistry are discussed.
Keywords:addiction pharmacology; plant alkaloids; opioid receptors; cannabinoids; mesolimbic dopamine; neurotoxicity

Summary
This article reviews the pharmacology of major classes of psychoactive plant metabolites and the neurobiological substrates through which they produce both therapeutic and harmful effects. Opioid, nicotinic, dopaminergic, cannabinoid, and serotonergic systems are each examined for their receptor pharmacology, physiological consequences, and clinical relevance. A recurring theme is that addiction liability and therapeutic efficacy are not separable properties of these molecules but are mechanistically linked, arising from the same receptor interactions that produce desired clinical effects. The review closes by considering strategies in medicinal chemistry and precision pharmacology intended to widen the therapeutic window of these historically important compounds.

Introduction
Plants do not produce alkaloids, terpenoids, and phenolic compounds for the benefit of the animals that consume them. These secondary metabolites evolved primarily as chemical defenses against herbivory, and their potency in animal nervous systems is, from an evolutionary standpoint, incidental to their ecological function. Yet this same potency has made plant-derived psychoactive compounds central to human medicine, ritual practice, and, unfortunately, to the global burden of substance use disorders. The opium poppy, coca leaf, cannabis plant, tobacco leaf, and a range of psychedelic fungi and shrubs have supplied the pharmacological scaffolds for some of the most consequential drugs in clinical history, from morphine and cocaine's original use as a local anesthetic to modern interest in psilocybin-assisted psychotherapy.
Understanding why the same molecule can relieve suffering in one context and produce catastrophic harm in another requires attention to three intersecting levels of analysis: the medicinal chemistry of the compound itself (its structure, metabolism, and receptor affinity), the neurobiology of the receptor systems it engages, and the adaptive changes that chronic receptor stimulation produces in neural circuits. This review integrates these three levels for the major classes of plant-derived psychoactive metabolites, intending to clarify the structural and mechanistic basis for the therapeutic-toxic duality that characterizes this pharmacological family, and to identify research directions that might allow the therapeutic signal to be captured with less toxicological noise.

Research And Findings
The compounds surveyed below are organized by their principal receptor target, as receptor pharmacology is the most reliable predictor of both therapeutic applications and toxicity profiles within this class of natural products.

Opioid Alkaloids and the Mu-Opioid Receptor
Morphinan alkaloids, principally morphine and codeine, are biosynthesized in Papaver somniferum and act as agonists at mu-opioid receptors (MORs), with lower affinity for kappa and delta subtypes. MOR activation in the periaqueductal gray and dorsal horn produces potent analgesia by inhibiting nociceptive neurotransmission, while MOR activation in the ventral tegmental area disinhibits dopaminergic projections to the nucleus accumbens, producing euphoria and reinforcing drug-seeking behavior. The same receptor mechanism that relieves pain also depresses brainstem respiratory centers, and it is this action — rather than any secondary toxicity — that accounts for the majority of fatal opioid overdoses. Chronic MOR stimulation drives receptor desensitization and downstream adaptations in cyclic AMP signaling that produce tolerance, physical dependence, and a withdrawal syndrome upon cessation. The clinical challenge posed by opioids is thus not the presence of an off-target toxicity but an unusually narrow separation between the therapeutic and lethal actions of a single receptor mechanism.

Nicotine and Nicotinic Acetylcholine Receptors
Nicotine, a pyridine alkaloid from Nicotiana tabacum, is a potent agonist at neuronal nicotinic acetylcholine receptors (nAChRs), particularly the alpha4-beta2 subtype expressed on midbrain dopaminergic neurons. Nicotine binding produces rapid but transient increases in mesolimbic dopamine release, and the very short half-life of nicotine in plasma promotes a pattern of frequent redosing that is central to its exceptionally high addiction liability relative to its modest acute toxicity. Therapeutically, nicotine and nAChR-targeted compounds have been investigated for cognitive enhancement and for reducing symptoms in some neuropsychiatric conditions, and nicotine replacement therapy remains a first-line tool for smoking cessation — an application in which the drug is used to treat dependence on a more toxic delivery vehicle (combusted tobacco) rather than on nicotine itself. Chronic exposure

produces nAChR upregulation, a paradoxical receptor response that is thought to underlie withdrawal-driven craving.

Cocaine and the Dopamine Transporter

Cocaine, a tropane alkaloid from Erythroxylum coca, blocks the presynaptic dopamine transporter (DAT) as well as the norepinephrine and serotonin transporters, producing a rapid surge in synaptic monoamine concentrations. Its local anesthetic properties, mediated by voltage-gated sodium channel blockade, gave it a genuine place in early clinical anesthesia, and it remains used topically in some otolaryngologic procedures. However, its DAT-blocking action produces both intense reinforcement, through supraphysiological dopamine signaling in the nucleus accumbens, and significant cardiovascular toxicity, through sympathomimetic effects that can precipitate vasospasm, arrhythmia, and myocardial infarction even in young, otherwise healthy users. Repeated use produces sensitization of mesolimbic circuitry alongside blunted baseline dopaminergic tone, a combination thought to drive escalating and compulsive use patterns.

Phytocannabinoids and Cannabinoid Receptors

Cannabis sativa produces over a hundred phytocannabinoids, of which delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are best characterized. THC is a partial agonist at CB1 receptors, which are densely expressed in the hippocampus, prefrontal cortex, and basal ganglia, producing the characteristic psychoactive, analgesic, and appetite-stimulating effects of cannabis. CBD, in contrast, has low direct affinity for CB1/CB2 receptors and instead modulates the endocannabinoid system indirectly, contributing to its anticonvulsant efficacy — most notably in the FDA-approved treatment of Dravet and Lennox-Gastaut syndromes — without meaningful abuse liability. The duality within this single plant is instructive: THC's CB1 agonism confers analgesic and antiemetic benefit but is also associated with dose-dependent anxiety, psychotomimetic effects, and a defined cannabis use disorder in a subset of users, particularly with adolescent-onset or high-potency exposure, while CBD's distinct mechanism largely avoids these liabilities.

Serotonergic and Atypical Psychedelic Alkaloids

Psilocybin (from Psilocybe fungi), mescaline (from Lophophora williamsii), and ibogaine (from Tabernanthe iboga) engage distinct but overlapping serotonergic and, in ibogaine's case, additional NMDA-receptor and opioid-receptor mechanisms. Psilocybin's active metabolite psilocin is a potent 5-HT2A receptor agonist, and 5-HT2A activation in cortical layer V pyramidal neurons is believed to underlie both the acute hallucinogenic state and the sustained increases in neural plasticity that have generated interest in psilocybin-assisted psychotherapy for treatment-resistant depression and end-of-life anxiety. Unlike the opioid and stimulant classes discussed above, classic serotonergic psychedelics show minimal physical dependence liability and no defined withdrawal syndrome, though acute cardiovascular effects and the risk of precipitating psychotic or dissociative episodes in vulnerable individuals warrant careful patient screening. Ibogaine presents a more complex toxicity profile: its ability to interrupt opioid and stimulant dependence, plausibly through kappa-opioid and NMDA-receptor mechanisms, is counterbalanced by a narrow therapeutic index and a risk of fatal cardiac arrhythmia via hERG potassium channel blockade, which has limited its clinical adoption outside of tightly monitored settings.

Mitragynine and Mixed-Mechanism Alkaloids

Mitragynine and its oxidized metabolite 7-hydroxymitragynine, alkaloids from Mitragyna speciosa (kratom), display an unusual pharmacological profile combining partial MOR agonism with monoaminergic and adrenergic receptor activity. This mixed mechanism has been proposed to explain kratom's reported analgesic and mood-elevating effects at lower doses alongside stimulant-like effects at higher doses, and has generated interest in mitragynine analogs as opioids with a potentially reduced respiratory depression profile. However, kratom's largely unregulated availability, variable alkaloid content across preparations, and case reports of hepatotoxicity and dependence with prolonged heavy use illustrate the risk of extrapolating from single-molecule receptor pharmacology to the safety of a botanical product containing dozens of related alkaloids in variable ratios.

Convergent Neuroadaptation in Reward Circuitry

Despite differing primary receptor targets, all of the compound classes reviewed here converge functionally on the mesolimbic dopamine pathway connecting the ventral tegmental area to the nucleus

accumbens, and each produces some degree of neuroadaptation with repeated exposure. Common features include downregulation or desensitization of the initially stimulated receptor, compensatory changes in intracellular signaling cascades (notably cyclic AMP response element-binding protein, CREB, and delta-FosB accumulation in the nucleus accumbens), and structural remodeling of dendritic spines in reward-related circuitry. These shared neuroadaptive mechanisms explain why disorders of use across pharmacologically distinct substances present with a common clinical phenotype of tolerance, craving, and relapse vulnerability, even though the acute receptor pharmacology and organ toxicity of each compound class differ substantially.

The Therapeutic Window as a Structural Property

A structural theme emerges across these compound classes: therapeutic efficacy and toxicity frequently arise from the same receptor-binding event rather than from independent, separable mechanisms, which constrains the degree to which safety can be improved through simple dose reduction. Advances that have shown promise for widening the therapeutic window include the development of biased agonists that preferentially activate G-protein signaling over beta-arrestin recruitment at the MOR, subtype-selective cannabinoid ligands that spare CB1-mediated psychoactivity while retaining peripheral analgesic benefit, and pharmacogenomic approaches that identify individuals at elevated risk of toxicity or dependence before prescribing. None of these strategies has yet fully decoupled therapeutic benefit from abuse or toxicity liability, underscoring that this duality is a structural property of the pharmacology rather than a solvable side effect.

Conclusion

Plant-derived psychoactive metabolites occupy a uniquely dual position in pharmacology: the same molecular interactions that make morphine an indispensable analgesic, that make cannabidiol an effective anticonvulsant, and that make psilocybin a promising tool in psychiatry are inseparable from the mechanisms that produce respiratory depression, psychotomimetic risk, and dependence. Effective clinical and public health responses to these compounds therefore cannot rely on treating toxicity as an avoidable side effect; rather, they require precision pharmacology approaches — biased agonism, receptor-subtype selectivity, pharmacogenomic risk stratification, and careful attention to dose, route, and population vulnerability — that manage this duality rather than attempt to eliminate it. Continued investigation of the structure-activity relationships underlying these plant alkaloids, informed by the neurobiology of the mesolimbic reward system and by the adaptive changes that chronic receptor stimulation produces, remains essential to expanding the therapeutic use of this pharmacologically important class of natural products while reducing the substantial public health burden associated with their misuse.

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FROM MOLECULES TO MIND: THE GUT–BRAIN AXIS AS A MOLECULAR LINK BETWEEN MICROBIOTA, NEUROTRANSMITTERS, INFLAMMATION, AND MENTAL HEALTH

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ABSTRACT
The gastrointestinal microbiota has emerged as a central regulator of central nervous system function, communicating with the brain through a bidirectional network known as the gut–brain axis. This review synthesizes current evidence on the molecular pathways linking intestinal microbial communities to mood, cognition, and psychiatric disease. Microbiota-derived short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, regulate microglial maturation, blood–brain barrier integrity, and histone acetylation in neurons, while microbial metabolism of dietary tryptophan governs substrate availability for host serotonin synthesis and generates kynurenine-pathway metabolites with direct neuroactive properties. Enteroendocrine and enterochromaffin cells translate luminal microbial signals into vagal afferent activity, providing a fast neural route by which gut contents influence brainstem and limbic circuits. In parallel, disruption of intestinal barrier integrity — often termed increased intestinal permeability — permits translocation of bacterial lipopolysaccharide and peptidoglycan into systemic circulation, activating toll-like receptor signaling and a pro-inflammatory cytokine cascade implicated in the pathophysiology of major depressive disorder, generalized anxiety, and neurodegenerative disease. The hypothalamic–pituitary–adrenal axis further integrates microbial and immune signals, with germ-free animal models demonstrating exaggerated corticosterone responses to stress that are normalized by microbial colonization. We review clinical and preclinical evidence for these mechanisms, evaluate the therapeutic rationale for psychobiotic and dietary interventions, and identify methodological limitations — including reliance on rodent models and heterogeneity in human microbiome sequencing — that currently constrain translation to clinical psychiatry. We conclude that the gut–brain axis represents a molecularly tractable and modifiable pathway of substantial relevance to future precision psychiatry.
Keywords*:gut–brain axis; microbiota; short-chain fatty acids; neuroinflammation; tryptophan-kynurenine pathway; psychobiotics*

Summary
This article reviews the molecular architecture of the gut–brain axis, the bidirectional communication network linking the intestinal microbiota to central nervous system function. Four principal signaling routes are examined: microbial metabolite signaling (short-chain fatty acids and tryptophan-kynurenine metabolites), neuroendocrine and vagal afferent signaling, immune and inflammatory signaling arising

from intestinal barrier function, and hypothalamic–pituitary–adrenal axis regulation. Evidence linking dysbiosis to depression, anxiety, and neurodevelopmental and neurodegenerative conditions is summarized, along with the current state of psychobiotic and dietary intervention research. The review concludes that, while causal mechanisms in humans remain incompletely established, the gut–brain axis constitutes a biologically plausible and pharmacologically accessible target for future psychiatric intervention.

Introduction

The human gastrointestinal tract harbors an estimated 10^{13}–10^{14} microbial cells, a genetically diverse community whose collective metabolic output rivals that of the human liver in scope. Historically regarded as relevant chiefly to digestion and immunity, this microbial ecosystem is now understood to communicate continuously with the central nervous system through neural, endocrine, and immune channels collectively termed the gut–brain axis. The recognition that germ-free mice — animals raised in the complete absence of microbiota — display measurable differences in anxiety-like behavior, stress reactivity, and even the structural maturation of microglia has reframed the microbiota not as a passive digestive bystander but as an active participant in neurodevelopment and the maintenance of adult brain function.

This shift in understanding has considerable clinical stakes. Major depressive disorder, generalized anxiety disorder, autism spectrum conditions, and several neurodegenerative diseases have each been associated with alterations in microbial community composition, a state broadly termed dysbiosis. Yet the field faces a persistent challenge in distinguishing correlation from mechanism: cross-sectional differences in microbial composition between psychiatric patients and controls do not, by themselves, establish that the microbiota causally contributes to disease. This review therefore emphasizes molecular mechanisms with demonstrated plausibility in controlled preclinical models — mechanisms capable, in principle, of explaining how a microbial signal in the gut lumen becomes a change in neurotransmission, neuroinflammation, or neuroendocrine tone in the brain — before considering the current, more limited, state of human clinical evidence.

Research And Findings

Four broad signaling routes are thought to mediate gut–brain communication: microbial metabolite signaling, vagal and enteroendocrine neural signaling, immune and inflammatory signaling arising from intestinal barrier function, and hypothalamic–pituitary–adrenal (HPA) axis regulation. Each is considered in turn below, followed by an evaluation of intervention strategies that target this axis.

Short-Chain Fatty Acid Signaling

Dietary fiber that escapes host digestion is fermented by colonic bacteria into short-chain fatty acids (SCFAs), principally acetate, propionate, and butyrate. Butyrate serves as the primary energy substrate for colonocytes but also crosses the blood–brain barrier, where it functions as a histone deacetylase inhibitor, promoting histone acetylation and altering transcriptional programs in neurons and glia. SCFAs additionally regulate microglial maturation and morphology; germ-free mice display immature, hyper-ramified microglia that are substantially normalized by SCFA supplementation, implicating these metabolites in the maintenance of normal neuroimmune surveillance. SCFAs further support blood–brain barrier integrity by upregulating tight-junction protein expression in brain endothelial cells, a mechanism with direct relevance to the neuroinflammatory hypotheses of depression discussed below.

Tryptophan Metabolism and the Kynurenine Pathway

Approximately ninety percent of the body's serotonin is synthesized in the gut, primarily by enterochromaffin cells, and the microbiota exerts substantial influence over this process by regulating the availability of its precursor, dietary tryptophan. Certain bacterial taxa, notably spore-forming species within the Clostridia class, promote host serotonin biosynthesis by elevating enterochromaffin cell tryptophan hydroxylase expression. Independently, the microbiota diverts a substantial fraction of dietary tryptophan away from serotonin synthesis and toward the kynurenine pathway, generating metabolites including kynurenic acid and quinolinic acid. Quinolinic acid is an NMDA-receptor agonist with excitotoxic potential, while kynurenic acid is an NMDA-receptor antagonist; the balance between these two metabolites, which is sensitive to microbial and inflammatory status, has been proposed as a mechanistic link between dysbiosis, low-grade inflammation, and glutamatergic dysfunction observed in mood disorders.

Enteroendocrine and Vagal Afferent Signaling

Enteroendocrine cells embedded in the gut epithelium detect luminal microbial metabolites, including SCFAs and secondary bile acids, and transduce these signals into afferent vagal nerve activity that projects to the nucleus tractus solitarius and, from there, to limbic and cortical structures. This neural route operates on a timescale of seconds to minutes, far faster than metabolite or cytokine diffusion through systemic circulation, and several rodent studies have shown that the behavioral effects of specific probiotic strains are abolished by subdiaphragmatic vagotomy, directly implicating vagal afferent signaling as a necessary mechanistic route for at least some microbiota-to-brain effects.

Intestinal Permeability and Neuroinflammation

The intestinal epithelium, sealed by tight-junction proteins such as occludin and the claudin family, ordinarily restricts luminal bacterial components to the gut lumen. Dysbiosis, dietary factors, and chronic psychological stress can each compromise this barrier, a state commonly termed increased intestinal permeability, permitting translocation of bacterial lipopolysaccharide (LPS) and peptidoglycan into the portal and systemic circulation. Circulating LPS engages toll-like receptor 4 on circulating monocytes and on brain-resident microglia, triggering nuclear factor kappa B signaling and the release of pro-inflammatory cytokines including interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha. Elevated peripheral inflammatory markers are among the most consistently replicated biological findings in major depressive disorder, and experimentally induced systemic inflammation in healthy volunteers reliably produces transient depressive and anxiety-like symptoms, together supporting a plausible causal chain from barrier dysfunction to mood disturbance via innate immune activation.

Hypothalamic–Pituitary–Adrenal Axis Regulation

The hypothalamic–pituitary–adrenal axis, the principal neuroendocrine mediator of the physiological stress response, is itself shaped by microbial colonization. Germ-free mice display an exaggerated corticosterone and adrenocorticotropic hormone response to restraint stress relative to conventionally colonized animals, an abnormality that is substantially reversed by colonization with a defined microbial community early in life but not in adulthood, indicating a developmental window of particular sensitivity. Because glucocorticoid signaling in turn regulates intestinal barrier permeability and microbial community composition, the HPA axis, the microbiota, and gut barrier integrity together form a feedback loop in which chronic stress and dysbiosis may reinforce one another over time.

Clinical and Translational Evidence

Clinical translation of these mechanisms remains at an early stage. Meta-analyses of probiotic and 'psychobiotic' interventions in depressive and anxiety symptoms report modest but statistically significant effects, generally smaller than those of established pharmacotherapy, with substantial heterogeneity in strain selection, dosing, and outcome measurement across trials. Fecal microbiota transplantation from depressed human donors to germ-free or antibiotic-treated rodents transfers depressive-like behavioral phenotypes, offering some of the strongest available evidence for a causal microbial contribution, though the degree to which rodent behavioral assays capture human depressive symptomatology remains debated. Dietary pattern interventions, particularly Mediterranean-style diets rich in fiber and polyphenols, have shown more consistent, if still modest, antidepressant benefit in randomized trials, plausibly acting in part through the SCFA and barrier-integrity mechanisms reviewed above.

Conclusion

The gut–brain axis provides a coherent, molecularly grounded framework linking intestinal microbial ecology to central nervous system function through short-chain fatty acid signaling, tryptophan-kynurenine metabolism, vagal afferent neurotransmission, innate immune activation secondary to barrier dysfunction, and hypothalamic–pituitary–adrenal axis regulation. Preclinical evidence for each of these mechanisms is substantial, and each offers plausible, testable explanations for the epidemiological association between dysbiosis and psychiatric illness. Clinical evidence in humans, while growing, remains more modest in effect size and more heterogeneous in methodology than the preclinical literature would predict, reflecting both the biological complexity of the human microbiome and the current immaturity of standardized psychobiotic intervention protocols. Future progress will likely depend on strain-specific mechanistic studies, longitudinal human cohorts capable of establishing

temporal precedence between microbial change and symptom onset, and the development of microbiota-informed biomarkers that can guide individualized dietary, probiotic, or pharmacological intervention within a precision psychiatry framework.

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LIVER LACERATION, HEMOPNEUMOTHORAX AND MULTIPLE COMPLICATIONS DURING A PROLONGED INTENSIVE CARE COURSE FOLLOWING POLYTRAUMA: A CASE REPORT

POLİTRAVMA SONRASI GELİŞEN KARACİĞER LASERASYONU, HEMOPNÖMOTORAKS VE UZAMIŞ YOĞUN BAKIM SÜRECİNDE MULTİPL KOMPLİKASYONLAR: BİR OLGU SUNUMU

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ABSTRACT

Objective: Multiple organ injuries following high-energy trauma are associated with high morbidity and mortality. In particular, liver injuries due to blunt abdominal trauma accompanied by thoracic trauma constitute emergencies requiring rapid and accurate decision-making. In this study, we aimed to present the diagnostic and treatment process of a patient who suffered severe polytrauma after a traffic accident and recovered at the end of a complicated intensive care course lasting approximately two months.

Material and method: A 30-year-old female patient was brought to the emergency department with impaired consciousness following a pedestrian-vehicle traffic accident. The patient, who had a Glasgow Coma Scale score of 8 and was tachycardic and hypoxemic, underwent bilateral tube thoracostomy and was intubated. Emergency laparotomy was performed after active intra-abdominal bleeding was detected on FAST ultrasonography and computed tomography; primary suturing and packing were applied due to a deep laceration in liver segments 6-7. Simultaneous thoracotomy with right upper lobectomy and middle lobe wedge resection was performed. The case was retrospectively evaluated in terms of the complications and treatment approaches that developed during the intensive care course.

Results: Depacking and liver segmentectomy were performed on postoperative day 2. During intensive care follow-up, the patient developed ventilator-associated pneumonia due to multidrug-resistant Acinetobacter baumannii, candidemia, deep vein thrombosis, focal epileptic seizures, and persistent bile leakage; due to the bile leak, ERCP was performed three times, and a biliary stent was placed twice. Tracheostomy was performed on day 38 due to the need for prolonged mechanical ventilation; cardiac arrest occurred on day 43 due to inadequate ventilation through the tracheostomy cannula and on day 46 during cannula exchange, and emergency endotracheal intubation performed via the stoma on day 46 was lifesaving. Following an unplanned extubation due to a secretion plug on day 47, the patient was observed to be breathing spontaneously without requiring reintubation. The patient was discharged in good health without neurological sequelae on the 86th day of hospitalization.

Conclusion: Early damage-control surgery is lifesaving in combined thoraco-abdominal injuries following severe polytrauma; however, it should be kept in mind that respiratory, infectious, biliary, neurological, and thromboembolic complications may develop during the intensive care course of these patients, and a continuous multidisciplinary approach with close nursing observation should be maintained.

Keywords: Polytrauma, Liver laceration, Tracheostomy complication, Damage control surgery, Intensive care

ÖZET

Amaç: Yüksek enerjili travmalar sonrası gelişen çoklu organ yaralanmaları yüksek morbidite ve mortalite ile seyretmektedir. Özellikle künt batın travmasına bağlı karaciğer yaralanmaları ile eşlik eden toraks travmaları, hızlı ve doğru karar verilmesini gerektiren acil durumlardır. Bu çalışmada, trafik kazası sonrası ağır politravma geçiren ve yaklaşık iki aylık komplike bir yoğun bakım süreci sonunda iyileşen bir olgunun tanı ve tedavi süreciyle birlikte sunulması amaçlanmıştır.

Materyal ve Yöntem: Otuz yaşında kadın hasta, araç dışı trafik kazası sonrası bilinç bulanıklığı ile acil servise getirildi. Glasgow Koma Skalası 8 olan, taşikardik ve hipoksemik hastaya bilateral tüp torakostomi uygulanarak entübe edildi. FAST-USG ve bilgisayarlı tomografide batın içi aktif kanama saptanması üzerine acil laparotomi yapıldı; karaciğer segment 6-7'de derin laserasyon nedeniyle primer sütür ve packing uygulandı. Eş zamanlı torakotomi ile sağ üst lobektomi ve orta lob wedge rezeksiyonu gerçekleştirildi. Olgu, yoğun bakım süreci boyunca gelişen komplikasyonlar ve tedavi yaklaşımları açısından retrospektif olarak değerlendirildi.

Bulgular: Postoperatif 2. günde depacking ve karaciğer segmentektomisi yapıldı. Yoğun bakım izleminde çoklu ilaç dirençli Acinetobacter baumannii'ye bağlı ventilatör ilişkili pnömoni, kandidemi, derin ven trombozu, fokal epileptik nöbet ve persistan safra kaçağı gelişti; safra kaçağı nedeniyle üç kez ERCP yapıldı ve iki kez biliyer stent yerleştirildi. Uzamış mekanik ventilasyon ihtiyacı nedeniyle 38. günde trakeostomi açıldı; 43. günde trakeostomi kanülünden yetersiz ventilasyona bağlı, 46. günde ise kanül değişimi sırasında olmak üzere iki ayrı kardiyak arrest gelişti, 46. günde stoma yoluyla yapılan acil endotrakeal entübasyon hayat kurtarıcı oldu. 47. günde sekresyon tıkacına bağlı planlanmamış ekstübasyon sonrası hasta reentübe edilmeden spontan solunumda izlendi. Hasta yatışının 86. gününde nörolojik sekelsiz olarak şifa ile taburcu edildi.
Sonuç: Ağır politravma sonrası gelişen kombine toraks-batın yaralanmalarında erken damage-control cerrahisi hayat kurtarıcıdır; ancak bu hastaların yoğun bakım sürecinde solunumsal, enfeksiyöz, biliyer, nörolojik ve tromboembolik komplikasyonların gelişebileceği unutulmamalı, sürekli multidisipliner yaklaşım ve yakın hemşirelik gözlemi sürdürülmelidir.
Anahtar Kelimeler: Politravma, Karaciğer laserasyonu, Trakeostomi komplikasyonu, Hasar kontrol cerrahi, Yoğun bakım

GİRİŞ

Yüksek enerjili travmalar sonrası gelişen çoklu organ yaralanmaları, morbidite ve mortalitesi yüksek klinik tablolardır. Özellikle künt batın travmasına bağlı karaciğer yaralanmaları ile eşlik eden toraks travmaları (hemopnömotoraks, kot fraktürleri), hastane öncesi ve erken hastane döneminde hızlı ve doğru karar verilmesini gerektiren acil durumlardır. “Damage control” cerrahi prensipleri (kanama kontrolü, geçici paketleme, planlı re-operasyon) bu tür olgularda hayat kurtarıcı olabilmektedir [1]. Ancak bu hastaların yoğun bakım sürecinde uzamış mekanik ventilasyon, nozokomiyal enfeksiyonlar, biliyer/intraabdominal komplikasyonlar ve nörolojik olaylar gibi ikincil sorunlarla sıklıkla karşılaşılmaktadır. Bu yazıda, trafik kazası sonrası ağır politravma geçiren ve iki aylık komplike bir yoğun bakım süreci sonunda iyileşen bir olgu, tanı ve tedavi süreciyle birlikte sunulmuştur.

GELİŞME

Başvuru ve İlk Değerlendirme

Otuz yaşında kadın hasta, araç dışı trafik kazası sonrası bilinç bulanıklığı ile acil servise getirildi. Yakınları eşlik etmediğinden ayrıntılı anamnez alınamadı. Genel durumu kötü, bilinci letarjik; Glasgow Koma Skalası 8 (E:2, M:4 V:2), Vital bulguları: taşikardik (nabız ~160/dk), TA: 100/64 mmHg ve SpO2:89. İlk değerlendirmede sağ pnömotoraks saptanarak 5. interkostal aralıktan tüp torakostomi uygulandı; hava kaçağı ve hemorajik drenaj izlendi. Hasta acil şartlarda entübe edildi; zorlu havayolu olarak değerlendirildi. Sol hemitorakstan da tüp torakostomi uygulandığı (bilateral toraks tüpü) belirtildi.

Laboratuvar (başvuru): Hb 13,8→7,2 g/dL’ye düşüş, WBC 16,35×10⁹/L, PLT 166×10⁹/L, ALT 747 U/L, AST 799 U/L, INR 1,23, CRP 28,1 mg/L.

Yatak başı FAST-USG ve BT bulguları ile batın içi aktif kanama saptanarak hayati risk nedeniyle acil laparotomi kararı alındı.

İlk Cerrahi Girişimler (Yatış günü)

Tanısal laparotomi + karaciğer primer sütürü (Genel Cerrahi): Batında yaygın hemorajik mayi izlendi; dalak ve pelvis doğaldı, barsaklarda patoloji saptanmadı. Karaciğer segment 6-7’de 10 cm’den derin laserasyon alanı tespit edildi. Bipolar/monopolar koter ile kanama kontrolü sağlandı, çoklu Z-sütür ile parankim yaklaştırıldı, hemostatik ajan uygulandı. Sağ diyaframın vaka boyunca bombeleşerek görüş alanını kapatması ve satürasyon düşüklüğü üzerine intraop göğüs cerrahisi konsülte edildi. Kanamanın sızıntı tarzında devam etmesi nedeniyle karaciğer çevresine 4 adet kompresle packing (paketleme) uygulandı; subhepatik alan, dalak lojuna ve pelvise dren yerleştirildi.

Torakotomi + sağ üst lobektomi + orta lob wedge rezeksiyonu (Göğüs Cerrahisi): Masif hava kaçağı ve hızlı desatürasyon nedeniyle yapılan bronkoskopide entübasyon tüpünün sağ ana bronşa kaçtığı görülüp trakeaya geri çekildi. Sol lateral dekübit pozisyonda sağ 5. interkostal aralıktan posterolateral torakotomi yapıldı; diyaframın yükselmiş, sağ alt lobun kollabe olduğu, deplase kot fraktür hattının üst lobu yaygın lasere ettiği görüldü. Yaygın parankimal laserasyon ve bronş kaçağı nedeniyle sağ üst lobektomi ve orta

lob laserasyon alanına wedge rezeksiyon uygulandı; toraksa 28F göğüs tüpü yerleştirildi. Hasta entübe olarak yoğun bakıma devredildi.
Patoloji: Sağ üst lobektomi ve orta lob wedge rezeksiyon materyalinde kanama, konjesyon ve reaktif pnömosit hiperplazisi; kot biyopsisinde kırık kallusu saptandı.
Erken Yoğun Bakım Süreci (Postop 1-4. gün)
Hasta erişkin yoğun bakım ünitesine entübe, sedatize, inotrop desteksiz olarak kabul edildi. Sağ femoral hemodiyaliz kateteri, sağ radiyal arter kanülü, bilateral toraks tüpleri ve üç adet batın dreni mevcuttu. Postoperatif kan gazında ağır metabolik asidoz (pH 7,0, laktat 3,2 mmol/L, BE −14) izlendi; 4 ünite eritrosit süspansiyonu, 4 ünite taze donmuş plazma, 2 ünite aferezli trombosit ve yaklaşık 11 litre dengeli elektrolit solüsyonu replasmanı yapıldı.
Postop 2. günde nöroşirürji konsültasyonunda (spinal BT'de lomber transvers proses fraktürleri saptanmış, akut nöroşirürjikal girişim gerektirmedi) çelik korse önerisi verildi. Genel cerrahi tarafından depacking planlanan hasta postop 2. günde tekrar ameliyata alındı:
Re-operasyon – Karaciğer segmentektomi + primer sütür: Önceki packing kompresleri çıkarıldı; segment 6-7'deki iki laserasyon alanı arasındaki nekrotik parankim ve safra sızıntısı olan doku eksize edildi, defekte omentum yerleştirilerek karaciğer sütürüyle onarım tamamlandı, batın drenajı sağlanarak kapatıldı.
Postoperatif dönemde batın drenlerinden safralı geliş persiste etti; genel cerrahi tarafından parenteral beslenmeye devam edilmesi, safra kaçağı açısından takip önerildi.

Enfeksiyöz Komplikasyonlar
Yatışında ampirik seftriakson/metronidazol başlanan hastanın ilerleyen günlerde ateşi yükseldi, akut faz reaktanları progrese oldu; kan kültüründe gram pozitif kok üremesi üzerine tedavisi Meropenem, Vankomisin olarak düzenlendi.
•Yatışın 9. günü: Trakeal aspirat kültüründe çoklu ilaç dirençli (yalnızca kolistine duyarlı) Acinetobacter baumannii üremesi → ventilatör ilişkili pnömoni (VİP) düşünüldü; meropenem kesilerek polimiksin B + inhaler kolistin tedavisine geçildi.
•Takip eden haftalarda hastanın Prokalsitonin ve CRP değerleri süreç boyunca dalgalı seyretti (CRP aralığı ~45–291 mg/L, prokalsitonin zaman zaman >10 ng/mL). Tekrarlayan kan/idrar/trakeal aspirat kültürleri ve antibiyogram sonuçlarına göre tedavisi günlük enfeksiyon hastalıkları konsültasyonları ile ampirik olarak tigesiklin, sulbaktam, flukonazol kombinasyonları şeklinde tedavisi düzenlendi.
•Kandidemi: Kan kültüründe Candida türü üremesi (flukonazol MIC değeri yüksek saptanarak dirençli kabul edildi) üzerine flukonazol kesilip mikafungin başlandı, sağ femoral kateteri çekilerek periferik damar yollarından tedavileri devam edildi.

Solunumsal Seyir ve Trakeostomi
Hastada tekrarlayan weaning (ayırma) başarısızlıkları izlendi; spontan/PSV modlara geçiş denemeleri taşikardi ve takipne ile sonuçlanınca defalarca kontrollü moda dönülmek zorunda kalındı. Sağ akciğerde atelektazi ve sekresyon birikimi nedeniyle göğüs cerrahisi tarafından tekrarlayan bronkoskopik temizlik işlemleri uygulandı.
•Yatışın 19. ve 27. günlerinde çekilen toraks BT'lerinde: Bilateral hemotoraks/plevral efüzyon, yaygın buzlu cam dansiteleri (kontüzyon), bilateral kot fraktürleri, postoperatif değişiklikler ve atelektatik alanlar izlendi.
•Yatışın 38. günü: Uzamış mekanik ventilasyon ihtiyacı nedeniyle elektif trakeostomi açıldı.
•Yatışın 43. günü: Trakeostomi kanülünden yeterli ventilasyon sağlanamaması üzerine gelişen kardiyak arrest nedeniyle yaklaşık 5 dakikalık kardiyopulmoner resüsitasyon (KPR) uygulandı ve spontan dolaşım sağlandı; kanülden yeterli havalanma olmadığı için hasta tekrar orotrakeal entübe edildi. Kardiyoloji konsültasyonunda anlamlı kapak vejetasyonu saptanmadı.
•Yatışın 44. günü: Trakeostomi kanülü, göğüs cerrahisi tarafından yatak başında sedo-analjezi eşliğinde eski yerinden tekrar takıldı.

Yatışın 46. Günü – Akut Trakeostomi Kanül Tıkanıklığı, Acil Hava Yolu Krizi ve İkinci Kardiyak Arrest
Sabah devir teslimi sırasında hastanın satürasyonunun kademeli olarak %96'dan %86'ya gerilediği fark edildi. Ventilatör kontrol edildiğinde, ayarlanan hedeflere rağmen yalnızca 80-90 mL tidal volüm

oluştuğu görüldü. Kanülün trakea dokusuna dayanmış olabileceği düşünülerek kanül ve boyun pozisyonu değiştirildi, ancak tidal volümde herhangi bir artış sağlanamadı. Kanül içi tıkaç şüphesiyle acil aspirasyon denendi; aspirasyon sondası ilerletilemedi, yıkamalı aspirasyon da başarısız oldu. Desatürasyonun devam etmesi üzerine ambu ile (yüksek basınç uygulanmadan) manuel ventilasyon denendi, ancak hasta bu şekilde de havalandırılamadı.

Satürasyonun %60'lara gerilemesi üzerine acil orotrakeal entübasyona geçildi; ancak hasta o anda kürarize olmadığından dişlerini sıkması nedeniyle ağız açıklığı anlık olarak sağlanamadı. Kas gevşetici etkisinin başlaması beklenirken desatürasyon derinleşti (SpO_2 %20-30) ve nabız düşmeye başladı. Bu kritik anda trakeostomi kanülü çıkarılarak trakeostomi stoma sahasından endotrakeal tüp yerleştirildi; bu manevra ile satürasyon %60'lara yükseltilerek etkin ventilasyon sağlandı. Bu aşamada kardiyak arrest gelişmedi; tüpten ventilasyon sonrası satürasyon ve nabız hızla toparladı, ventilatörde hedeflenen tidal volümlere ulaşıldı. Bu sırada kürarize edilen hasta orotrakeal entübe edilerek trakeostomi deliğindeki tüp çekilerek delik pansumanla kapatıldı.

Ancak işlem sonrası cilt altı amfizem gelişmesi üzerine acil PA akciğer grafisi istenerek göğüs cerrahisine konsülte edildi. Grafide sol pnömotoraks saptandı, göğüs cerrahisi tarafından sol tüp torakostomi uygulandı, hasta düşük basınçlı basınç-kontrollü modda ventile edilmeye başlandı. Kontrol grafisinde sol akciğerin ekspanse olduğu doğrulandı. Aynı seansta göğüs cerrahisi tarafından bir kez daha trakeostomi kanülü bronkoskopi eşliğinde yerleştirildi ve orotrakeal tüp çekildi.

Gün içerisindeki takiplerde önceki kullanılan kanüllerle aynı çapta (7,5 numara) olan yeni kanülün kafı yeterince şişirilmiş olmasına rağmen ağız ve burundan belirgin hava kaçağı izlendi; ventilatör %80-90 oranında kaçak uyarısı vermeye devam etti (toraks tüpünde osilasyon mevcuttu, ancak hava kaçağı yoktu). Göğüs cerrahisi ile tekrar görüşülerek daha büyük çaplı kanüle geçilmesi planlandı.

Saat 16:30 sularında göğüs cerrahisi tarafından bronkoskopi eşliğinde kanül değişimi işlemi sırasında hasta ani bradikardik hale geldi ve nabız alınamadı. İvedilikle bir kez daha endotrakeal entübasyon uygulandı, yaklaşık 5 dakika KPR yapıldı, 2 ampul adrenalin uygulandı ve spontan dolaşım sağlandı. İzleyen saatlerde hastanın bilincinin hızla açıldığı gözlendi. Bu olay sonrasında hasta orotrakeal entübe olarak takibe alındı; trakeostomi kanülüne bu aşamada dönülmedi.

Yatışın 47. Günü – Endotrakeal Tüp Tıkanıklığına Bağlı Zorunlu (Planlanmamış) Ekstübasyon

Sabah devir teslimi sırasında hasta bilinci açık, koopere, hemodinamisini bozmayan hafif bir taşikardi ile ve iyi ventile olur durumda (bilateral akciğer sesleri rahat alınır, düşük basınçla yeterli tidal volüm oluşturur şekilde) devralındı. Yakın takipte herhangi bir ventilasyon sorunu izlenmezken, saat 09:00 sularında tidal volümde ani düşüş (<100 mL) gözlendi; hasta bilinci açık halde spontan solunum çabası gösterirken ventilatörden ayrıldı ve tüpten hava geçişi olmadığı saptandı. İvedilikle tüp kafı ve bağı kesilerek tüp çıkarıldı; tüp içerisinde sekresyon tıkacı izlendi. Ekstübasyon sonrası hasta spontan solumaya başladı, bilinci kapanmadı ve desatüre olmadı. Bilincinin açık ve spontan solunumunun yeterli olması nedeniyle hasta tekrar entübe edilmedi; $ETCO_2$ ve SpO_2 ile sürekli izlem, sık-aralıklı kan gazı takibi, nazotrakeal aspirasyon ve öksürerek sekresyon atımı için teşvik ile konservatif takip planlandı.

Sağ Alt Ekstremite Derin Ven Trombozu

Yatışın 47. gününde sağ bacakta çap artışı fark edilmesi üzerine Doppler ultrasonografi istendi ve sağ femoral vende derin ven trombozu (DVT) saptandı. Kalp-damar cerrahisi konsültasyonu istendi; hastanın tromboprofilaktik dozda aldığı düşük molekül ağırlıklı heparin (enoksaparin) tedavi (terapötik) doza yükseltildi. Bu komplikasyon, uzamış immobilizasyon, kritik hastalık, santral/femoral kateterizasyonu ve travma sonrası hiperkoagülabl durumun bir arada bulunduğu bu olguda beklenen bir risk olarak değerlendirilmiştir [2].

Tekrarlayan Sağ Akciğer Kollapsı Nedeniyle Elektif Entübasyon-Bronkoskopi Uygulamaları

Ekstübe takip edilen hastada, sağ akciğerde tekrarlayan total kollaps/atelektazi epizotları izlenmiştir. Yatışın 53. gününde sağ akciğerde total olarak kapalı görünüm alması üzerine hasta elektif şartlarda entübe edilerek terapötik bronkoskopi ile sekresyonlar temizlenmiş, işlem sonrası akciğerin açıldığı doğrulanarak hasta aynı gün ekstübe edilmiştir. Yatışın 55. gününde Endoskopik Retrograd Kolanjiyopankreatografi (ERCP) öncesi yapılan değerlendirmede sağ akciğerin yine kapalı olduğu görülmesi üzerine benzer şekilde elektif entübasyon ve bronkoskopi uygulanmış; hasta bu kez entübe halde ERCP işlemine alınmış, işlem entübe olarak tamamlanmış ve aynı gün içinde tekrar ekstübe edilmiştir.

Bu tekrarlayan epizotlar, enfektif süreçler, uzamış immobilizasyon, ve zayıflamış öksürük refleksine bağlı sekresyon birikiminin, ekstübe kritik hastalarda dahi elektif bronkoskopik girişim gerektirebileceğini göstermektedir.

Biliyer Komplikasyon ve ERCP

Batın drenlerinden persistan safralı drenaj nedeniyle yapılan görüntülemelerde belirgin biloma/apse saptanmamakla birlikte biliyer kaçak şüphesi devam etti. Gastroenteroloji tarafından planlanan ilk ERCP girişimi hastanın işlemi tolere edememesi nedeniyle tamamlanamadı; ikinci denemede (yatışın 19. günü) ERCP ile plastik biliyer stent başarıyla yerleştirildi (başlangıçta 2 ay sonra çıkarılması planlanmıştı) [3]. İşlem sonrası safra drenajında belirgin azalma izlendi.

Takip sürecinde, planlanan sürenin öncesinde, yatışın 55. gününde kaçak kontrolü amacıyla tekrar ERCP yapıldı ve bilier stent çıkarıldı. Ancak sonrasında batın dreninden gelen sıvı miktarının artması üzerine yatışın 72. gününde üçüncü kez ERCP uygulanarak yeniden biliyer stent yerleştirildi.

Nörolojik Komplikasyon

Yatışın 27. günü: Hastada sağ yüz yarısında klonik kasılma ve sağ göz kapağında düşme şeklinde ani başlayan bulgular üzerine nöroloji konsültasyonu istendi; bulgular fokal epileptik nöbet olarak değerlendirildi. Levetirasetam 2000 mg yükleme dozu sonrası 500 mg 2×1 idame tedavisi başlandı; acil beyin BT'sinde akut patoloji saptanmadı. Daha sonra yapılan MR görüntülemeler ve EEG'de de nöbeti açıklayacak patoloji izlenmedi. Hastanın takibinde daha sonra nöbeti tekrarlamadı.

İyileşme Süreci ve Servis Devri

Yatışının ilk haftasından itibaren aktif ve pasif ROM egzersizleri devam edildi. Ekstübasyon öncesi hastanın bilinç ve vital bulgular olarak uygun olduğu dönemlerde ve ekstübasyon sonrası sürekli olarak solunum egzersizi uygulandı. 55. günden itibaren hastanın genel durumunda progresif iyileşme gözlendi; oral beslenmeye geçildi, antibiyoterapi enfeksiyon parametrelerindeki gerilemeye paralel olarak daraltıldı. Yatışın 62. gününde hasta, bilinci açık, oryante, koopere durumda, erişkin yoğun bakım ünitesinden göğüs cerrahisi servisine devredildi.

Göğüs cerrahisi servisinde yatışın 65. gününe kadar takip edilen hastaya antibiyoterapisine devam edildi ve solunum rehabilitasyonu uygulandı. Bu süreçte batın dreninden gelen sıvının karakterinin pürülan hal alması üzerine hasta genel cerrahi servisine devredildi.

Genel cerrahi servisindeki takibinde enfeksiyon hastalıkları kontrolünde antibiyotik tedavisi düzenlendi, 72. günde ERCP ile ikinci kez bilier stent yerleştirildi. Tedavilere yanıt alınması üzerine hasta yatışın 86. gününde, oral antibiyoterapi ile önerilerle birlikte şifa ile taburcu edilmiştir.

TARTIŞMA

Bu olgu, künt travmaya bağlı gelişen ağır karaciğer laserasyonu ve hemopnömotoraksın "damage control" prensipleriyle başarılı şekilde yönetildiği, ancak sonrasında gelişen yoğun bakım komplikasyonlarının uzun ve multidisipliner bir tedavi süreci gerektirdiği bir vakayı temsil etmektedir. Karaciğer travmalarında hemodinamik olarak instabil hastalarda ilk basamak, kanama kontrolüdür; ciddi olgularda "packing" ile geçici tamponad sağlanıp planlı re-laparotomi ile definitif onarım yapılması güncel literatürle uyumlu bir yaklaşımdır. Bu olguda olduğu gibi, travmatik karaciğer laserasyonlarına eşlik eden safra yolu yaralanmaları sıklıkla gözden kaçabilmekte ve postoperatif dönemde persistan biliyer drenaj ile ortaya çıkabilmektedir; bu durumda ERCP ile stent yerleştirilmesi hem tanısal hem tedavi edici bir yöntem olarak öne çıkmaktadır [3].

Toraks travmalarında masif hava kaçağı ve akciğer parankim yaralanmalarının anatomik rezeksiyon (lobektomi/wedge rezeksiyon) gerektirebilmesi, konservatif yöntemlerin (tüp torakostomi, primer onarım) yetersiz kaldığı ağır olgularda beklenen bir durumdur.

Trakeostomili hastalarda akut kanül tıkanıklığı veya malpozisyonu, hızla hayatı tehdit eden bir hava yolu acilidir ve saniyeler içinde müdahale gerektirir [4]. Bu olguda kanül içi obstrüksiyon şüphesiyle yapılan aspirasyon denemelerinin başarısız olması, ardından ambu ile ventilasyonun da sağlanamaması, "can't ventilate" tablosuna işaret etmektedir. Böyle bir durumda kanülün çıkarılıp trakeostomi stoma sahasından endotrakeal tüp ilerletilmesi, tanınmış kurtarma manevralarından biridir [4] ve bu olguda hayat kurtarıcı olmuştur.

Ancak hastanın kürarize olmaması nedeniyle orotrakeal/transtrakeal entübasyonun anlık olarak gecikmesi, kritik hava yolu yönetiminde önceden hazırlanmış hızlı ardışık entübasyon (RSI) protokolü ve kas gevşetici ajanların yatak başında hazır bulundurulmasının önemini vurgulamaktadır. Ayrıca acil stoma yoluyla tüp yerleştirme girişimlerinin, tüpün istenmeyen şekilde ilerlemesi/malpozisyonu sonucu iyatrojenik pnömotoraksa yol açabileceği unutulmamalı, işlem sonrası klinik ve radyolojik doğrulama rutin hale getirilmelidir. Nitekim İngiltere Kraliyet Anestezistler Koleji'nin Dördüncü Ulusal Denetim Projesi (NAP4), trakeostomili hastalardaki hava yolu olaylarının önemli bir kısmının yoğun bakım ortamında meydana geldiğini ve bu olguların ölüm/kalıcı beyin hasarı ile sonuçlanma oranının yüksek olduğunu göstermiştir [5,6]. Bu olguda ayrıca aynı çaptaki tüple dahi belirgin kaf çevresi hava kaçağının izlenmesi, trakeal/stoma çapı ile tüp/kanül uyumsuzluğunun tekrarlayan ventilasyon yetersizliklerine ve nihayetinde kanül değişimi sırasında gelişen ikinci kardiyak arreste zemin hazırlamış olabileceğini düşündürmektedir; bu da trakeostomili kritik hastalarda kanül değişiminin, mümkünse ek personel, video-laringoskopi/bronkoskopi desteği ve resüsitasyon ekibi hazır bulunacak şekilde planlı ve kontrollü koşullarda yapılmasının önemine işaret etmektedir.

Uzamış yoğun bakım yatışı olan politravma hastalarında ventilatör ilişkili pnömoni [7], özellikle çoklu ilaç dirençli Gram-negatif patojenler (bu olguda A. baumannii) [8] ve invaziv kandidiyazis [9], mortaliteyi belirgin şekilde artıran komplikasyonlardır. Bu olguda olduğu gibi tekrarlayan kültür takibi ve enfeksiyon hastalıkları ile yakın işbirliği, uygun antibiyotik/antifungal seçiminde kritik önem taşımaktadır. Ayrıca travma sonrası gelişen fokal nöbetler ve kardiyak arrest gibi olaylar, kritik hasta yönetiminde sürekli çok disiplinli izlemin gerekliliğini bir kez daha ortaya koymaktadır.

SONUÇ

Ağır politravma sonrası gelişen kombine toraks-batın yaralanmalarında erken damage-control cerrahisi hayat kurtarıcıdır; ancak bu hastalarda yoğun bakım sürecinde solunumsal, enfeksiyöz, biliyer, nörolojik ve tromboembolik komplikasyonların gelişebileceği unutulmamalı ve multidisipliner yaklaşım sürdürülmelidir.

Yaklaşık üç aylık hastane yatışı boyunca sayısız kritik olay yaşanmasına rağmen hasta nörolojik sekelsiz olarak iyileşmiş ve şifa ile taburcu edilmiştir. Özellikle yatışın 46. gününde gelişen ve trakeostomi kanülü tıkanıklığına bağlı ventilasyon yetersizliğiyle seyreden hava yolu acilinin, kanülün stoma sahasından endotrakeal tüple değiştirilmesi yoluyla zamanında yönetilmesi; ertesi gün (yatışın 47. günü) yeni yerleştirilen tüpün akut sekresyon tıkacıyla obstrükte olması üzerine ekip tarafından güvenli şekilde ekstübasyon uygulanarak hastanın reentübasyon gerektirmeden spontan solunumda izlenebilmesi, klinik seyrin dönüm noktaları olarak değerlendirilmiştir. Bu dönemde hasta başında sürdürülen yakın hemşirelik gözlemi, olası solunum yetersizliğinin erken tanınması ve müdahale edilmesinde önemli katkı sağlamıştır. Bu olgu, kritik politravma hastalarının yönetiminde cerrahi ve yoğun bakım tedavisinin yanı sıra sürekli yatak başı gözlem ve ekip koordinasyonunun da klinik sonucu belirleyen önemli bir bileşen olduğunu ortaya koymaktadır.

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FERMENTED FOODS AS MODULATORS OF THE GUT MICROBIOME: IMPLICATIONS FOR METABOLIC, IMMUNE AND BRAIN HEALTH

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Background
Fermented foods have been part of the human diet for thousands of years, and increasing scientific attention has recently focused on their potential effects on the gut microbiome, immune regulation, metabolic health, and brain function. Fermentation induces complex microbial and biochemical transformations that can modify the nutritional composition, digestibility, bioavailability, and bioactive properties of foods.

Objective
This presentation aims to review the potential health effects of fermented foods, with particular emphasis on their interactions with the gut microbiome and their possible metabolic, immunological, and neuropsychological implications.

Results
Fermented foods may provide live microorganisms, microbial metabolites, polyphenols, dietary fibres, and other bioactive compounds capable of influencing the composition and metabolic activity of the intestinal microbiome. Fermentation-related changes in nutrient availability, the formation of bioactive metabolites, and the degradation of certain antinutritional compounds may contribute to the regulation of intestinal barrier integrity, immune responses, and host metabolism. Available human evidence suggests that the consumption of selected fermented foods may be associated with favourable effects on glucose metabolism, cardiometabolic health, body-weight regulation, inflammatory and immune parameters, as well as mood and cognitive function. Potential gut–brain mechanisms include microbiota-derived metabolites, immune signalling, intestinal barrier function, and neuroendocrine pathways. However, current evidence remains heterogeneous, and the biological effects of individual fermented foods cannot be generalized across all products because of substantial differences in food matrices, microbial composition, fermentation processes, and study design.

Conclusion
Fermented foods represent a promising component of functional nutrition and may influence metabolic, immune, and brain health partly through modulation of the gut microbiome and its metabolic activity. Nevertheless, further standardized, adequately powered, and well-controlled human studies are required to determine which fermented foods, microbial communities, and fermentation-derived metabolites provide clinically meaningful health benefits.
Keywords: fermented foods; gut microbiome; probiotics; short-chain fatty acids; functional nutrition; gut–brain axis

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Introduction

Fermentation is one of the oldest methods of food processing and has been used for thousands of years to improve food preservation, safety, sensory properties, and digestibility (Sawant et al., 2025). Fermented dairy products, vegetables, cereals, legumes, and other foods remain important components of traditional diets worldwide (Taveira et al., 2021). Beyond their technological role, increasing attention has focused on their potential health effects, particularly in relation to the gut microbiome, metabolic regulation, immune function, and brain health (Lehoczki, et al., 2025).

During fermentation, bacteria, yeasts, and fungi transform carbohydrates, proteins, lipids, and plant-derived compounds within the food matrix (Sawant et al., 2025). These processes may generate organic acids, bioactive peptides, vitamins, exopolysaccharides, and phenolic metabolites, while improving nutrient bioavailability and reducing certain antinutritional factors. As a result, fermented foods represent complex biological matrices containing varying combinations of microorganisms, microbial metabolites, and structurally modified nutrients (Kryczyk-Poprawa et al., 2026).

The gut microbiome plays a major role in nutrient metabolism, intestinal barrier integrity, immune homeostasis, and the production of bioactive metabolites (Sułkowska-Ziaja et al., 2026). Diet is one of its most important modifiable determinants, making fermented foods particularly relevant because they may influence both microbial composition and metabolic activity (Jarecsny, et al., 2025). Some food-associated microorganisms may transiently survive gastrointestinal transit and interact with the resident microbiota, while fermentation-derived compounds may modify the intestinal environment without requiring persistent microbial colonization (Nyáry et al., 2026).

Importantly, fermented foods should not be considered synonymous with probiotic foods. Not all fermented products contain viable microorganisms at the time of consumption, and microorganisms present in fermented foods cannot automatically be classified as probiotics without demonstrated strain-specific health benefits (Mukherjee et al., 2024). The biological effects of fermented foods may therefore arise from multiple mechanisms, including live microorganisms, microbial metabolites, improved nutrient bioavailability, bioactive peptides, and changes in the substrates available to the gut microbiota (Mukherjee et al., 2024).

Among the key mediators of host–microbiome interactions are short-chain fatty acids, bile acid metabolites, tryptophan-derived indoles, phenolic metabolites, and other microbial signalling molecules (Krautkramer et al., 2021). These compounds may influence intestinal barrier function, inflammatory and immune pathways, glucose and lipid metabolism, and communication with distant organs. Of particular interest is the microbiota–gut–brain axis, through which microbial, immune, endocrine, and neural signals may contribute to the regulation of mood, stress responses, and cognitive function (Lehoczki et al., 2025).

Human observational and interventional studies suggest that selected fermented foods may be associated with favourable effects on glucose metabolism, cardiometabolic health, body-weight regulation, inflammatory markers, and gut microbial diversity (Santa et al., 2025). Evidence regarding mental health and cognitive outcomes is emerging but remains less consistent. Interpretation is further complicated by substantial heterogeneity among fermented foods, including differences in microbial composition, food matrix, fermentation methods, storage, heat treatment, and nutrient content (Kryczyk-Poprawa et al., 2026).

This review summarizes current evidence on fermented foods as modulators of the gut microbiome, with particular emphasis on their potential metabolic, immunological, and neuropsychological effects. It also examines the main microbial and biochemical mechanisms involved and highlights key methodological limitations that must be addressed before specific fermented foods can be translated into evidence-based clinical or public health recommendations.

Methods

A narrative literature review was conducted using PubMed/MEDLINE, Scopus, and Web of Science. Relevant peer-reviewed studies published in English were identified using combinations of keywords related to fermented foods, gut microbiome, probiotics, microbial metabolites, metabolic health, immune function, inflammation, gut barrier integrity, gut–brain axis, mood, and cognitive function. Priority was given to recent systematic reviews, meta-analyses, randomized controlled trials, and well-

designed observational studies. Additional relevant references were identified from the bibliographies of selected articles. Evidence was synthesized thematically, focusing on microbiome-related mechanisms and metabolic, immunological, and neuropsychological outcomes.

Results

Fermented foods as modulators of the gut microbiome

The available evidence indicates that fermented foods may influence the gut ecosystem through several complementary mechanisms (Gao et al., 2025). Depending on the product and processing conditions, they may provide viable microorganisms, microbial metabolites, modified nutrients, bioactive peptides, phenolic derivatives, and other fermentation-derived compounds. These components can interact with the resident gut microbiota, alter substrate availability, and modify microbial metabolic activity (Table 1) (Gonçalves et al., 2026; Leeuwendaal et al., 2022).

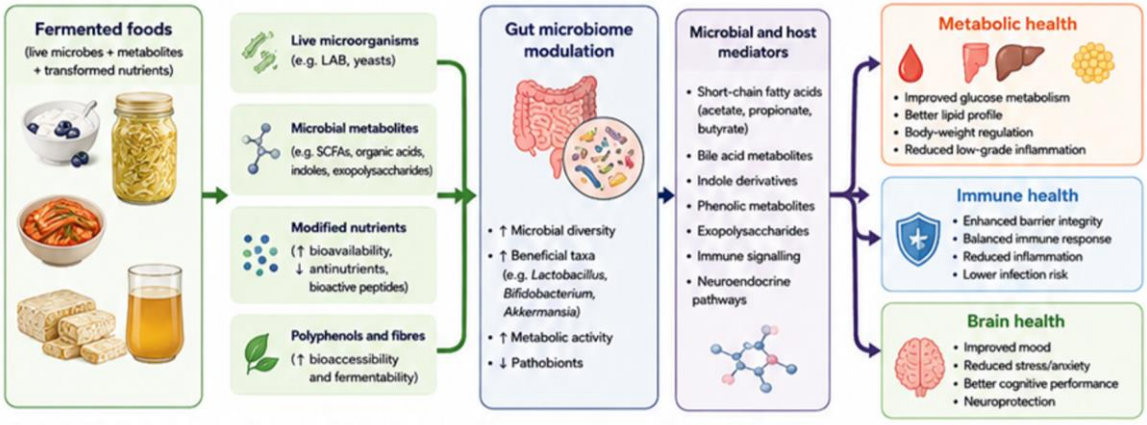
Table 1. Major fermented foods, characteristic microorganisms and potential biological relevance.

Fermented food	Main microbial groups	Important fermentation-related components	Potential microbiome-related effects	Main health domains investigated
Yogurt	*Lactobacillus delbrueckii* subsp. *bulgaricus*, *Streptococcus thermophilus*	Lactic acid, peptides, microbial biomass	Transient microbial exposure; altered substrate metabolism	Gastrointestinal, metabolic, immune
Kefir	Lactic acid bacteria, acetic acid bacteria, yeasts	Organic acids, peptides, exopolysaccharides	Potential modulation of microbial composition and function	Metabolic, inflammatory, gastrointestinal
Kimchi	*Leuconostoc*, *Lactiplantibacillus*, *Weissella* spp.	Organic acids, transformed phytochemicals	Increased exposure to lactic acid bacteria and plant-derived substrates	Metabolic, immune, gastrointestinal
Sauerkraut	Lactic acid bacteria	Lactic acid, transformed cabbage phytochemicals	Modification of intestinal microbial activity	Gastrointestinal, metabolic
Tempeh	*Rhizopus* spp. with associated bacteria	Peptides, transformed isoflavones	Improved digestibility and altered bioactive profile	Metabolic, cardiometabolic
Miso	*Aspergillus oryzae*, yeasts, bacteria	Peptides, amino acids, transformed isoflavones	Fermentation-derived metabolic compounds	Metabolic, cardiovascular
Natto	*Bacillus subtilis* var. *natto*	Poly-γ-glutamic acid, menaquinone-7, peptides	Microbial and metabolite exposure	Cardiometabolic, bone-related
Kombucha	Acetic acid bacteria and yeasts	Organic acids, transformed tea polyphenols	Potential modulation through microbial metabolites	Metabolic, oxidative and gastrointestinal
Sourdough	Lactic acid bacteria and yeasts	Organic acids, modified carbohydrates and peptides	Altered digestibility and fermentable substrate profile	Glycaemic and gastrointestinal

Food-associated microorganisms do not necessarily establish permanent colonization. Nevertheless, transient gastrointestinal passage may still allow biologically relevant interactions with resident microbes and the intestinal mucosa.

The magnitude and direction of these effects vary substantially among products because fermented foods differ in microbial composition, food matrix, processing conditions, storage, and post-fermentation heat treatment (Figure 1).

Figure 1. Proposed mechanisms linking fermented foods, the gut microbiome, and host health (Mukherjee et al., 2024).



Recent human studies generally support the capacity of selected fermented foods to modify gut microbial composition or function, although changes are not uniform across studies (Valentino et al., 2024). Effects on microbial diversity appear to depend on baseline diet, habitual fermented-food intake, host characteristics, and the type and dose of the fermented product (Gao et al., 2025).

Microbial metabolites and intestinal barrier function

Fermented foods may affect host physiology partly by modifying microbial metabolic output. Short-chain fatty acids, particularly acetate, propionate, and butyrate, are primarily generated by colonic fermentation of dietary substrates by the resident gut microbiota. These metabolites contribute to epithelial energy metabolism, maintenance of intestinal barrier integrity, immune regulation, and host metabolic signalling (Sankarganesh et al., 2025).

Other relevant mediators include secondary bile acids, tryptophan-derived indoles, phenolic metabolites, organic acids, bioactive peptides, and exopolysaccharides (Ramos et al., 2025). Collectively, these compounds may influence tight-junction integrity, mucin production, epithelial signalling, oxidative balance, and inflammatory pathways (Miller et al., 2024). The biological effects of fermented foods should therefore be considered as the result of interactions among the food matrix, food-associated microorganisms, resident gut microbiota, and host metabolism rather than as a simple probiotic effect (Biagi et al., 2012).

Metabolic health

Human observational and intervention studies suggest that selected fermented foods may favourably influence several cardiometabolic outcomes (Zhang et al., 2024). The most frequently investigated endpoints include fasting glucose, insulin sensitivity, lipid metabolism, body-weight regulation, blood pressure, and markers of systemic inflammation (Summer et al., 2025).

Potential mechanisms include modulation of gut microbial metabolism, altered bile acid signalling, increased production of microbial metabolites, improved intestinal barrier function, and changes in inflammatory tone. Fermented dairy products have been among the most extensively investigated foods, whereas evidence for fermented vegetables, legumes, and beverages is less consistent (Gonçalves et al., 2026; Jyoti & Dey, 2025; Santhiravel et al., 2022) (Table 2). Overall, the available data support a potential role for fermented foods within cardiometabolically healthy dietary patterns (Miller et al., 2024). However, product-specific effects remain difficult to disentangle from the overall nutritional quality of the diet, and direct causal evidence for individual fermented foods is still limited (Ramos et al., 2025).

Table 2. Proposed mechanisms linking fermented foods with host health

Mechanistic pathway	Key mediators	Principal target	Potential biological consequence	Evidence level
Microbial ecosystem modulation	Food-associated microorganisms, altered substrates	Gut microbiota	Changes in composition and metabolic activity	Moderate human evidence
SCFA-related signalling	Acetate, propionate, butyrate	Gut epithelium, immune and metabolic tissues	Barrier support, immune and metabolic regulation	Strong mechanistic evidence
Tryptophan metabolism	Indoles and related metabolites	Intestinal and immune signalling	Barrier regulation and gut–brain communication	Strong mechanistic, emerging clinical evidence
Bile acid metabolism	Primary and secondary bile acids	FXR/TGR5-related pathways	Metabolic and immune signalling	Strong mechanistic evidence
Phenolic biotransformation	Phenolic metabolites	Gut, vascular and neural pathways	Antioxidant and signalling effects	Moderate mechanistic evidence
Barrier modulation	Tight junctions, mucus layer	Intestinal epithelium	Reduced permeability and altered inflammatory signalling	Moderate evidence
Immune modulation	Cytokines, immune-cell signalling	Mucosal/systemic immunity	Altered inflammatory tone	Moderate human evidence
Gut–brain signalling	Metabolites, vagal, immune and endocrine pathways	Central nervous system	Potential effects on mood and cognition	Emerging hum

Immune regulation and inflammation

The gut microbiome is closely integrated with mucosal and systemic immune regulation. Fermented foods may influence immune homeostasis through microbial–epithelial interactions, microbial metabolites, and changes in intestinal barrier function (Zhang, 2022).

Human intervention data provide some evidence that diets enriched in fermented foods can influence inflammatory and immune parameters. Nevertheless, these effects should not be generalized across all fermented products. Variability in microbial strains, dose, duration, matrix composition, and host immune status probably contributes to differences between studies (Zhang, 2022).

Potential mechanisms include modulation of cytokine signalling, regulatory immune responses, epithelial barrier preservation, and microbial metabolite-mediated effects on innate and adaptive immune cells. These pathways provide a biologically plausible link between fermented-food consumption and systemic inflammatory regulation (Zhang, 2022).

Fermented foods and the microbiota–gut–brain axis

The microbiota–gut–brain axis provides a mechanistic framework through which fermented foods could influence neuropsychological outcomes (Casertano et al., 2022). Communication between the gut and the central nervous system involves microbial metabolites, immune mediators, vagal signalling, enteroendocrine pathways, tryptophan metabolism, and hypothalamic–pituitary–adrenal axis regulation (Brunt et al., 2021).

SCFAs, indole derivatives, phenolic metabolites, and other microbial products may influence neuroinflammation, blood–brain barrier function, neurotransmitter-related pathways, and neural signalling. Fermented foods may therefore affect brain function indirectly by reshaping intestinal microbial activity rather than through a single bioactive component (Chaudhari et al., 2023).

Clinical evidence, however, remains preliminary. A recent randomized placebo-controlled trial in healthy women showed that an 8-week probiotic fermented dairy intervention was associated with changes in gut microbiome beta diversity and selected hippocampal-related outcomes, although several neuroimaging findings did not remain significant after correction for multiple comparisons (Marx et al., 2025). Thus, current evidence supports biological plausibility but is insufficient to establish clinically meaningful cognitive or neuropsychiatric benefits (Fehér et al., 2022) (Table 3).

Table 3. Current strength of evidence across major health domains.

Health domain	Main outcomes studied	Overall interpretation
Gut microbiome	Diversity, composition, functional potential	Evidence supports product-dependent modulation
Gastrointestinal health	Stool frequency, consistency, GI symptoms	Generally favourable but heterogeneous
Metabolic health	Glucose, insulin sensitivity, lipids, weight	Promising; strongest for selected fermented foods
Immune/inflammatory health	Cytokines, inflammatory markers, immune profiles	Biologically plausible with supportive human data
Cardiovascular health	Blood pressure, lipid-related outcomes	Potential benefit, strongly product- and diet-dependent
Mood and stress	Depression, anxiety, stress-related measures	Emerging and inconsistent
Cognition/brain function	Memory, neuroimaging, neural connectivity	Preliminary evidence; insufficient for firm conclusions

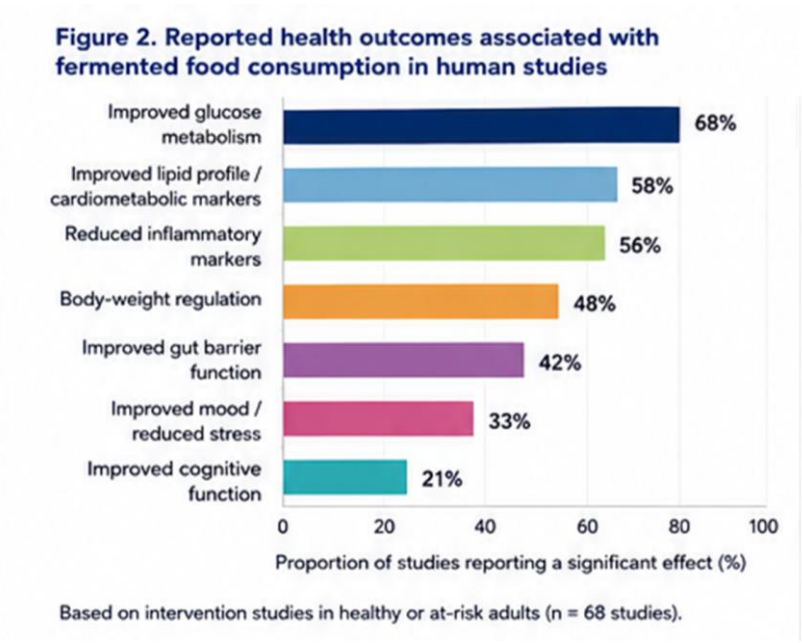
Product-specific heterogeneity

The health effects of fermented foods cannot be generalized across the entire category. Yogurt and kefir typically contain lactic acid bacteria and, in the case of kefir, complex bacterial–yeast communities. Fermented vegetables such as kimchi and sauerkraut are dominated by dynamic lactic acid bacterial ecosystems. Soy-based products such as tempeh, miso, and natto involve distinct fungal or bacterial fermentation processes and generate different bioactive compounds (Gonçalves et al., 2026; Leeuwendaal et al., 2022).

Processing is equally important. Pasteurization may eliminate viable microorganisms while leaving microbial metabolites and modified food components intact. Salt, sugar, alcohol, and energy content may also influence the net health effect of individual products. Consequently, future research should characterize fermented foods at the level of microbial composition, metabolite profile, food matrix, and processing history rather than treating them as a single homogeneous dietary exposure (Palani Kumar et al., 2026; Park & Mannaa, 2025).

Overall interpretation of the evidence

Taken together, current evidence supports fermented foods as biologically active dietary matrices capable of interacting with the gut microbiome and its metabolic functions. The most consistent mechanistic pathways involve microbial metabolism, intestinal barrier integrity, immune regulation, and metabolic signalling. Human evidence is strongest for gastrointestinal, inflammatory, and selected cardiometabolic outcomes, whereas evidence for mood, cognition, and other brain-related outcomes remains emerging (Park & Mannaa, 2025) (Figure 2).



Future trials should use standardized fermented-food characterization, adequately powered study designs, objective compliance measures, microbiome and metabolome profiling, and clinically meaningful outcomes. Greater attention should also be given to interindividual variability, baseline microbiome composition, habitual diet, age, metabolic phenotype, and the distinction between live-microbe effects and fermentation-derived metabolites.

Discussion

The available evidence suggests that fermented foods may influence host physiology through interactions among the food matrix, food-associated microorganisms, microbial metabolites, and the resident gut microbiota (Santa et al., 2025). These effects appear to extend beyond gastrointestinal function and may involve metabolic regulation, immune homeostasis, and gut–brain signalling. However, the strength of evidence differs considerably between these domains and among individual fermented foods (Kryczyk-Poprawa et al., 2026; Marco et al., 2017).

One important finding is that the biological activity of fermented foods cannot be attributed solely to the presence of viable microorganisms (Mikó et al., 2024). Fermentation alters the biochemical composition of the food itself, including nutrient availability, peptide profiles, organic acids, phenolic compounds, and other microbial products (Santa et al., 2025). In addition, microorganisms ingested with fermented foods may interact transiently with the intestinal ecosystem without establishing permanent colonization (Curlej-Wądrzyk et al., 2026). This distinction is relevant when interpreting microbiome studies, since functional changes may occur even in the absence of major or persistent shifts in taxonomic composition (Lewandowski, 2026).

Metabolic outcomes are among the better studied clinical endpoints. Improvements in glucose regulation, lipid metabolism, and selected cardiometabolic markers have been reported for several fermented foods, particularly fermented dairy products (Gao et al., 2025). These effects may involve altered microbial metabolism, bile acid signalling, SCFA production by the resident microbiota, and changes in intestinal barrier function. Nevertheless, responses are inconsistent across studies and cannot be separated easily from differences in baseline diet, energy intake, body composition, and other lifestyle factors (Jarecsny, et al., 2025; Fekete et al., 2024).

The relationship between fermented foods and immune regulation is also biologically plausible. The intestinal microbiota and its metabolites contribute to epithelial barrier maintenance and both innate and adaptive immune signalling (Varga et al., 2026). Changes in microbial activity may therefore affect local and systemic inflammatory responses. Human intervention studies have reported changes in selected inflammatory and immune markers, but the clinical relevance of these findings remains uncertain (Santa et al., 2025). Differences in study duration, participant characteristics, fermented-food composition, and measured biomarkers limit direct comparison between trials (Fekete et al., 2022).

Evidence related to brain and mental health is less developed (Mehta et al., 2025). The microbiota–gut–brain axis provides several plausible mechanisms, including microbial metabolites, immune mediators, vagal signalling, tryptophan metabolism, and neuroendocrine pathways (Ungvari et al., 2025). Some intervention studies suggest possible effects on stress, mood, or cognitive measures, but the number and size of trials remain limited (Cao et al., 2025; Fekete et al., 2024). At present, these findings should be considered preliminary and do not support specific fermented-food recommendations for the prevention or treatment of neuropsychiatric or cognitive disorders (Major et al., 2026; Mózes et al., 2026; Ungvari et al., 2025).

A major limitation of the current literature is the heterogeneity of fermented foods themselves. Products such as yogurt, kefir, kimchi, sauerkraut, tempeh, miso, natto, and kombucha differ substantially in microbial composition, fermentation process, nutrient profile, salt and sugar content, storage conditions, and post-fermentation processing. Even foods within the same category may contain markedly different microbial communities and metabolite profiles. Future studies should therefore move from broad comparisons of "fermented food consumption" toward better characterized, product-specific interventions. Detailed reporting of microbial composition, fermentation conditions, viability of microorganisms at consumption, metabolite content, food matrix characteristics, and dose is essential. Longer randomized controlled trials with clinically relevant endpoints are also needed to determine whether observed microbiome and biomarker changes translate into meaningful health benefits (Mózes et al., 2026; Lipécz, et al., 2026).

Conclusion

Fermented foods may influence metabolic, immune, and gastrointestinal health through interactions with the gut microbiome, microbial metabolites, and fermentation-induced changes in the food matrix. Evidence for brain-related effects is promising but remains limited. Given the substantial heterogeneity among fermented products and study designs, future research should focus on well-characterized, product-specific interventions and clinically relevant outcomes. Such studies are needed to define which fermented foods and fermentation-derived components provide reproducible health benefits.

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ARTIFICIAL INTELLIGENCE AND MEDICAL DECISION-MAKING: REDEFINING PHYSICIAN AUTONOMY, PATIENT CONSENT, AND LIABILITY

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Abstract
The growing integration of artificial intelligence (AI) into medical decision-making is profoundly reshaping the relationship between physician and patient, redefining professional autonomy, the consent framework, and the mechanisms of liability alike. Drawing on French and Moroccan law, this contribution examines how clinical decision-support tools redistribute medical knowledge, expose practitioners to new categories of legal risk, and weaken the quality of informed consent when algorithmic systems operate according to a "black box" logic. The article successively analyses the French "human guarantee" mechanism introduced by the Bioethics Act of 2 August 2021, the classification of AI-based medical devices as high-risk systems under the European Union's Artificial Intelligence Act, and the specific features of Moroccan law governing medical consent. The study concludes that a balanced ethical and legal framework is required, one capable of reconciling technological innovation with the preservation of the relationship of trust that underlies the practice of medicine.
Keywords: artificial intelligence, medical decision-making, informed consent, medical liability, human guarantee, patient autonomy.

Introduction

The physician has traditionally been the one entrusted with making sense of the patient's complaint, drawing on science, clinical experience, empathy, and respect for human dignity. This role is now called upon to evolve so as to incorporate digital tools as complements to medical decision-making. The rise of artificial intelligence raises questions, in this respect, about the physician's free judgment and clinical intuition: by redistributing responsibilities between physician and patient, it is reshaping the traditional model of medical decision-making — hitherto borne essentially by the practitioner alone — in favour of a more collaborative approach. Algorithmic systems indeed make it possible to establish diagnoses, anticipate the effects of treatments, and tailor decisions to the specific characteristics of each patient with growing precision, such that recourse to reliable technological tools, whose effectiveness may now exceed that of healthcare professionals, is becoming ever more pressing in medical practice, including under the influence of the law of liability.

Several questions then arise: how can it be ensured that the results produced by algorithms are used solely as an aid to decision-making, without diminishing physicians' autonomy or their control over the medical act? By what means can practitioners be enabled to evaluate these results and, where appropriate, to depart from them?

The upheavals that artificial intelligence is bringing to the social and professional structures of healthcare also give rise to broader concerns, relating to fears of job losses, the dehumanisation of care, or algorithmic bias. These issues call for critical reflection and open social dialogue on the way AI is transforming society, so that its transformative potential does not dispense with rigorous ethical oversight or adequate regulation.

The major international health authorities already regulate medical AI tools, such as clinical decision-support software (Software as a Medical Device, SaMD), which support medical decision-making without replacing it. Prior to commercialisation, such devices must demonstrate their clinical performance, their safety, and their integration within a supervised protocol; post-marketing surveillance remains necessary thereafter to ensure the reliability of their results over time. At the European level, Regulation (EU) 2024/1689 of 13 June 2024 laying down harmonised rules on artificial intelligence (the "AI Act") classifies the majority of AI systems used as medical devices, or as safety components of such

devices, as high-risk systems, thereby subjecting them to reinforced obligations concerning risk management, data quality, technical documentation, transparency, and human oversight.

Towards an Alienation of Medical Knowledge

The introduction of artificial intelligence into the field of healthcare calls into question the classical conception of the singular consultation, in which an expert engages with a person lacking specialised knowledge. In France, the Act of 4 March 2002 on patients' rights, known as the "Kouchner Law", put an end to medical paternalism by enshrining the principle of health democracy and recognising the patient's ability to become an active participant in his or her own health. It represents the culmination of a process begun as early as 1991 by the Act on hospital reform, which was the first to enshrine the notion of patients' rights, within a broader movement toward the democratisation of the health field.

With the rise of the Internet, patients increasingly and autonomously seek out information regarding their health; in 2015, 41% of French Internet users had already consulted health-related websites. This development has fostered the combination of academic knowledge with patients' personal experience, nourished by their own research and their exchanges on online forums. The development of artificial intelligence in healthcare thus raises fears of a dispossession of medical knowledge in favour of algorithms, which requires physicians to retain a critical faculty, particularly when interpreting the results produced by AI, in order to preserve control over diagnosis and treatment. The principal risk would lie in reducing the physician to a mere executor of algorithmic recommendations, which would be liable to generate disengagement and a loss of accountability. It therefore appears essential to establish a synergistic collaboration between physician and AI, so as to prevent any dehumanisation of care practices. While it would be excessive to speak of a total dispossession of medical knowledge, it remains nonetheless necessary for the physician to stay fully engaged in the decision-making process, so that his or her expertise continues to occupy a central place within the care pathway.

This risk of dispossession of knowledge is compounded, moreover, by a weakening of consent: the patient must now be informed not only of the therapeutic approach envisaged, but also of the involvement of an algorithm in the decision that concerns him or her. Since AI systems frequently function as "black boxes" whose internal logic remains largely inaccessible, the information thereby provided is correspondingly impoverished, which weakens the care relationship from a legal standpoint (this issue is examined further in Section III.3). The physician nonetheless retains the ability to depart from AI recommendations, which preserves his or her professional liability without calling into question the traditional foundations of medical fault.

The Impact of Algorithms on Medical Decision-Making: Medical Liability

The growing integration of artificial intelligence into decision-making processes gives rise to a new category of legal risk, more complex than that associated with traditional technologies and accordingly requiring heightened vigilance. Algorithmic discrimination constitutes one of the foremost such risks: AI systems that appear neutral may in fact perpetuate, or even amplify, existing societal biases. The most emblematic example remains Amazon's automated résumé-screening tool, abandoned in 2018 after it was revealed that the algorithm, trained on hiring data historically dominated by male profiles, systematically penalised applications mentioning women's experience or educational institutions (Dastin, 2018). Comparable risks arise in other sectors, such as consumer credit, where scoring algorithms are liable to reproduce similar discrimination — a concern that explains the growing vigilance of financial regulators regarding AI systems used in credit-granting decisions.

Medical decisions, for their part, combine technical and moral dimensions: diagnosis and treatment must be accurate for the patient's physical health, while also respecting his or her moral well-being and autonomy, in keeping with his or her personal values. Algorithms are classically defined in the literature as a "plan setting out, in a well-defined language, a sequence of operations enabling a problem to be solved", or alternatively as a "set of operating rules whose application allows a stated problem to be resolved by means of a finite and organised number of operations". Decision-making approaches based on data analysis are not new; the current capacity to process immense quantities of raw data has, however, given rise to the notion of "Big Data", characterised by the three "V"s: volume, velocity, and variety. A 2013 Gartner report accordingly identified four approaches to data analytics applied to decision-making: descriptive analysis, diagnostic analysis, the prediction of future events, and prescription, the latter resting on the estimation of the consequences of possible courses of action. While descriptive and diagnostic approaches are today widely used, predictive algorithms already shape

everyday life — in recruitment or targeted advertising, for instance — whereas prescriptive tools, still less developed, are expected in future to play an increasing role in decisions directly affecting individuals' lives.

Recourse to artificial intelligence is also becoming necessary under the influence of the law of liability: inasmuch as the physician must provide care consistent with accepted scientific knowledge, it is increasingly necessary to rely on reliable technological tools, such as machine-learning-assisted medical imaging, whose effectiveness may now exceed that of a human operator. Artificial intelligence accordingly raises novel questions of liability: decisions entrusted to digital systems, often largely invisible to those affected by them, are liable to significantly influence patients' lives, such that it is essential for the reasons underlying them to remain intelligible. This requirement echoes Article 5 of the Oviedo Convention, which enshrines the patient's right to informed consent prior to any medical intervention and requires that clear and accessible information be provided. In the context of AI systems, this duty of explanation could shift from the healthcare professional to the system itself, or to its developer, raising novel challenges in terms of liability.

Under French law, Act No. 2021-1017 of 2 August 2021 on bioethics incorporated into the Public Health Code, at Article L. 4001-3, a human-oversight mechanism known as the "human guarantee" ("garantie humaine"), which requires, on the one hand, that the healthcare professional inform the patient of the use of an AI solution in the context of an act of prevention, diagnosis, or care and, where applicable, of the resulting outcome, and, on the other hand, that the algorithm's developer ensure the explainability of its operation for users. The first requirement fosters dialogue between physician and patient regarding the use of AI and the results obtained, and encourages the practitioner to take ownership of the diagnostic or therapeutic act rather than passively deferring to the machine. The second seeks to ensure that the physician has the information necessary to understand the functioning of the AI solution, to take ownership of it and, if need be, to depart from it: the text accordingly provides that the healthcare professionals concerned must be kept informed of the use of the data-processing system and that the resulting information and results must remain accessible to them, so as to guarantee the traceability of the augmented decision. This requirement has notably inspired the establishment of "human guarantee boards", bringing together healthcare professionals and patient representatives, tasked with subsequently reviewing medical records so as to bring human judgment to bear on decisions made or recommended by the algorithm (Eychenne, 2025).

Medicine remains, in any event, grounded in human relationships: it cannot rely entirely on algorithms, however high-performing they may be, given that such systems remain devoid of the nuance and empathy inherent to the care relationship. It is accordingly important to rethink the approach to digital medicine while safeguarding confidentiality and medical secrecy, and to train the users of such systems to fully understand the environment in which they operate. In the absence of an ethical framework and appropriate training, ethical risks would become both inevitable and uncontrollable — a conclusion that stands in contrast with the position of certain proponents of algorithmic governance, such as the American entrepreneur Tim O'Reilly, who advocates a form of "algorithmic regulation" in which individuals would merely define objectives, leaving it to algorithms to determine the means of achieving them (O'Reilly, 2013).

The Impact of AI on the Patient: Between Enhanced Autonomy and Algorithmic Dependence

After centuries of "medical paternalism", the caregiver-patient relationship is being transformed under the combined effect of e-health, telemedicine, and medical Big Data: patients are increasingly seeking information, reflecting a genuine digital revolution in healthcare and requiring a re-examination, from the standpoint of management ethics, of new organisational communications and of the relationship between caregiver and patient.

While recourse to algorithms offers the advantages of efficiency, low cost, speed, and the ability to process volumes of information beyond human capacity, their generalisation is not without cause for concern: beyond their inherent limitations, it raises a difficulty of a democratic nature, insofar as individuals are thereby deprived of the capacity for initiative and the autonomy that characterise them. Artificial intelligence is thus redefining the patient-physician relationship by making patients better informed and more demanding, while involving them more closely in their own care. It fosters a personalised medicine oriented toward prevention rather than cure, allowing for substantial savings by avoiding costly treatments; it risks, however, correspondingly increasing the degree of monitoring to which patients are subject and generating stress associated with constant surveillance.

The Impact of AI on the Patient within the Care Relationship

The model of the therapeutic relationship is evolving: the patient's dependence on the physician is gradually giving way to greater autonomy, as patients acquire the knowledge needed to better manage their condition. While new technologies, such as the Internet and AI, offer broader access to medical information, they also expose patients to the risk of misinformation. This transformation should not obscure its impact on patients' lived experience or on the very nature of medicine: the therapeutic relationship, often conceived as an ideal framework between an "expert" physician and a "vulnerable" patient, is rendered more complex by the emergence of patient autonomy, which calls for a thorough examination of its implications for trust and for healing.

At a time when AI is being deployed across medicine, the protection of confidentiality takes on critical importance, as does the reliability of medical advice available online. The role of the expert nonetheless remains essential in assessing the credibility to be accorded to such information: the therapeutic relationship carries ethical obligations which, even where partially transferred to other actors, must in every case continue to be taken into account. This framework could be reshaped so as to better value patient autonomy, at the risk, however, of reducing the physician to the role of a mere service provider.

The decision to resort to artificial intelligence must accordingly go beyond considerations of cost and benefit alone: while AI may improve the efficiency of care for a growing number of patients, it must also be assessed in light of the risks it poses to the human relationship in medicine, a relationship founded on trust and on the practitioner's contextual judgment — one that does not necessarily transpose to interaction with an AI system.

Ultimately, the introduction of artificial intelligence does not alter the nature of the motivations that lead patients to seek care, but it does transform the manner in which such care is delivered, with implications of concern for the quality of care and for compliance with the ethical standards governing medicine.

Patients today have become proactive agents in the management of their own health, under the influence of digital technology, which has reduced the information asymmetry characterising the care relationship: patients search for information online, take part in teleconsultations, and make use of health applications or connected devices, all of which are tools capable of usefully supplementing medical care — some oncologists, for instance, have developed applications that help detect cancer recurrence by monitoring patients' symptoms, thereby strengthening the relationship with the treating physician. Access to applications providing medical advice by algorithmic means nonetheless raises safety concerns: while such tools may direct patients toward a consultation where necessary, they carry the risk that such advice will substitute for conventional medical consultations and encourage self-medication, which could, paradoxically, weaken rather than strengthen the relationship between patient and physician.

Contemporary medicine is moving toward more reliable and more personalised care through the use of artificial intelligence. Physicians who employ it for diagnosis, therapeutic choice, or early screening may expect a better integration of available scientific data, thereby helping to reduce the risk of human error — which, it should be noted, is not invariably attributable to fault. By drawing on biological and genetic analyses specific to each individual, AI fosters the growth of precision and preventive medicine, capable of better personalising care, acting on risk factors, and optimising medical practice, with a potentially significant impact on public health.

This progress is not, however, free of reservations: it is important that artificial intelligence not give rise to a two-tier medicine benefiting only the most privileged patients. In order to address the challenges of social acceptability of AI in healthcare, the Parliamentary Office for the Evaluation of Scientific and Technological Choices (OPECST) recommends strengthening confidence in algorithms through appropriate public education — information campaigns, public events, and awareness-raising initiatives aimed at the general public — while acknowledging that the effectiveness of such measures in demystifying AI and reducing the mistrust it engenders remains uncertain (De Ganay & Gillot, 2017). The OPECST accordingly advocates an AI that is well-controlled, safe, and transparent, capable of preventing potential abuses; the regulation of algorithmic processes is, moreover, oriented more toward ethics than toward positive law, which invites recourse to soft-law instruments to govern this technological development, in a continuing search for balance between innovation and ethical requirements.

The Impact of AI on Patients' Rights and Duties

The traditional definition of the patient should not be upset by artificial intelligence in healthcare: patients' rights must remain intact, even though technological developments may give rise to new rights and new obligations. The use of AI by physicians accordingly broadens the duty of information, which must now cover the use of personal data and the risks associated with AI. The personalised medicine that AI makes possible correspondingly increases the patient's own responsibility, with implications such as a potential link between reimbursement and patient behaviour — a dynamic that certain authors describe as "insurance paternalism", whereby insurers, relying on digital tools and behavioural data, would themselves define what is "good" for the insured's health, at the risk of shifting patient accountability toward a form of control over their lifestyle. It would, however, be mistaken to assume that only physicians benefit from artificial intelligence, since some solutions are already directly accessible to patients, who are, under personalised medicine, asked to become more cooperative, by sharing information about their lifestyle and adhering to prescribed treatments.

Within the relationship of trust that binds them to their patients, physicians bear an ethical duty to use the information and access granted to them by patients solely for the latter's benefit, rather than in their own interest. Under French law, the duty to inform patients when devices employing algorithms are used was reaffirmed in 2021: it falls to the healthcare professional to explain the resulting outcomes. In return, artificial intelligence holds the promise of relieving physicians of repetitive tasks, allowing them to focus more fully on care and patient support, which fosters complementarity between practitioner and digital tools and, in turn, strengthens the relationship of trust with the patient.

Some patients may nonetheless remain distrustful of these technologies, or even reject them outright, particularly where they require the patient's active participation in treatment; conversely, where patients embrace them, such appropriation may make them more accountable in diagnosis and care. Further risks remain, in particular that of unequal access to care, given that regions at the forefront of AI adoption will benefit from more advanced technologies, thereby creating disparities in the quality of care provided. The impact of artificial intelligence on medical practice will ultimately depend on the degree to which it is integrated with human expertise: to the extent that it complements rather than replaces such expertise, the human dimension of care will be preserved; failing that, the physician-patient relationship, essential to sound medical practice, could be correspondingly degraded.

Informed Consent and Algorithmic Opacity: The Case of Moroccan Law

The use of artificial intelligence within the care relationship raises profound questions concerning the quality of patients' informed consent, a fundamental principle of Moroccan medical law. This consent is enshrined in Act No. 131-13 on the practice of medicine, promulgated by Dahir No. 1-15-26 of 19 February 2015, as well as in the Code of Medical Ethics, Article 30 of which provides that "no medical act or treatment may be performed without the free and informed consent of the person examined or treated." This principle also finds an echo in international law, through the instruments ratified by the Kingdom, as well as in the Oviedo Convention which, although not ratified by Morocco, continues to inform its case law and legal scholarship. Consent presupposes that the patient receives clear, fair, and intelligible information regarding the medical acts envisaged, the available alternatives, and the risks involved, but also, henceforth, regarding the technological tools used in the decision-making process, particularly where AI systems are concerned.

Yet artificial intelligence systems, particularly where they rely on complex and poorly transparent machine-learning models — described as "black boxes" — render medical information more difficult to grasp: it becomes difficult to explain, in an intelligible manner, how an AI system arrives at a diagnostic or therapeutic conclusion. Several technical initiatives seek to address this challenge, such as the Explainable Artificial Intelligence (XAI) programme launched by DARPA, the Pentagon's research agency, which aims to design AI systems capable of constructing, over time, explanatory models of their own decisions (Gunning, 2019). This algorithmic opacity nonetheless impairs the patient's ability to exercise a genuinely free and informed consent, in the legal sense of the term.

The technical, at times barely intelligible, character of AI reasoning thus weakens the validity of consent and, consequently, undermines the care relationship from a legal standpoint. The physician is thereby confronted with a twofold requirement, both novel and complex: sufficiently understanding how the tool functions so as to be able to explain it, and ensuring that the patient genuinely grasps its implications.

Conclusion

The integration of digital technologies and artificial intelligence into healthcare entails considerable transformations and a wide range of challenges. AI improves diagnosis, personalises treatment, and increases the efficiency of health systems, while also raising ethical concerns regarding data confidentiality, equity of care, and medical liability.

The current regulatory framework must adapt to these rapid technological developments in order to guarantee patient safety and rights. Recent initiatives — the human guarantee under French law, the classification of AI-based medical devices as high-risk under the European regulation, and the requirements of informed consent and medical ethics under Moroccan law — converge toward a common objective: keeping the physician at the centre of the decision and preserving the relationship of trust that binds physician and patient. Equitable global adoption of artificial intelligence further requires narrowing the digital divide, strengthening cybersecurity, and ensuring the absence of bias in algorithms. International cooperation and harmonised rules appear essential to maximise the benefits of AI while minimising its risks; commitment to the continuing training of healthcare professionals and to the transparency of deployed systems remains, ultimately, the primary condition for lasting patient trust in medicine augmented by artificial intelligence.

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COMPARATIVE EVALUATION OF LAPAROSCOPIC TRANSABDOMINAL PREPERITONEAL (TAPP) AND OPEN LICHTENSTEIN MESH REPAIR FOR PRIMARY INGUINAL HERNIA: A RETROSPECTIVE STUDY

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Abstract

Background

Inguinal hernia repair remains one of the most commonly performed operations in general surgery. Although the Lichtenstein tension-free mesh repair has long been considered the gold standard, laparoscopic transabdominal preperitoneal (TAPP) repair has gained increasing popularity due to its minimally invasive nature and improved postoperative recovery. The present study aimed to compare perioperative and early postoperative outcomes between laparoscopic TAPP and open Lichtenstein mesh repair.

Materials and Methods

A retrospective comparative study was conducted on 240 patients undergoing elective primary inguinal hernia repair between 2019 and 2025. Among them, 120 patients underwent laparoscopic TAPP repair, while 120 patients underwent open Lichtenstein mesh repair. Operations were performed at the clinical bases of Azerbaijan Medical University and the Department of Surgery of the Azerbaijan State Advanced Training Institute for Doctors. Demographic characteristics, operative time, postoperative pain, length of hospital stay, postoperative complications, recovery period, cosmetic satisfaction, and recurrence rates were evaluated.

Results

Both procedures demonstrated excellent safety profiles and satisfactory surgical outcomes. Patients undergoing laparoscopic TAPP experienced significantly lower postoperative pain, earlier mobilization, shorter hospitalization, faster return to daily activities, and superior cosmetic outcomes. The incidence of wound complications was lower in the laparoscopic group. No significant difference in early recurrence rates was observed between the two techniques.

Conclusion

Laparoscopic TAPP represents a safe and effective alternative to open Lichtenstein repair. Reduced postoperative pain, rapid rehabilitation, improved cosmetic outcomes, and earlier return to normal life make TAPP an attractive surgical option in experienced centers.

Keywords: Inguinal hernia, TAPP, Lichtenstein repair, mesh hernioplasty, laparoscopic surgery, minimally invasive surgery.

Introduction

Inguinal hernia is among the most prevalent surgical diseases worldwide, accounting for nearly 75% of all abdominal wall hernias. More than 20 million inguinal hernia repairs are performed annually worldwide, making this procedure one of the most frequently conducted operations in general surgery. Despite numerous advances in surgical technology, the optimal approach for inguinal hernia repair remains an area of continuous discussion.

The introduction of prosthetic mesh significantly reduced recurrence rates and improved long-term surgical outcomes. The open Lichtenstein tension-free mesh repair has become the standard technique because of its simplicity, reproducibility, and excellent long-term results. Nevertheless, the open approach is associated with postoperative pain, wound-related complications, delayed return to normal activities, and chronic groin discomfort in some patients.

Over the past two decades, laparoscopic techniques have gained increasing acceptance. Among these, the transabdominal preperitoneal (TAPP) approach allows placement of a large prosthetic mesh within the preperitoneal space through minimally invasive access.

The laparoscopic technique offers several theoretical and practical advantages, including reduced tissue trauma, less postoperative pain, shorter hospital stay, earlier mobilization, faster return to work, and improved cosmetic appearance.

Recent international guidelines recommend laparoscopic repair, particularly for bilateral and recurrent inguinal hernias, when adequate surgical expertise is available. However, open Lichtenstein repair continues to be widely performed because of its technical simplicity, shorter learning curve, and lower equipment costs.

Numerous studies have compared laparoscopic and open mesh repairs; however, variations in patient populations, surgeon experience, and institutional protocols continue to produce differing conclusions. Therefore, additional comparative studies remain valuable for evaluating outcomes in different healthcare settings.

The present study compares laparoscopic TAPP and open Lichtenstein mesh repair performed in two major surgical institutions in Azerbaijan, focusing on perioperative safety, postoperative recovery, complications, cosmetic results, and early recurrence.

Materials and Methods

A retrospective comparative study was conducted involving 240 consecutive patients who underwent elective surgery for primary inguinal hernia between January 2019 and December 2025.

Patients were treated at the clinical bases of Azerbaijan Medical University and the Department of Surgery of the Azerbaijan State Advanced Training Institute for Doctors.

The study population consisted of 240 adult patients divided into two equal groups.

Group I (n = 120): Laparoscopic Transabdominal Preperitoneal (TAPP) mesh repair.

Group II (n = 120): Open Lichtenstein tension-free mesh repair.

Patients with strangulated hernias, incarcerated hernias requiring bowel resection, recurrent hernias after laparoscopic repair, severe cardiopulmonary diseases contraindicating general anesthesia, and patients younger than 18 years were excluded. Preoperative evaluation included complete physical examination, laboratory investigations, abdominal ultrasonography when indicated, electrocardiography, chest radiography, and anesthetic assessment.

All laparoscopic procedures were performed under general anesthesia using the standard three-port TAPP technique. After opening the peritoneum, the preperitoneal space was carefully dissected, the hernia sac reduced, and a polypropylene mesh measuring approximately 10 × 15 cm was positioned to cover the myopectineal orifice. The peritoneum was then closed using continuous absorbable sutures.

Patients in the open group underwent conventional Lichtenstein tension-free mesh hernioplasty through an anterior inguinal approach under spinal or general anesthesia. A polypropylene mesh was placed over the posterior wall of the inguinal canal and fixed according to the standard Lichtenstein technique.

The following variables were analyzed:

- Age and sex distribution
- Type and side of hernia
- Operative time
- Postoperative pain assessed using the Visual Analogue Scale (VAS)
- Duration of analgesic use
- Time to first mobilization
- Length of hospital stay
- Time to return to normal daily activities

Early postoperative complications (seroma, hematoma, wound infection, urinary retention)

- Cosmetic satisfaction
- Early recurrence

Statistical analysis was performed using SPSS software. Continuous variables were expressed as mean ± standard deviation. Student's t-test and Chi-square test were applied where appropriate. A p-value <0.05 was considered statistically significant.

Results

A total of 240 patients were included in the study. The laparoscopic TAPP group consisted of 120 patients, while 120 patients underwent open Lichtenstein mesh repair. No statistically significant

differences were observed between the groups regarding age, gender distribution, body mass index, or hernia characteristics (p>0.05).
The mean age was 48.6 ± 13.2 years in the TAPP group and 49.8 ± 12.7 years in the Lichtenstein group, with no statistically significant difference between the groups (p > 0.05).
The TAPP group included 109 male patients (90.8%) and 11 female patients (9.2%), whereas the Lichtenstein group included 111 male patients (92.5%) and 9 female patients (7.5%) (p > 0.05).
The mean BMI was 27.4 ± 3.6 kg/m² in the TAPP group and 27.1 ± 3.4 kg/m² in the Lichtenstein group, with no significant difference (p > 0.05).
The mean operative time was 61.5 ± 12.4 minutes for TAPP and 52.8 ± 10.7 minutes for Lichtenstein repair (p < 0.05).
Mean intraoperative blood loss was 18 ± 8 mL in the TAPP group compared with 43 ± 15 mL in the Lichtenstein group (p < 0.001).
At 6 hours postoperatively, the mean VAS pain score was 2.8 ± 0.9 in the TAPP group and 4.9 ± 1.1 in the Lichtenstein group (p < 0.001).
At 24 hours, the mean VAS score was 2.0 ± 0.8 versus 3.8 ± 1.0, respectively (p < 0.001).
On postoperative day 7, the mean VAS score decreased to 0.6 ± 0.4 in the TAPP group compared with 1.8 ± 0.7 in the Lichtenstein group (p < 0.001).
First mobilization occurred after 5.2 ± 1.4 hours in the TAPP group and 11.6 ± 2.8 hours in the Lichtenstein group (p < 0.001).
The mean hospital stay was 1.3 ± 0.5 days for TAPP and 2.8 ± 0.8 days for Lichtenstein repair (p < 0.001).
Patients returned to daily activities after 8.4 ± 2.6 days in the TAPP group compared with 17.2 ± 3.8 days in the Lichtenstein group (p < 0.001).
The mean time to return to work was 14.6 ± 3.7 days in the TAPP group and 25.9 ± 5.3 days in the Lichtenstein group (p < 0.001).
Seroma occurred in 4 patients (3.3%) in the TAPP group and 9 patients (7.5%) in the Lichtenstein group (p > 0.05).
Hematoma was observed in 2 patients (1.7%) following TAPP and 6 patients (5.0%) following Lichtenstein repair (p > 0.05).
Wound infection occurred in 1 patient (0.8%) in the TAPP group compared with 7 patients (5.8%) in the Lichtenstein group (p < 0.05).
Urinary retention developed in 2 patients (1.7%) after TAPP and 5 patients (4.2%) after Lichtenstein repair (p > 0.05).
Chronic groin pain was reported in 2 patients (1.7%) in the TAPP group and 11 patients (9.2%) in the Lichtenstein group (p < 0.01).
Excellent cosmetic satisfaction was reported by 95.8% of patients after TAPP compared with 76.7% after Lichtenstein repair (p < 0.001).
During early follow-up, recurrence occurred in 2 patients (1.7%) in the TAPP group and 3 patients (2.5%) in the Lichtenstein group, with no statistically significant difference (p > 0.05).

Discussion. The present study compared the clinical outcomes of open Lichtenstein hernioplasty and laparoscopic inguinal hernia repair. Both techniques proved to be safe and effective methods for the treatment of inguinal hernia. However, important differences were observed regarding postoperative recovery, pain, return to normal activity, and patient satisfaction.
The Lichtenstein technique has long been considered the gold standard for open inguinal hernia repair because of its simplicity, reproducibility, and low recurrence rate. It can be performed under spinal or local anesthesia and requires less specialized equipment. These advantages make it particularly suitable for elderly patients and for healthcare centers with limited resources.
In contrast, laparoscopic repair offers several important clinical benefits. Patients generally experience less postoperative pain, require fewer analgesics, and return to work and daily activities earlier than patients undergoing open surgery. Better cosmetic results and reduced incidence of chronic postoperative groin pain are additional advantages reported in many studies.
The present findings are consistent with previously published randomized clinical trials and systematic reviews. Several investigators have demonstrated that laparoscopic repair significantly decreases

postoperative discomfort while maintaining recurrence rates comparable to open repair when performed by experienced surgeons.

Although operative time was slightly longer in the laparoscopic group, this disadvantage became less significant as surgical experience increased. The learning curve remains one of the major limitations of laparoscopic hernia repair, requiring appropriate training and adequate case volume.

Hospital stay was shorter following laparoscopic surgery. Earlier mobilization also reduces the risk of postoperative complications such as venous thromboembolism and improves overall patient satisfaction.

No statistically significant difference in recurrence rate was identified between the two techniques during follow-up. Recurrence depends not only on the operative technique but also on mesh placement, surgical expertise, patient-related factors, and postoperative compliance.

Postoperative wound complications, including hematoma and surgical site infection, occurred more frequently after open repair. Conversely, laparoscopic surgery was associated with fewer wound-related complications because of the minimally invasive approach.

One limitation of this study is its retrospective design and relatively limited follow-up period. Prospective multicenter randomized studies with longer follow-up are required to evaluate long-term recurrence and chronic pain more accurately.

Overall, the results support current international recommendations suggesting that both procedures remain valuable options, while laparoscopic repair provides superior early postoperative recovery in appropriately selected patients.

Conclusion. Both open Lichtenstein hernioplasty and laparoscopic inguinal hernia repair are effective and reliable surgical techniques with low recurrence rates.

Lichtenstein repair remains an excellent option because of its technical simplicity, lower cosət, and wide availability. It is particularly appropriate for primary unilateral hernias, elderly patients, and institutions where laparoscopic equipment is limited.

Laparoscopic repair demonstrates clear advantages in terms of reduced postoperative pain, shorter hospitalization, faster recovery, earlier return to work, and improved cosmetic outcomes. These benefits make it especially suitable for bilateral, recurrent, and physically active patients.

The choice of surgical technique should be individualized according to patient characteristics, surgeon experience, available resources, and patient preference.

Future prospective randomized studies with larger patient populations are needed to further define the long-term outcomes of both techniques.

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COMBINED FIXED–REMOVABLE PROSTHETIC REHABILITATION OF THE MAXILLA IN A PARTIALLY DENTATE PATIENT: A CLINICAL CASE REPORT

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ABSTRACT

Aim. Prosthetic rehabilitation of partially dentate patients with extensive tooth loss may be challenging when the number and distribution of the remaining teeth do not allow treatment with an exclusively fixed prosthetic restoration. A combined fixed–removable approach may enable preservation and functional use of the remaining teeth while providing adequate support, retention, function, and aesthetics. The aim of this clinical report is to present the rehabilitation of a partially dentate maxilla using a combined fixed–removable prosthetic treatment approach.

Materials and Methods
Following clinical and prosthetic evaluation, the remaining maxillary teeth were selected as abutments and prepared for fixed prosthetic restorations. Definitive impressions were obtained, followed by successive clinical and laboratory procedures for fabrication of the prosthetic reconstruction. The treatment combined tooth-supported fixed prosthetic components with a removable partial prosthesis designed to restore the missing dental segments. Particular attention was given to the relationship between the fixed and removable components, prosthetic support and retention, occlusal relationships, and aesthetic integration. The clinical and laboratory workflow was documented through representative photographs of the treatment stages and the definitive prosthetic reconstruction.

Results
The combined fixed–removable approach restored the continuity of the maxillary dental arch and provided satisfactory retention, stability, function, and aesthetics. Preservation and appropriate use of the remaining teeth contributed to the support and integration of the definitive prosthetic restoration.
Conclusion: Combined fixed–removable prosthetic treatment represents a valuable therapeutic option for maxillary rehabilitation in patients with reduced dentition when exclusively fixed rehabilitation is not feasible. Careful case selection, treatment planning, and coordination of the clinical and laboratory stages are important for achieving a functional, stable, and aesthetically acceptable prosthetic outcome.
Keywords: combined prosthodontics; fixed–removable prosthesis; maxillary rehabilitation; partial edentulism; removable partial denture; prosthetic rehabilitation; clinical case.

Introduction

Prosthetic rehabilitation of patients with extensive partial tooth loss can be challenging when the number and distribution of the remaining teeth do not allow treatment with a conventional fixed prosthesis alone. In such cases, a combined fixed–removable prosthetic approach may provide an effective alternative by using the remaining teeth for support and retention while restoring the missing dental segments.
The combination of fixed restorations with a removable partial prosthesis may improve retention, stability, function, and aesthetics, particularly in patients with extensive edentulous areas.

Successful treatment depends on appropriate selection of the abutment teeth, careful prosthetic planning, and coordination between the fixed and removable components [1–3].
The aim of the present clinical report is to describe the rehabilitation of a partially dentate maxilla using a combined fixed–removable prosthetic approach and to illustrate the principal clinical and laboratory stages of treatment.

Clinical Case / Initial Situation

A 78-year-old male patient presented for prosthetic rehabilitation of the maxilla because of extensive partial tooth loss and impaired masticatory function. Clinical examination revealed a markedly reduced and asymmetrically distributed maxillary dentition. The remaining teeth were 11, 13, 21, 22, 23, 24, 25, 26, and 27 according to the FDI notation, while all other maxillary teeth were missing (Fig. 1).
The preserved teeth were clinically evaluated with regard to their periodontal condition, position, and potential use as prosthetic abutments. Due to the extent and distribution of the edentulous areas, rehabilitation with a conventional fixed prosthesis alone was considered unsuitable. Following treatment planning, the teeth with a favorable prognosis were selected as abutments for the fixed component of a combined fixed–removable prosthetic reconstruction.
The treatment objective was to preserve and functionally utilize the remaining maxillary teeth, restore the missing dental segments, and achieve adequate retention, stability, function, and aesthetics through a combined prosthetic approach.



Figure 1. Initial clinical situation: (A) frontal view; (B) occlusal view demonstrating the distribution of the remaining maxillary teeth.

TREATMENT PLAN

Following evaluation of the clinical situation, a combined fixed–removable prosthetic rehabilitation of the maxilla was planned. The remaining teeth with a favorable prognosis were preserved and selected as abutments for the fixed component of the reconstruction. The fixed restorations were designed to provide support and retention for the removable prosthetic component, which was planned to restore the extensive edentulous areas.
The treatment concept aimed to achieve functional rehabilitation, adequate retention and stability of the prosthesis, and an acceptable aesthetic outcome while preserving the remaining natural teeth.

CLINICAL AND LABORATORY PROCEDURES

Abutment Preparation and Definitive Impression

The selected maxillary abutment teeth were prepared according to the requirements of the planned fixed prosthetic components. Particular attention was paid to achieving appropriate preparation geometry and sufficient space for the definitive restorations. After completion of tooth preparation, a definitive maxillary impression was obtained for fabrication of the working casts and subsequent laboratory procedures (Fig. 2).

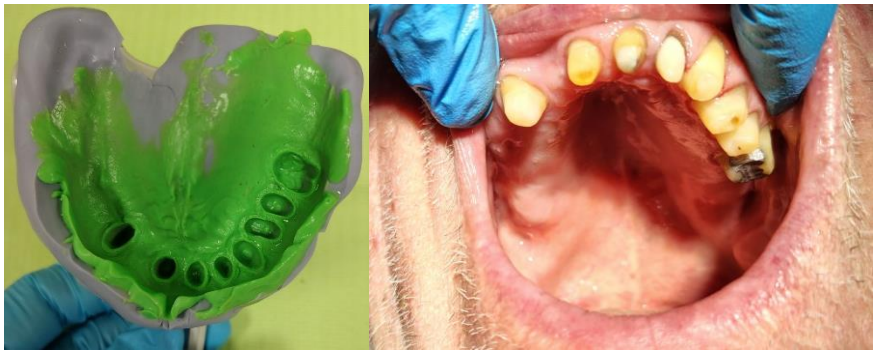


Figure 2. Tooth preparation and definitive impression.

Laboratory Fabrication of the Combined Prosthetic Reconstruction

Working casts were fabricated from the definitive impression and used for laboratory planning of the prosthetic reconstruction. The fixed and removable components were designed as parts of a single combined prosthetic concept. The removable partial prosthesis included a metal framework adapted to the morphology of the maxillary arch and to the planned fixed restorations.

The fixed and removable components were connected by stud-type attachments, providing retention and contributing to the stability of the removable prosthesis. During the laboratory stages, the relationship between the fixed and removable components was carefully evaluated to ensure adequate support, retention, stability, and a common path of insertion (Figs. 3, 4).

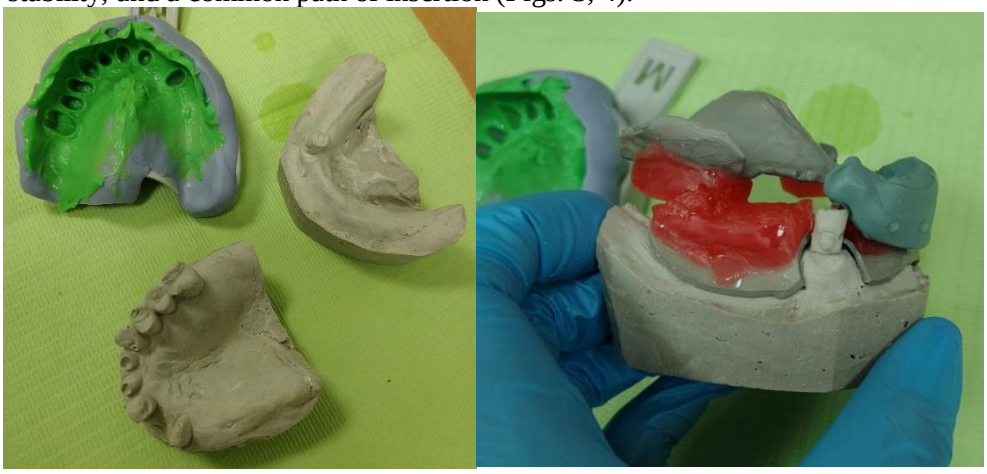


Figure 3. Laboratory and prosthetic planning stages: (A) definitive impression and working casts; (B) intermaxillary relationship registration



Figure 4. Fixed and removable components

Clinical Try-In and Definitive Placement

The prosthetic components were clinically evaluated during successive try-in procedures. The fit of the fixed restorations, adaptation of the removable framework, retention, stability, occlusal relationships, and aesthetic integration were assessed and adjusted when necessary. A silicone index trial was performed to evaluate the planned prosthetic reconstruction before definitive placement (Fig. 5).

Following completion of the clinical and laboratory stages, the definitive combined fixed–removable prosthetic reconstruction was delivered. The final reconstruction restored the continuity of the maxillary dental arch and provided a functional and aesthetically acceptable clinical result (Fig. 6).



Figure 5. Silicone index trial of the planned prosthetic reconstruction: (A) extraoral view; (B) intraoral evaluation.

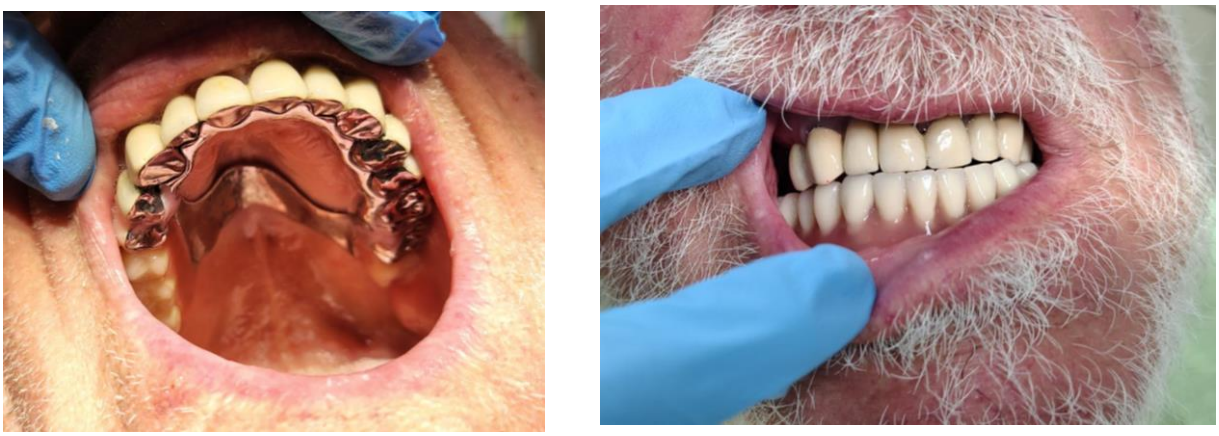


Figure 6. Final clinical outcome: (A) palatal view; (B) frontal view.

Results

The definitive combined fixed–removable prosthetic reconstruction achieved satisfactory clinical adaptation, retention, and stability. The stud-type attachments provided a functional connection between the fixed restorations and the removable prosthetic component.

The treatment restored the continuity of the maxillary dental arch and provided satisfactory occlusal function and aesthetics while preserving and utilizing the remaining natural teeth as prosthetic abutments. The final clinical evaluation demonstrated satisfactory integration of the fixed and removable components and an acceptable functional and aesthetic outcome (Fig. 6).

Discussion

Combined fixed–removable prosthetic rehabilitation represents an important treatment option for patients with extensive partial tooth loss when the number and distribution of the remaining teeth do not permit predictable rehabilitation with a conventional fixed prosthesis alone. The use of attachments enables the fixed and removable components to function as an integrated prosthetic system and may provide improved retention and aesthetics compared with conventional clasp-retained removable partial dentures. Attachments can be classified according to their location, manufacturing method, resiliency, and design, including intracoronal, extracoronal, stud, bar, and other configurations [1,2].

The combination of fixed partial dentures and attachment-retained removable partial dentures has previously been described as a valuable alternative in complex oral rehabilitation, particularly when

implant-supported treatment or exclusively fixed rehabilitation is limited or contraindicated. Reis et al. reported successful maxillary rehabilitation using fixed and removable partial dentures connected by attachments and emphasized potential advantages related to aesthetics and biomechanics [3]. This treatment concept is particularly relevant in patients with extensive edentulous areas in whom strategically distributed remaining teeth can be incorporated into the prosthetic reconstruction.

Preservation of suitable remaining teeth is an important aspect of treatment planning. Natural teeth selected as prosthetic abutments may contribute to support, retention, and stability and can therefore improve the biomechanical conditions of a removable reconstruction. However, their long-term prognosis depends strongly on appropriate case selection and periodontal condition. Evidence indicates that periodontal prognosis is an important predictor of abutment tooth survival and should therefore be carefully considered before incorporating remaining teeth into complex prosthetic reconstructions [4,5].

In the present clinical case, the remaining maxillary teeth were preserved and incorporated into the fixed component of the reconstruction. The removable component was retained by stud-type attachments, allowing the two parts of the prosthesis to function as a combined reconstruction. Stud attachments belong to the established group of precision or semi-precision attachment designs used to provide direct retention without relying on visible conventional clasp assemblies [1,2]. Their use may therefore contribute not only to retention but also to improved aesthetics, particularly in visible regions of the dental arch.

Biomechanical considerations are particularly important in attachment-retained removable partial dentures because functional forces are transferred between the abutment teeth, the fixed restorations, the removable framework, and the residual supporting tissues. Experimental investigations of maxillary distal-extension removable partial dentures have demonstrated that attachment design, retention characteristics, supporting rests, and splinting of abutment teeth can significantly influence stress distribution [6]. These findings emphasize that the attachment itself should not be considered independently but as part of the overall prosthetic design.

Another important advantage of attachment-retained prostheses is the possibility of avoiding visible clasp arms. Conventional clasps may negatively affect aesthetics, particularly when abutment teeth are located in the anterior or premolar region. Precision and semi-precision attachments provide an alternative retentive mechanism and have historically been associated with favorable aesthetics and load distribution, although they require more complex clinical and laboratory procedures [2,3]. Patient-centered studies also indicate that retention, chewing ability, and aesthetics are important determinants of satisfaction with removable partial dentures [7,8].

Despite these advantages, attachment-retained prostheses are not without limitations. They require careful preparation of the abutment teeth, sufficient prosthetic space, precise laboratory procedures, and accurate coordination between the fixed and removable components. Technical complications may include wear or loss of retention of the attachment components, while biological complications may involve caries, periodontal deterioration, or loss of abutment teeth. A five-year clinical follow-up of prefabricated precision attachments demonstrated better clinical performance for bilaterally retained removable prostheses than for unilateral designs, while attachment wear and abutment tooth fracture were among the observed causes of failure [9].

Maintenance of the remaining dentition is therefore essential for long-term success. Earlier reviews have shown that removable partial dentures can be compatible with periodontal health when appropriate prosthetic design, adequate oral hygiene, and regular maintenance are provided [10]. More recent systematic evidence similarly indicates high five-year survival rates for removable partial dentures, although abutment teeth may present a higher risk of extraction and require careful monitoring [11]. Other studies have reported an increased risk of plaque accumulation, gingival inflammation, and dental caries in RPD wearers, with direct abutment teeth requiring particularly careful monitoring [12,13].

The present clinical case illustrates the practical application of these principles. The use of preserved maxillary teeth as abutments for the fixed component, combined with stud-type attachments for retention of the removable component, enabled rehabilitation of extensive edentulous areas without relying exclusively on a conventional removable prosthesis. The resulting reconstruction provided satisfactory retention, stability, function, and aesthetics at the time of delivery. Nevertheless, as this report describes a single clinical case without long-term follow-up, no conclusions regarding long-term survival can be drawn. Regular clinical monitoring of the abutment teeth, attachment components, and removable prosthesis remains necessary.

Conclusion

Combined fixed–removable prosthetic rehabilitation can provide an effective treatment option for patients with extensive partial tooth loss when exclusively fixed rehabilitation is not feasible. In the presented clinical case, preservation of the remaining maxillary teeth and their incorporation into the fixed prosthetic component, combined with stud-type attachments for retention of the removable component, resulted in satisfactory retention, stability, function, and aesthetics.

Careful selection of the abutment teeth, appropriate prosthetic design, precise clinical and laboratory procedures, and regular follow-up are essential for maintaining the functional integrity of the reconstruction.

INFORMED CONSENT: Written informed consent was obtained from the patient for treatment documentation and publication of the clinical photographs.

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RESOURCE-UTILISATION AND INTERNAL EFFICIENCY OF MEDICAL AND HEALTH SCIENCES PROGRAMMES IN EKITI STATE UNIVERSITIES, NIGERIA: IMPLICATIONS FOR QUALITY AND SUSTAINABLE HEALTH WORKFORCE DEVELOPMENT

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ABSTRACT
This study examines the correlation between resource utilisation and internal efficiency of medical and health sciences programmes in Ekiti State universities, and it implications for sustainable health workforce development. A survey research design was employed for the study. The sample size for this study is 240 academic and clinical personnel in three universities, sampled through proportionate stratified sampling technique. Resource Utilisation and Internal Efficiency Questionnaire (RUIEQ) was used to gather data for this study, and this yielded a reliability coefficient of 0.91. Mean, Standard Deviation, Pearson Product-Moment Correlation and Multiple Regression methods were used to analyse the data at 0.05 level of significance. It was found that human resources and physical/infrastructural resources were utilised at a high level, whereas the utilisation of clinical-resources, technological resources and financial resources were moderate. The internal efficiency was found to be significantly positively related to human-resource utilisation ($r = .486$, $p < .001$), physical/infrastructural-resource utilisation ($r = .421$, $p < .001$), clinical-resource utilisation ($r = .583$, $p < .001$), technological-resource utilisation ($r = .396$, $p < .001$) and financial-resource utilisation ($r = .424$, $p < .001$). The five dimensions together accounted for 51.5% of the variance ($R^2 = .515$; $F(5, 234) = 49.67$; $p < .001$) in internal efficiency as revealed by regression analysis. Clinical-resource utilisation contributed the most ($\beta = .398$, $p < .001$). The study therefore concluded that appropriate resource utilization is significantly correlates with the efficiency of medical and health sciences programmes in Ekiti State universities, Nigeria and it was recommended that the universities system should adopt integrated resource planning to improve the efficient utilisation and allocation of available resources in order to enhance the efficiency of medical and health sciences programmes in Nigeria, among others.
Keywords*:* resource-utilisation; internal efficiency; medical education; health sciences education; health workforce

Introduction
Universities constitute a major component of the human-capital development system of any nation, and their contribution is particularly critical in medical and health sciences, since graduates of these programmes make up a significant share of the professional workforce required to deliver healthcare services. According to the World Health Organization (WHO, 2026; WHO, 2024a) the world would experience a shortage of around 11 million health workers by 2030, a situation that will be disproportionately affecting LLMICs such as Nigeria. In order to address this gap, Frenk et al. (2010) has argued that a more profound change is needed in the way health-professions education is delivered; the competencies that are generated by training institutions need to match the needs of the current health systems. This shifts the focus from the internal capacity of universities to train health professionals and the efficiency of their use from the educational to the public-health perspective.
But the creation of competent health workers is a heavy resource demand. The success of medical and health sciences programmes relies on the quality of the academic and clinical teaching staff, laboratories, teaching hospitals, simulation facilities, libraries, digital infrastructure, practical equipment, and adequate funding. In a recent critical review of undergraduate medical education in Nigeria, Basil et al (2026) attribute chronic underfunding, poor infrastructure, faculty shortage and lack of clinical exposure as endemic structural problems faced by the sector. Most importantly, the availability of these resources does not ensure positive educational results; also important is how available resources are accessed, used and allocated appropriately. The distinction between provision and use of resources is a well-established body of educational-management literature. Abdulkareem, Fasasi and Akinnubi (2011), for example, revealed a significant positive relationship between human-resource utilisation and internal efficiency in Nigerian state universities ($r = .347$) while Akinnubi (2010) observed that effectiveness of resource

utilisation, not the amount of resources, was the key factor in institutional efficiency through strategic plans. A similar study that targeted physical resources specifically, Akinnubi and Oladimeji (2021) studied space utilisation, time utilisation and wastage indicators, and concluded that there was a significant relationship between physical-resource utilisation and internal efficiency in Nigerian universities.

The present study's outcome variable of interest is internal efficiency, or how effective an educational system is at making the expected outputs from its inputs with minimal wastage. Completion, drop-out, promotion and repetition rates are cited as some of the empirical indicators of inefficiency by Onyali and Nnebedum (2021), whereas in the secondary-education sub-sector, Akinsolu (2012) found that poor resource utilisation had a significant relationship with inefficiency which had a downstream effect on professional programmes that require a steady and well-trained stream of graduates, like medicine. The medical and health sciences are particularly vulnerable to these concerns as there is a strong practical and clinical emphasis in education: students' progress is affected if they cannot gain access to working laboratories, clinical placements, equipment, qualified supervisors, etc. and if any of these are underutilized, it can have a direct impact on delayed progress, repetition of coursework, and extended time-to-completion.

From an empirical point of view, five sub-dimensions of resource utilisation are of special importance for medical and health sciences programmes. The first is human-resource utilisation; this has been observed to be significantly related to institutional efficiency (Abdulkareem et al., 2011). The second, physical/infrastructural-resource utilisation relates to lecture rooms and laboratories/teaching hospital facilities, which has also been associated with internal efficiency by Akinnubi and Oladimeji (2021), and supported by Ebehikhalu and Dawam (2016) who noted that teaching and learning infrastructure among Nigerian universities is often below the national minimum standards. The third – instructional/clinical-resource utilisation – is arguably the most unique to health-professions training, and is a persistent problem in health-professions education in Nigeria as Ogunode and Mgbemena (2023) reported the lack of adequate and poorly prioritised funding as a persistent obstacle to the effective clinical and laboratory training of medical students in Nigeria, while KingPriest et al. (2023) reported poor exposure of Nigerian medical trainees to basic surgical procedures and Olasoji, Mu'azu and Garba (2019) reported limited exposure of clinical teachers to bedside-teaching in Nigeria. Technological-resource utilisation' is the fourth domain, which is of growing importance as digital infrastructure, such as learning-management systems, internet-based databases and digital learning materials, contribute to the learning beyond the classroom. In the fifth, utilisation of financial resources, it is explored if funding, no matter how limited is used for programme priorities such as clinical training, equipment maintenance and student support, Ogunode and Mgbemena (2023) have once again identified funding misallocation as being a recurrent constraint particularly for clinical and laboratory training.

This is accentuated by the current trend of health workers' migration in Nigeria. Umar, Salihu and Azuine (2025) noted the trend of brain drain of Nigerian health professionals, citing factors such as low remuneration, poor working environment and limited career progression opportunities as drivers which led to the Federal Government in collaboration with WHO and the UK Government authorising a National Health Workforce Migration Policy in 2024 (WHO, 2024b). In this context, the efficient production of competent health personnel, not in terms of speed, but in terms of timely and appropriately prepared students in their programmes, is an increasingly urgent national concern.

Despite all of this evidence, the literature on the utilization of these resources in Nigeria has been based on discrete analysis of a single category of resource utilization or based on university education in general and not on medical and health sciences education specifically. Abdulkareem et al (2011) studied human-resource utilisation and Akinnubi and Oladimeji (2021) studied physical-resource utilisation but none of both studies studied the combined and synergistic effect of human, physical/infrastructural, instructional/clinical, technological and financial resources together and none of both studies focused on programmes that are very clinical and practical like medical and health sciences education. This is an important empirical deficiency since medical and health sciences programmes are unique in that they require a wide range of resources, from staffing to infrastructure and clinical placement, technology and funding, to be deployed and used to create one competent medical graduate. The present study, therefore, examined the relationship between resource utilisation and internal efficiency of medical and health sciences programmes in Ekiti State, Nigeria's Universities, with the goal of informing sustainable health workforce development and quality assurance.

Statement of the Problem

The health system in Nigeria requires a large of number of heath care workers. However, it faces the challenges of insufficient quantity and quality of health workers, migration of health workers, disparity in distribution and poor retention. Underinvestment in the education and training of health workers and a disconnect between educational and job strategies are contributing factors to these professional shortages, as identified by WHO (2024a). A competent health professional is expected to be produced by the universities to help address this challenge. However, medical and health sciences education demands significant investments in human resources, infrastructure, clinical facilities, equipment and technology, and instructional materials and the supply of these may not result in educational efficiencies. Laboratories might be lacking equipment and/or consumables, teaching hospitals might be available but have limited clinical placement opportunities; teaching staff might be overworked; digital resources might not be used to their full extent; and available funding may not always align with programme priorities. This is exactly what Ebehikhalu and Dawam (2016) observe in Nigerian universities, that teachers and learner's infrastructure is generally not always up to the national minimum standard, and Ogunode and Mgbemena (2023) in their study of medical education, identify lack of adequate and poorly prioritised funding as a constant challenge to effective clinical and laboratory training in medical education in Nigeria. This mismatch between the provision of resources and their use can also be reflected in pupil repetition, pupils taking longer to leave, and pupils dropping out and other measures of educational wastage

Previous studies in Nigeria have established the relationship between certain resource utilisation categories and internal efficiency in universities in general. Abdulkareem et al. (2011) also reported that there was significant relationship between human-resource utilisation and internal efficiency; and Akinnubi and Oladimeji (2021) noted that there was significant relationship between physical-resource utilisation and internal efficiency. There has, however, been relatively little empirical research on the synergistic effect of human, physical/infrastructural, instructional/clinical, technological and financial resources, taken together, on medical and health sciences programmes in particular - programmes that are characterised by a strong practical and clinical component that differentiates them from other university programmes. This study therefore aims to examined the relationship between resource utilisation and internal efficiency of medical and health sciences programmes in universities in Ekiti State. Specifically, this study seeks to:

1. assess the level of internal efficiency of medical and health sciences programmes in universities in Ekiti State.
2. determine the level of human-resource utilization of medical and health sciences programmes in universities in Ekiti State
3. examine the relationship between each resource-utilisation dimension and internal efficiency; and
4. investigate the joint and relative contributions of the resource-utilisation dimensions to internal efficiency.

Research Questions

The following research questions were answered:

1. What is the level of internal efficiency of medical and health sciences programmes in universities in Ekiti State?
2. What is the extent of resource utilization for medical and health sciences programmes in universities in Ekiti State
3. What is wastage rate in medical and health sciences programmes in universities in Ekiti State?

Hypotheses

$H0_1$: There is no significant correlation between human-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State

$H0_2$: There is no significant correlation between physical/infrastructural-resource and internal efficiency of medical and health sciences programmes in universities in Ekiti State

$H0_3$: There is no significant correlation between instructional/clinical-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State

$H0_4$: There is no significant correlation between technological-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State
$H0_5$: There is no significant correlation between financial-resource utilisation and internal efficiency of medical and health sciences programmes in universities in Ekiti State

$H0_6$: Resource utilization (human-resource utilization, physical/infrastructural-resource, instructional/clinical-resource utilization, technological-resource utilization, and financial-resource utilisation) will not significantly have relative correlation with internal efficiency of medical and health sciences programmes in universities in Ekiti State

$H0_7$: There is no significant joint correlation between resource utilization (human-resource utilization, physical/infrastructural-resource, instructional/clinical-resource utilization, technological-resource utilization, and financial-resource utilisation) and internal efficiency of Medical and Health Sciences programme in universities in Ekiti State

Conceptual Framework

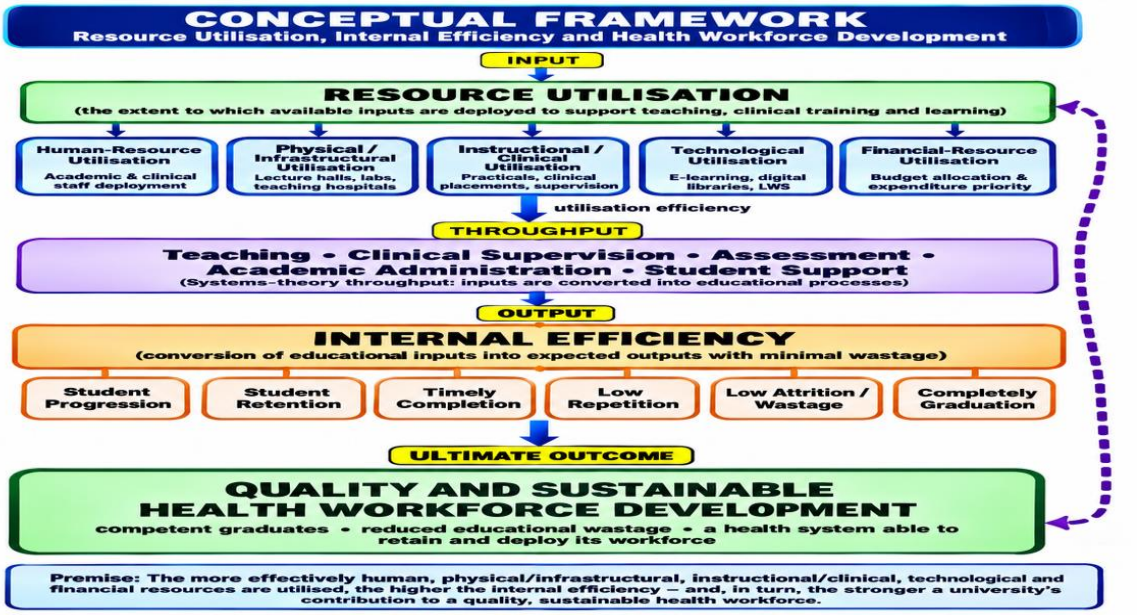


Figure 1: Conceptual Framework of Resource Utilisation, Internal Efficiency and Health Workforce Development

Source: Researcher's conceptualisation (2026), informed by Bertalanffy's (1968) systems theory and the internal-efficiency indicators used by Onyali and Nnebedum (2021).
The conceptual framework for this study is represented in the above diagram which positions resource utilisation as an input in medical and health sciences education, internal efficiency as an output and as an ultimate outcome, sustainable health workforce development sits in between the two. Resource utilisation is broken down into five distinct categories: human-resource, physical/infrastructural-resource, instructional/clinical-resource, technological-resource and financial-resource utilisation, all of which represent a different type of educational input that can be used more or less efficiently regardless of the provisioning of the underlying resource. Throughput of teaching, clinical supervision, assessment, academic administration and student support are influenced by these five dimensions and are a determinant of internal efficiency. The internal efficiency is broken down into six specific indicators which can be observed: student progression, student retention, timely completion, low repetition, low attrition/wastage, and completion/graduation. The framework also assumes a feedback relationship, as theorized for the study under a systems perspective. Results of internal efficiency – and ultimately health workforce development – re-inform planning and resource allocation in successive cycles in universities.

From this perspective, better resource use should improve the capacity of medical and health sciences education to keep students in the system, support their advancement and graduation on time, thus creating a stronger health workforce that these programs would provide over time.

Theoretical Framework

This research was based on the formulation of Bertalanffy (1968) of the System Theory. In this view, a university is a collection of elements, interconnected and which are constantly exchanging information and resources with its surroundings, it can be classified as an open system. The inputs of the system are the academic and clinical staff, students, finance, physical infrastructure, equipment, technology and instructional resources in medical and health sciences education. The inputs are passed through the system through educational processes, which include teaching and practical training, clinical supervision, assessment, counselling and academic administration. The outputs include graduates, professional competencies and, ultimately, health professionals entering the healthcare system. A systems theory approach is relevant to the study because inefficiency in one part of the system can be passed on to affect the other parts of the system. For example, lack of clinical facilities may limit hands-on learning, impacting student progress and potentially leading to delayed graduation. This interrelatedness makes it more appropriate than examining these categories of resource utilisation separately and means that the feedback loop shown in the conceptual framework in figure 1 exist.

Methodology

This study used correlational survey design to study the relationship of resource utilisation and internal efficiency, where the study variables were not manipulated. The population consisted of the academic and clinical staff of three universities in Ekiti State which include Ekiti State University (EKSU), Federal University Oye-Ekiti (FUOYE) and Afe Babalola University (ABUAD) involved in medical and health science programmes. Proportionate stratified sampling was used to select a sample of 240 respondents, each stratum being the individual universities. The researcher developed Resource Utilisation and Internal Efficiency Questionnaire (RUIEQ) which consisted of the items pertaining to human-resource, physical/infrastructural, instructional/clinical, technological, financial-resource utilisation and internal efficiency were measured on five-point scales. The instrument was validated by specialists of Educational Management, Medical Education and Measurement and Evaluation. The internal consistency of the pilot test was high with a Cronbach alpha coefficient of 0.91. Questionnaires were face-to-face administered to those who consented with assurance of confidentiality and anonymity. The 240 questionnaires were collected and 100% of them were usable. The Research Questions were analysed using mean and standard deviation, the hypotheses were tested by Pearson Product-Moment Correlation and $H0_6$ was tested by Multiple Regression. All hypotheses were tested at the p value of 0.05 with null hypotheses being rejected if p values were < 0.05.

Result and Findings

Research Question 1: What is the level of internal efficiency of medical and health sciences programmes in universities in Ekiti State?

Table 1: Level of internal efficiency of medical and health sciences programmes in universities in Ekiti State

Cohort		Output at the end of 6th Session			
	No of Students Admitted	Enrolled	Graduated	Quotient	Percentage
2019/2020	108	92	79	0.86	86
2020/2021	136	129	102	0.79	79
2021/2022	142	140	108	0.77	77
2022/2023	215	207	164	0.79	79
2023/2024	232	224	188	0.84	84
Average	167	158	128	0.81	81

Table 1 presented that level of internal efficiency of medical and health sciences programmes in universities in Ekiti State. The table revealed that the internal efficiency quotient of the medical and

health sciences programmes in universities in Ekiti State at the end of the 6th session was 0.81, representing 81%. By implication, 81% of the students who enrolled for medical and health sciences programmes graduated after the statutory 6 years. This is further represented as shown in the graph below

Figure 2: Level of Internal Efficiency of Medical and Health Sciences Programmes

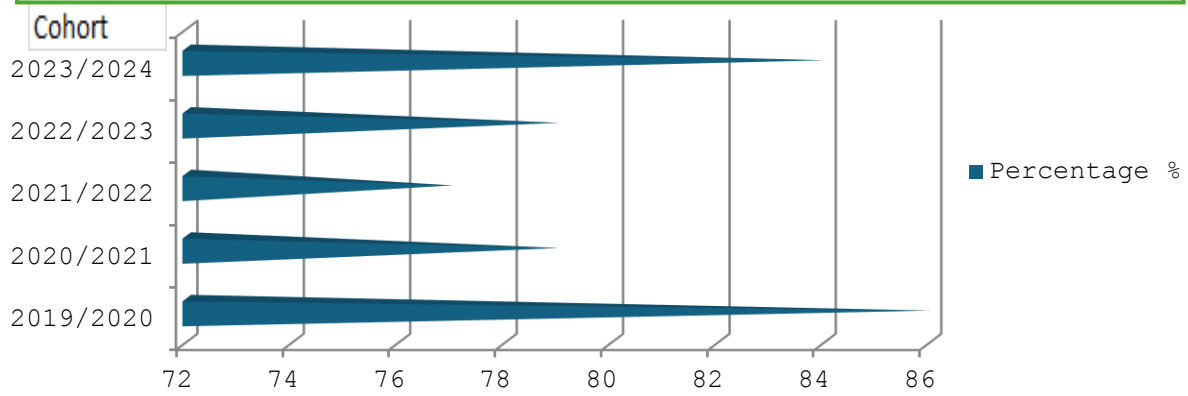


Figure 2 shows that the internal efficiency of medical and health sciences programmes in the universities in Ekiti State was relatively high in the five cohorts. It was highest at 86% in 2019/2020, declined to 79% in 2020/2021, reached its lowest point of 77% in 2021/2022, and subsequently improved to about 79% in 2022/2023 and 84% in 2023/2024. This indicated a temporary dip in internal efficiency which was subsequently made good by a significant improvement in the most recent cohort, thus suggesting a relatively effective achievement of programmes within the statutory period.

Research Questions 2: What is the extent of resource utilization for medical and health sciences programmes in universities in Ekiti State

Table 2: Extent of Resource Utilization for Medical and Health Sciences Programmes in Universities in Ekiti State

Items	Highly Utilized	Moderately Utilized	Slightly Utilized	Not Utilized	Mean	SD
Human-resource utilization	136 56.7%	95 39.6%	6 2.5%	3 1.3%	3.41	0.72
Physical/infrastructural utilization	169 70.4%	41 17.1%	28 11.7%	2 0.8%	3.28	0.76
Instructional/clinical utilization	144 60.0%	84 35.0%	9 3.8%	3 1.3%	3.17	0.81
Technological utilization	108 45.0%	89 37.1%	36 15.0%	7 2.9%	3.09	0.84
Financial utilization	127 52.9%	66 27.5%	31 12.9%	16 6.7%	3.05	0.79
Weighted Mean (WM) =					3.20	0.65

Decision Level (DL) = 2.5; WM > DL

The weighted mean score of all the resource utilization variables was 3.20, which was used as the criterion for the assessment. Human-resource utilisation and physical/infrastructural-resource utilisation had highest mean scores, with utilisations scored as high (M = 3.41, SD = 0.72) and very high (M = 3.28, SD = 0.76), respectively. Instructional/resourc utilisation (M = 3.17), technological-resource utilisation (M = 3.09) and financial-resource utilisation (M = 3.05) were lower than the grand mean and thus were used to a moderate level. The overall picture suggests that in general the participating universities have utilised resources positively, but that clinical-resource utilisation, technological-resource utilisation and financial-resource utilisation needs special attention, especially as medical and health sciences education is based on hands-on practice.

Research Questions 3: What is wastage rate of medical and health sciences programmes in universities in Ekiti State?

Table 3: Wastage Rate of Medical and Health Sciences Programmes in Universities in Ekiti State

				Total Dropout at Graduation (6th Session)			Total Spill over			Total Wastage		
Cohort	Admit	Enrol	Grad	No	Quotient	%	No	Quotient	%	No	Quotient	%
2019/2020	108	92	79	7	0.076	7.6	9	0.097	9.7	16	0.174	17.4
2020/2021	136	129	102	13	0.101	10.1	14	0.109	10.9	27	0.209	20.9
2021/2022	142	140	108	2	0.014	1.4	0	0	0	2	0.014	1.4
2022/2023	215	207	164	1	0.005	0.5	7	0.034	3.4	8	0.039	3.9
2023/2024	232	224	188	3	0.013	1.3	5	0.022	2.2	8	0.036	3.6
Average	167	158	128	5.2	0.042	4.5		0.052	5.24	12.2	0.094	9.44

Note: Admit = No of Student admitted; Enrol = No of Student Enrolled; Grad = No of Student Graduated

As shown in table 3, the percentage of wastage in Medical and Health Sciences programmes in the universities in Ekiti State is an average of 9.44% which accounts for an average of 4.5% dropout rate and an average of 5.24% spill-over rate. The highest wastage rate was 20.9% among the cohort 2020/2021 and the lowest was 1.4% in 2021/2022. The finding indicates that the programmes have a relatively high internal effectiveness, but there is still a drop-out or delayed completion of some students. This has implications for the effective use of institutional resources and requires greater academic support and monitoring of students as well as better planning to reduce wastage and to make the programmes more efficient and sustainable.

Test of Hypotheses

$H0_1$: There is no significant correlation between human-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State

Table 4: Correlation between Human-Resource Utilisation and Internal Efficiency

Variable	N	Df	r-cal	P-value	Decision
Human-Resource Utilisation	240	238	0.486	< .001	Rejected
Internal Efficiency	240				

Not Significant P>0.05

Table 4 shows a moderate positive relationship between human-resource utilisation and internal efficiency with a correlation coefficient of r = .486. The relationship is statistically significant, thus, $H0_1$ rejected, because p < .001, suggesting that there is significant correlation between human-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State.

$H0_2$: There is no significant correlation between physical/infrastructural-resource and internal efficiency of medical and health sciences programmes in universities in Ekiti State

Table 5: Correlation between Physical/Infrastructural-Resource Utilisation and Internal Efficiency

Variable	N	Df	r-cal	P-value	Decision
Physical/Infrastructural Utilisation	240				
		238	0.421	< .001	Rejected
Internal Efficiency	240				

Not Significant P>0.05

Table 5 reveals a significant positive relationship between physical/infrastructural-resource utilisation and internal efficiency (r = .421, p < .001) and the null hypothesis that there is no significant correlation between physical/infrastructural-resource and internal efficiency of medical and health sciences programmes in universities in Ekiti State is therefore rejected.

$H0_3$: There is no significant correlation between instructional/clinical-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State

Table 6: Correlation between Instructional/Clinical-Resource Utilisation and Internal Efficiency

Variable	N	Df	r-cal	P-value	Decision
Instructional/Clinical Utilisation	240				
		238	0.583	< .001	Rejected
Internal Efficiency	240				

Not Significant P>0.05

Table 6 shows that the bivariate correlation between the dimension of instructional/clinical-resource utilisation and internal efficiency was significant (r = .583, p < .001) and therefore, the null hypothesis was rejected.

$H0_4$: There is no significant correlation between technological-resource utilization and internal efficiency of medical and health sciences programmes in universities in Ekiti State

Table 7: Correlation between Technological-Resource Utilisation and Internal Efficiency

Variable	N	Df	r-cal	P-value	Decision
Technological-Resource Utilisation	240				
		238	0.396	< .001	Rejected
Internal Efficiency	240				

Not Significant P>0.05

Table 7 shows there was a significant positive correlation between technological-resource utilisation and internal efficiency (r = .396 p < .001) and the null hypothesis was rejected, indicating that access to technological resources and their effective use will help student progress and institutional efficiency.

$H0_5$: There is no significant correlation between financial-resource utilisation and internal efficiency of medical and health sciences programmes in universities in Ekiti State

Table 8: Correlation between Financial-Resource Utilisation and Internal Efficiency

Variable	N	Df	r-cal	P-value	Decision
Financial Utilisation	**240**				
		238	**0.424**	**< .001**	**Rejected**
Internal Efficiency	**240**				

Not Significant P>0.05

Table 8 indicates that a significant correlation was found between financial-resource utilisation and internal efficiency (r = .424, p < .001) with which led to the rejection of the null hypothesis that there is no significant correlation between financial-resource utilisation and internal efficiency of medical and health sciences programmes in universities in Ekiti State.

H0$_6$: Resource utilization (human-resource utilization, physical/infrastructural-resource, instructional/clinical-resource utilization, technological-resource utilization, and financial-resource utilisation) will not significantly have relative correlation with internal efficiency of medical and health sciences programmes in universities in Ekiti State

Table 9: Relative Correlation of Resource utilization (human-resource utilization, physical/infrastructural-resource, instructional / clinical-resource utilization, technological-**resource** utilization, and financial-resource utilisation) on internal efficiency of medical and health sciences programmes in universities in Ekiti State

Dependent Variable	Independent Variable	Unstandardized Coefficient		Stand. Coefficient	t	Sig.
		B	Std. Error	Beta Contribution		
Internal Efficiency of Medical and Health Sciences Programme	Human-Resource Utilization	0.239	0.051	0.239*	4.650	0.001
	Physical/Infrastructural Utilisation	0.134	0.051	0.134*	2.620	0.009
	Instructional/Clinical Utilisation	0.398	0.050	0.398*	7.911	0.001
	Technological Utilization	0.144	0.051	0.144*	2.837	0.005
	Financial Utilization	0.127	0.052	0.127*	2.457	0.015

Table 9 showed that the relative correlation of the dependent variable (Human-Resource Utilization, Physical/Infrastructural Utilisation, Instructional/Clinical Utilisation, Technological Utilization, and Financial Utilization) with resources utilization in universities in Ekiti State were obtained as, Human-Resource Utilization ($\beta = 0.239$, $P < 0.05$), Physical/Infrastructural Utilisation ($\beta = 0.134$, $P < 0.05$), Instructional/Clinical Utilisation ($\beta = 0.398$, $P < 0.05$), Technological Utilization ($\beta = 0.144$, $P < 0.05$), and Financial Utilization ($\beta = 0.127$, $P < 0.05$). The results from the table showed that all the five resource utilization variables (human-resource, physical/infrastructural, instructional/clinical, technological and financial-resource utilization) were found to be significantly correlated with internal efficiency of Medical and Health Sciences programmes with none of the five variables being non-significant. This indicates that all the dimensions of resource use studied in this study were correlated with the internal efficiency of the Medical and Health Sciences programmes in the Universities in Ekiti State, with the most of the relative contribution being instructional/clinical-resource utilisation ($\beta = 0.398$) followed by human-resource utilisation ($\beta = 0.239$).

Table 5:Joint Correlation of Resource utilization (human-resource utilization, physical/infrastructural-resource, instructional/clinical-resource utilization, technological-resource utilization, and financial-resource utilisation) on internal efficiency of medical and health sciences programmes in universities in Ekiti State

Model	Sum of Squares	Df	Mean Square	F	Sig	Rmks
Regression	5660.273	5	1132.055			
Residual	3547.179	235	15.094	75.0	0.005	Sig.
Total	9207.452	240				

R = 0.718
R Square = 0. 615
Adjusted R Square = 0.607
Std. Error of the Estimate = 0.859

The analysis of hypothesis seven, which was the correlation among the indicators of resource utilization (human-resource utilization, physical/infrastructural-resource utilization, instructional/clinical-resource utilization, technological-resource utilization and financial-resource utilisation) with the internal efficiency of Medical and Health Sciences programmes in the universities in Ekiti State, is presented in Table 10.

The result reveals that the resource utilization indicators have a high level of joint correlation, while the internal efficiency of the Medical and Health Sciences programmes in the universities in Ekiti State is also high ($R = 0.718$; $R^2 = 0.615$; $F = 75.0$). The result indicates that the internal efficiency of Medical and Health Sciences programmes in the universities in Ekiti State was explained by all the variables of resource utilization with an explanatory power of 61.5% (Adjusted R square of 0.607) which shows that the model explained the variance in the internal efficiency of Medical and Health Sciences programmes in the universities in Ekiti State despite the number of the variables of resource utilization and the sample size used. The other 38.5% may be picked up by other exogenous variables not accounted for in the study. Based on this, the joint correlation is found to be significant ($F(5, 235) = 75.0$; $P < 0.05$), so the null hypothesis ($H0_7$) is rejected. This suggests that the correlation between the two is joint in the case of resource utilisation (human-resource, physical/infrastructural, instructional/clinical, technological, and financial-resource utilisation) and internal efficiency of Medical and Health Sciences programmes of universities in Ekiti State.

Discussion of Findings

The major finding of this study was that the level of resource utilization was generally high in the participating universities, with clear variations between resources. The mean for human-resource utilisation was the highest, and the mean for financial and technological resources was comparatively low. This supports the argument of Abdulkareem et al. (2011) who discovered that human resources are important to the internal efficiency of the university and that there is significant relationship between human-resource utilisation and internal efficiency in the State universities of Nigeria.

The second finding was that physical/infrastructural-resource utilisation significantly predicted internal efficiency which is similar with Akinnubi and Oladimeji (2021). This is especially significant in medical and health sciences where laboratories, lecture space, simulation centres and clinical facilities are essential for the preparation of medical and health science professionals.

The third and strongest finding was that instructional/clinical-resource utilisation correlated most highly with internal efficiency with the highest bivariate correlation ($r = .583$) and the highest standardised regression coefficient ($\beta = .398$) of all five predictors. This finding is significant for health-professions education, because in contrast to many other university programs, medical and health sciences programmes demand a considerable amount of practical and clinical experience, and as argued by Frenk et al. (2010), this practical and clinical education needs to change to equip students with the competencies needed for today's health systems. The finding in the present study serves as an empirical support to that argument in the context of Ekiti State. This is also in line with the national evidence of clinical training gaps obtained from KingPriest et al (2023) on a nationwide survey of Nigerian medical trainees, where inadequate exposure to the necessary surgical procedures was reported among medical trainees in the various training institutions, with Olasoji, Mu'azu and Garba (2019) reporting that clinical teachers themselves report lack of time, lack of supervision structures and lack of bedside-teaching opportunities as recurrent challenges in effective clinical training in Nigeria. These studies provide some of the answers why the use of instructional/supervised resources was found to be most strongly associated with internal efficiency in the present sample: when clinical placement and supervision capacity are limited, students' practical experience (and, in turn, their timely and competent progress) are clearly influenced.

The result on technological resources indicates that digital infrastructure is increasingly significant in terms of the efficiency in the internal sphere; the students' access to digital learning materials, online databases and learning-management platforms can assist them to access academic resources and to learn outside the classroom. Last but not least, the use of financial resources was a significant predictor of internal efficiency, implying that the efficiency of university funding is equally related to the amount of resources, as well as to their prioritisation and utilization.

Overall, the findings reinforce the conceptual model proposed in Section 6.0 that each of the five dimensions of resource-utilisation makes a significant contribution, albeit of varying strength, to the internal efficiency; and that the magnitude of this contribution is disproportionate, with instructional/clinical-resource utilisation being a far stronger influence than would be expected given the relatively high clinical and educational demands of medical and health sciences training.

Implications for Quality and Sustainable Health Workforce Development

The findings of this study have great implications for the health workforce in Nigeria. According to the WHO, there is a potential 11 million shortage of health workers in the world by 2030, and key contributing challenges include insufficient investment in education and training, retention challenges and the mismatch between education and work requirements (WHO, 2024a). Nigeria therefore cannot afford significant losses of educational investment in medical and health sciences programmes because of unexpected delays, repetition or dropout of students: this means the loss of prospective health professionals and the educational resources invested in them.

The results indicate that an increase in the use of the resources such as instructional/clinical-resource utilisation may be associated with better student progress, better completion rates, less educational wastage, greater clinical competency, better use of academic personnel, better use of labs and teaching hospitals and more qualified health professionals.

But efficiency is not just about time saved in the training process, quality should be kept in focus. Ultimately, the goal is to maximize the output of competent health professionals through existing educational resources without lowering standards, which is in line with what Frenk et al. (2010) suggested that health-professions education should be organized around competencies and the needs of health systems.

Conclusion

The study investigated the relationship between resource utilisation and internal efficiency of medical and health sciences programmes in the universities in Ekiti State. The empirical findings show that all the four variables of human, physical/infrastructural, instructional/clinical and technological and financial-resource utilisation are positively and significantly related to internal efficiency. The most important finding was that the greatest predictor of internal efficiency was instructional/clinical-resource utilisation, with the five resource dimensions accounting collectively for 51.5% of the variance in internal efficiency. These results illustrate that the use of resources is not just an administrative concern, but rather an integral part of education efficiency and health workforce development. Based on the findings and conclusions of the study,

Recommendations

Based on the findings, the following recommendations are suggested

- The clinical and instructional resources, such as laboratories, simulation facilities, instruments and teaching aids, should be given priority in universities according to the requirements of the programme.
- Admission levels should be correlated to clinical facilities and qualified supervisors, and more academic and clinical staff members should be hired to alleviate workload and enhance student supervision.
- In addition to augmenting investments in digital databases, learning-management systems, Internet connectivity and electronic instructional resources, regular preventive maintenance is to be institutionalized for laboratories, equipment and simulation facilities.
- Financial resources must be directly related to programme priorities, particularly clinical training, laboratory consumables, equipment maintenance, staff development, and student-support services, and the efficiency indicators must be monitored regularly.
- A system of early warning for universities to detect learners at risk of poor progression, delayed graduation and/or drop-out should be established, and efficiency gains should not compromise professional, regulatory and accreditation requirements.

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INVESTIGATION OF FINDINGS BEFORE AND AFTER VOICE THERAPY IN A CASE WITH UNILATERAL VOCAL FOLD ATROPHY AND MUSCLE TENSION DYSPHONIA

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Objective: This study aimed to compare multidimensional voice assessment findings before and after voice therapy in a case with right vocal fold atrophy and muscle tension dysphonia.

Materials and Methods
A 15-year-old male underwent demographic and medical history review, laryngeal imaging, acoustic, aerodynamic, self- and proxy-report, and auditory-perceptual assessments. For acoustic analysis, a 5-second sustained /a/ vowel and connected speech samples were recorded. Twenty-two time-based parameters were visually examined using the Multi-Dimensional Voice Program (MDVP), and the multiparametric Acoustic Voice Quality Index (AVQI), which incorporates time- and frequency-based measures, was calculated using Praat software. Maximum phonation times (MPTs) for /a/, /s/, and /z/ were measured for aerodynamic assessment. The Pediatric Voice Handicap Index-10 (pVHI-10) and the Teacher-Reported Pediatric Voice Handicap Index were administered. The recordings used for acoustic analysis were also evaluated perceptually. Following the initial assessment, the patient received voice hygiene education, counseling, and an individualized voice therapy program.

Results
The patient reported a two-year history of voice complaints. Laryngeal imaging revealed right vocal fold atrophy and an I-shaped glottal closure defect. Marked muscle tension was observed during sustained phonation and connected speech. Before therapy, the MDVP display showed a large red area indicating parameters outside normative limits. After therapy, the green area representing parameters within normative limits increased, while the red area decreased substantially. The AVQI score decreased from 5.18 before therapy to 1.36 after therapy. No meaningful change was observed in MPT values. Self- and proxy-report scores decreased after therapy, indicating reduced perceived voice-related impact. Auditory-perceptual assessment also demonstrated a clear improvement in voice quality.
Conclusion: Voice hygiene education, counseling, and voice therapy provided by speech-language pathologists may improve voice quality and voice-related quality of life in individuals with vocal fold atrophy and muscle tension dysphonia.
Keywords: Voice therapy, vocal fold atrophy, dysphonia, muscle tension

Introduction
Voice disorder is defined as a condition in which an individual's voice quality, pitch, and/or loudness are inconsistent with age, sex, cultural background, or individual communication needs, or negatively affect the individual's ability to meet daily vocal demands (1). Voice disorders may arise from organic, functional, or neurogenic causes and may affect different components of the voice production mechanism depending on the etiology (2).
The management of voice disorders is planned according to the etiology and severity of the disorder, laryngeal findings, and the individual's communication needs, and may include voice therapy, medical treatment, surgical intervention, or a combination of these approaches (3). Among these approaches, voice therapy is an important intervention option, particularly for voice disorders in which behavioral and functional components predominate. In muscle tension dysphonia (MTD), behavioral voice therapy is considered the primary treatment approach, and therapy has been reported to be effective in improving vocal function and voice quality (4). Similarly, voice therapy is frequently preferred as a first-line conservative intervention for vocal fold nodules and may improve various voice outcomes (5). In addition, significant improvements in patient-reported, auditory-perceptual, and aerodynamic voice measures have been reported following voice therapy in individuals with vocal fold atrophy (6). Voice therapy may also be used as a conservative option in the management of selected neurogenic voice disorders, such as unilateral vocal fold paralysis, and may be combined with surgical interventions

depending on the patient's clinical characteristics (7). Therefore, voice therapy plays an important role in optimizing vocal function and reducing the impact of voice disorders in appropriately selected cases. The aim of this study was to comparatively present multidimensional voice assessment findings before and after voice therapy in a case with right vocal fold atrophy and muscle tension dysphonia.

Development

The voice complaints of the 15-year-old male patient had been present for approximately two years. The patient reported that the voice problem was more pronounced during the winter months and decreased during the summer but did not completely resolve. He described feeling as though there was an obstacle preventing him from producing his voice and stated that he was unable to increase his vocal loudness sufficiently. His voice was reported to be particularly worse in the morning. His medical history included rhinitis, and he had recently started nasal steroid treatment at the time of the assessment. The patient had no history of surgery. Examination of his vocal behaviors revealed frequent talking, shouting, and throat clearing; daily water intake was approximately 1 L, and coffee consumption was two cups per day.

Laryngeal imaging performed with a 70-degree rigid endoscope revealed right vocal fold atrophy and an I-shaped glottic closure defect. Marked muscle tension was observed during the auditory-perceptual evaluation of /a/ phonation and connected speech recordings containing CAPE-V sentences, as well as during spontaneous conversation (8, 9).

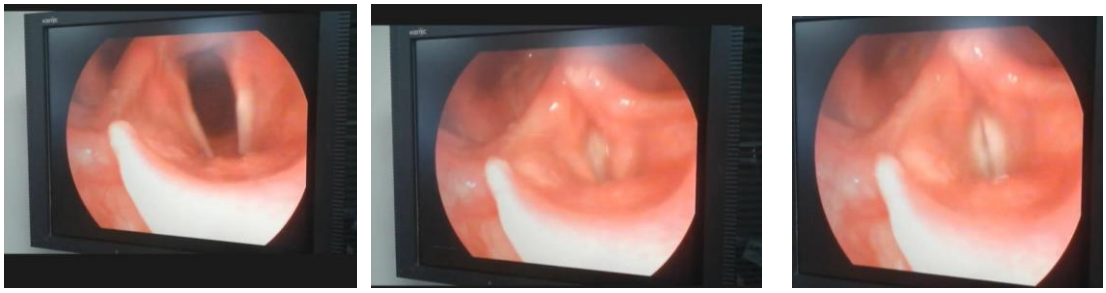


Figure 1. Laryngeal imaging findings of the patient

To obtain a multidimensional evaluation of the patient's voice characteristics, acoustic, aerodynamic, auditory-perceptual, and self-/proxy-report measures were performed. For the acoustic assessment, a 5-second sustained /a/ phonation and a connected speech recording using CAPE-V sentences were obtained. The sustained /a/ recording was analyzed using the Multi-Dimensional Voice Program (MDVP), and 22 time-domain acoustic parameters were visually evaluated. The Acoustic Voice Quality Index (AVQI) was calculated using Praat software based on a 3-second sustained /a/ phonation and the third and fourth CAPE-V sentences (10, 11). In the aerodynamic assessment, maximum phonation times for /a/, /s/, and /z/ were measured. To assess the extent to which the voice problem affected the patient physically, functionally, and emotionally, the Pediatric Voice Handicap Index-10 (pVHI-10) and the Teacher-Reported Pediatric Voice Handicap Index (TR-PVHI) were administered. For the auditory-perceptual assessment, the phonation and connected speech samples recorded for the acoustic analysis were used.

Following the assessments, the patient received counseling on vocal hygiene and underwent a voice therapy program. The therapy program included relaxation exercises, semi-occluded vocal tract exercises, transition from vegetative sounds to volitional phonation, laryngeal manipulation, and auditory awareness activities using the Voice Tools application.

In the pre-therapy MDVP analysis, a greater number of red areas indicating parameters outside the normative limits were observed, whereas after therapy the green areas indicating parameters within the normative limits increased and the red areas were substantially reduced. The AVQI, a multiparametric acoustic measure, decreased from 5.18 before therapy to 1.36 after therapy.

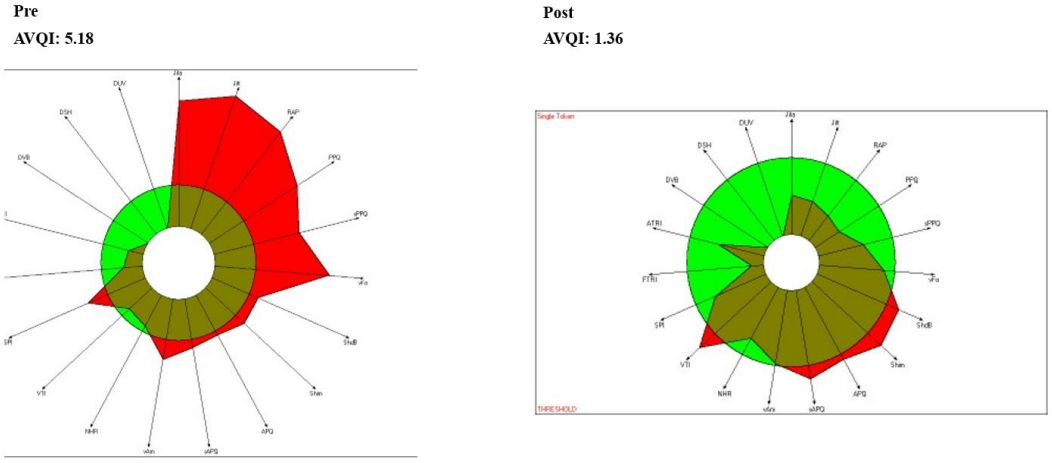


Figure 2. MDVP and AVQI findings before and after voice therapy

In the aerodynamic assessment, maximum phonation time before therapy was 15.8 s for /a/, 19.7 s for /s/, and 17.4 s for /z/; after therapy, the corresponding values were 13.8 s, 20.1 s, and 17.8 s. No marked change in maximum phonation times was observed after therapy.

A marked decrease was observed in the self- and proxy-report results. The total pVHI-10 score decreased from 12 before therapy to 2 after therapy. The total TR-PVHI score decreased from 48 before therapy to 3 after therapy. Examination of the TR-PVHI subdomains showed that the functional score decreased from 16 to 1, the physical score from 20 to 2, and the emotional score from 12 to 0. The auditory-perceptual assessment also demonstrated a marked improvement in overall voice quality and in the muscle tension observed during phonation after therapy.

Overall, marked improvements were observed after therapy in acoustic and auditory-perceptual voice characteristics and in the level of voice-related impact reported by the patient and the teacher, whereas no comparable change was observed in maximum phonation times.

Conclusion

In this case with right vocal fold atrophy and muscle tension dysphonia, marked improvements in acoustic and auditory-perceptual voice quality and in the perceived impact of the voice disorder were observed following vocal hygiene counseling and a voice therapy program tailored to the patient's needs. The marked reductions in AVQI, pVHI-10, and TR-PVHI scores indicate positive changes in both voice quality and voice-related functioning after therapy. In contrast, the absence of a marked change in maximum phonation times highlights the importance of evaluating voice therapy outcomes using a multidimensional approach that includes acoustic, aerodynamic, auditory-perceptual, and self-/proxy-report methods rather than relying on a single measure. The findings of this case suggest that voice therapy may be a useful intervention option for improving voice quality and voice-related functioning in individuals with vocal fold atrophy and muscle tension dysphonia.

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EXOSOMES IN ISCHEMIA-REPERFUSION INJURY: EXPERIMENTAL EVIDENCE AND EMERGING CLINICAL SIGNIFICANCE

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ABSTRACT

Aim: Ischemia-reperfusion injury (IRI) occurs when blood flow returns to tissue that has been deprived of it. Oxidative stress, inflammation, apoptosis and mitochondrial failure all contribute. This review asks what experimental studies show about exosomes in IRI, and how much of that work has reached patients.

Materials and Methods
We examined in vitro and in vivo studies of exosomes in cardiac, renal, cerebral, hepatic and testicular IRI. We also reviewed human ex vivo organ perfusion work, registered trials, and reports on circulating exosomal microRNAs. Studies were grouped by vesicle source, cargo, signaling pathway and target organ, then compared across models.

Results
Exosomes from MSC reduced apoptosis, infarct size and inflammation in every organ reviewed. Several mechanisms recurred. miR-486-5p suppressed PTEN and increased Akt phosphorylation. miR-223-3p acted on NLRP3 and restored mitophagy. miR-146a-5p targeted IRAK1 and reduced NF-κB signaling. miR-126a-3p engaged RISK pathway components after remote ischemic preconditioning. Nrf2/HO-1 signaling and microglial shift toward the M2 phenotype were also reported. Delivery depended partly on CXCR4 and SDF-1α, but uptake by other organs remained high. Human data were far more limited. Exosomes added during hypothermic oxygenated perfusion protected marginal donor kidneys ex vivo. Circulating exosomal microRNAs separated stroke patients from control. Therapeutic experience in patients is limited to a few early-phase stroke trials that remain confined to trial registries. In the most widely cited of these, exosomes were delivered about a month after stroke onset, well outside the reperfusion window that the preclinical rationale addresses.

Conclusion
The animal evidence agrees across organs. Clinical translation remains constrained by the lack of GMP-compatible isolation and scale-up protocols, of validated potency and release criteria, and of dose-response and pharmacokinetic data defining the therapeutic window, together with the absence of trials in which administration is timed to reperfusion.
Keywords: exosomes, extracellular vesicles, ischemia-reperfusion injury, microRNA, clinical translation

Introduction

Ischemia-reperfusion injury (IRI) is a pathological process that arises when perfusion is restored to a tissue subjected to an interruption of blood flow, and it can exceed the damage produced by ischemia alone. Clinically, it is encountered during reperfusion therapy for myocardial infarction, recanalization in ischemic stroke, implantation in solid organ transplantation, and removal of the cross-clamp in major vascular surgery. What these settings share is that the very intervention required to salvage the tissue also initiates a second and often more destructive phase of injury [1,2].

The molecular basis of this injury is multifactorial. During the ischemic phase, the arrest of oxidative phosphorylation depletes the intracellular ATP pool, ion pump function is impaired, and intracellular calcium accumulates. Upon reperfusion, the abrupt delivery of oxygen to mitochondria drives a rapid burst of reactive oxygen species. The combination of calcium overload and oxidative stress promotes opening of the mitochondrial permeability transition pore, loss of membrane potential, and cell death. Superimposed on this is a sterile inflammatory response, triggered by endogenous danger signals released from injured cells, together with neutrophil infiltration [1–4].

Over the past two decades, pharmacological interventions directed at this process have not produced comparable effects at experimental and clinical levels. Accordingly, the evaluation of any new

therapeutic candidate in IRI requires that translational conditions, and not efficacy alone, be examined from the outset [3,5].

In this context, exosomes have become one of the most extensively studied candidates of the past decade [6,7]. Their cell-free composition, low immunogenicity, capacity to cross biological barriers [8], and ability to carry regulatory RNA and protein [9] confer advantages over conventional cell-based therapies. Their protective effects have been demonstrated in five separate organ systems (heart [10,11], kidney [12,13], brain [8,14], liver [15] and testis [16]) using different cell sources and in independent laboratories. Studies conducted in different organs, in different models and with different preparations converge on largely the same signalling pathways and the same direction of effect [7,17]. Clinical progress, by contrast, has not matched this expectation [18].

Within the literature surveyed for this review, work on exosome-based treatment of ischemia-reperfusion injury remains limited. The aim of this review is to examine the gap between experimental consistency and clinical stagnation, and to show at which levels that gap arises. The text addresses exosome biology, IRI pathophysiology, mechanisms of action, organ-level findings, human data, differences between experimental and clinical study design, and the research priorities that follow from them.

Methods

This study is not a systematic review; a structured approach was nevertheless applied to the classification of sources. The references included were classified according to three criteria: (i) type of evidence — primary experimental study, primary human study, review, or clinical trial registration; (ii) level of model — in vitro, rodent in vivo, human ex vivo, human observational; and (iii) target organ. For each primary study, the vesicle source, the cargo carried, the targeted molecule and the signalling pathway affected were extracted separately.

Exosome Biology and Terminology

Exosomes are extracellular vesicles secreted by most cell types, with diameters ranging from approximately 40 to 150 nm [9]. They are of endosomal origin: during maturation of early endosomes, inward budding of the membrane gives rise to multivesicular bodies, and fusion of these bodies with the plasma membrane releases the intraluminal vesicles into the extracellular space. Their cargo includes proteins, lipids, messenger RNA and regulatory RNA species, most notably microRNA (miRNA) [8,19].

Exosomes may interact with recipient cells through three routes: direct membrane fusion, receptor-mediated endocytosis, or initiation of signalling via surface ligands [9,20]. Which of these predominates varies with cell type and microenvironment [20].

A substantial proportion of the preparations described as exosomes in the literature are mixed extracellular vesicle populations obtained without any separation based on biogenetic origin. Isolation methods such as differential ultracentrifugation, size-exclusion chromatography, polymer-based precipitation and immunoaffinity capture yield different purity and recovery profiles [6,21]. The International Society for Extracellular Vesicles has accordingly published minimal reporting requirements [21,22] for nomenclature, separation and characterisation. A substantial part of the existing literature, however, predates these requirements or does not comply with them. It therefore cannot be assumed that preparations bearing the same name across different studies are biologically equivalent [6,19].

The Pathophysiological Framework of Ischemia-Reperfusion Injury

The pathogenesis of IRI is considered in two successive phases. During the ischemic phase, interruption of oxygen supply halts oxidative phosphorylation, and anaerobic glycolysis leads to lactate accumulation and intracellular acidosis. Depletion of ATP impairs the function of the sodium potassium ATPase and the sarcoplasmic reticulum calcium ATPase, and intracellular sodium and calcium concentrations consequently rise [1,4].

During the reperfusion phase, the abrupt return of oxygen drives rapid production of reactive oxygen species from the electron transport chain. The swift normalisation of pH removes the protection conferred by acidosis during ischemia. The combination of calcium overload and oxidative stress leads to opening of the mitochondrial permeability transition pore and loss of mitochondrial membrane potential [2,3]. Beyond this point, cell death may proceed as necrosis, apoptosis or pyroptosis [4,23].

A sterile inflammatory response develops in parallel. Endogenous signals released from injured cells activate pattern recognition receptors, increase NF-κB dependent cytokine production [1] and trigger

assembly of the NLRP3 inflammasome. Inflammasome activation leads, through caspase-1, to maturation of interleukin-1β and to pyroptotic cell death.

This framework explains why exosome based interventions may act at several points at once. Unlike conventional pharmacological agents directed at a single molecular target, exosomes carry numerous regulatory RNAs and can therefore modulate multiple pathways simultaneously [7,8,17]. Although this property is presented as a therapeutic advantage, it complicates definition of the mechanism of action and, in turn, standardisation.

The Nature and Distribution of the Studies Reviewed

The distribution of the sources included by type of evidence is presented in Table 1. Approximately one third of the sources are reviews, and these reviews rest largely on the same set of primary studies. The volume of the literature therefore exceeds the amount of independent evidence by an appreciable margin. This suggests that part of the impression of consistency in the field may arise from repeated citation.

Table 1. Distribution of sources by type of evidence (n=40)

Type of evidence	n
Primary experimental study on the topic (animal / in vitro)	16
Primary human study on the topic	3
Review on the topic	8
Systematic review and meta-analysis	1
Clinical trial registration (no published results)	2
Background: IRI pathophysiology and cardioprotection	7
Background: vesicle biology and reporting requirements	3

The distribution of the primary studies by organ and level of model is shown in Table 2. The kidney and the heart are the most extensively investigated organs, with five studies each, and the only interventional study performed in human tissue also concerns the kidney. Two studies are available for the liver and two for the testis, so the findings for these organs rest on a narrow evidence base. Of the three human studies, two are observational and only one is interventional.

Table 2. Distribution of the primary studies by organ and level of model (n=19)

Organ	n	Level of model
Kidney	5	Rodent in vivo (4), human ex vivo (1)
Heart	5	Rodent in vivo (2), large animal (1), in vitro (2)
Brain / spinal cord	3	Rodent in vivo (2), human observational (1)
Liver	2	Rodent in vivo (2)
Testis	2	Rodent in vivo (2)
Systemic (remote ischemic preconditioning)	1	Human observational
Organ-independent (biodistribution)	1	Rodent in vivo

Two primary studies are preprints and have not undergone peer review. Since each is one of only two sources supporting the cerebral and testicular findings respectively, the corresponding results carry a lower level of evidence.

Mechanisms of Action of Exosomes

The cargo-target-pathway pairings extracted from the primary studies are collated in Table 3. These pairings are examined below on a mechanistic basis (Figure 1).

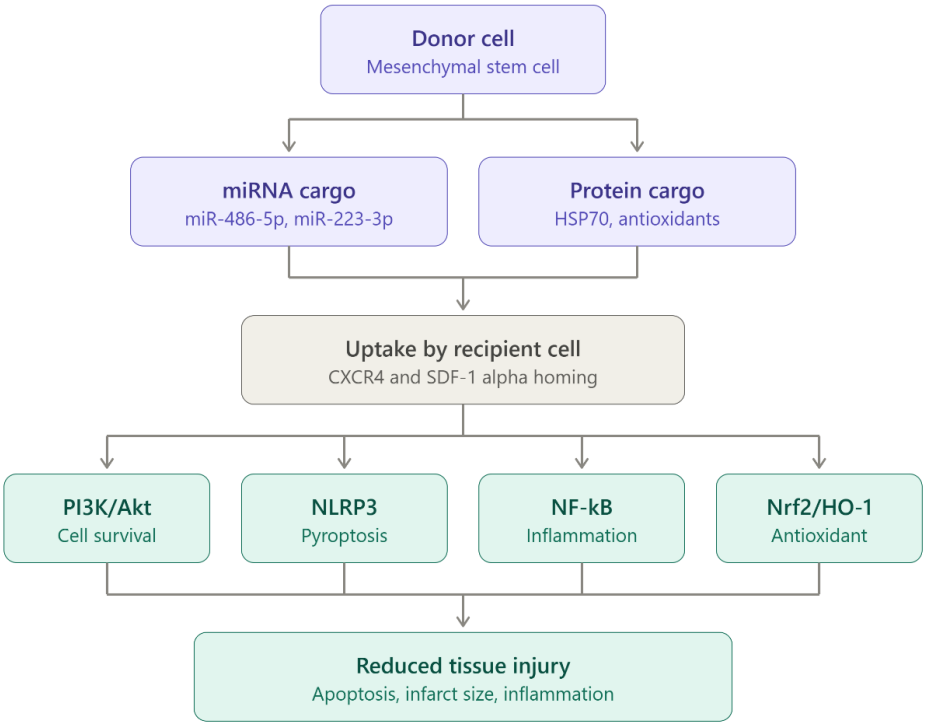


Figure 1. Exosomal cargo transfer and the protective signalling pathways engaged in ischemia-reperfusion injury

Table 3. Reported cargo-target-pathway pairings

Cargo / mediator	Target	Pathway or effect	Organ	Reference
miR-486-5p	PTEN	PI3K/Akt, anti-apoptotic	Kidney	[13]
miR-223-3p	NLRP3	Restoration of mitophagy	Kidney	[12]
miR-146a-5p	IRAK1	Reduced NF-κB signalling	Multiple	[17,24]
miR-126a-3p	RISK components	RISK pathway activation	Heart	[25]
miR-25	—	Anti-apoptotic protection	Spinal cord	[14]
miR-9, miR-124	—	Diagnostic discrimination (biomarker)	Brain	[26]
CXCR4 / SDF-1α	Receptor-ligand	Organ homing	Kidney	[20]
Nrf2 / HO-1	—	Antioxidant response	Multiple	[8,27]
MnSOD	—	Reduced oxidative stress	Liver	[15]
Microglial M1→M2	—	Reduced neuroinflammation	Brain	[8,23]

6.1. Cell survival: PTEN/PI3K/Akt and the RISK pathway. Phosphatase and tensin homologue (PTEN) is a tumour suppressor that dephosphorylates phosphatidylinositol-3,4,5-trisphosphate and thereby restrains PI3K/Akt signalling. In renal IRI models, exosomal miR-486-5p has been shown to reduce PTEN expression, with a consequent increase in Akt phosphorylation and a reduction in apoptotic cell death [13].

In cardiac models, the Reperfusion Injury Salvage Kinase (RISK) pathway is prominent. RISK comprises the PI3K/Akt and MEK1/ERK1-2 arms; it is activated at the moment of reperfusion, inhibits glycogen synthase kinase-3β and prevents opening of the mitochondrial permeability transition pore. The pathway was first defined in the context of myocardial reperfusion [2]. Plasma exosomes in the late phase of remote ischemic preconditioning have been reported to activate this pathway through transfer of miR-126a-3p and to reduce myocardial injury [25].

The identification of serum exosome profiles specific to remote ischemic preconditioning in humans is among the few findings that support the cross-species validity of this mechanism [28].

6.2. Inflammasome and pyroptosis: the NLRP3 axis.

The NLRP3 inflammasome is a multicomponent cytosolic complex activated by damage-associated molecular patterns. Its activation leads, through caspase-1, to maturation of interleukin-1β and to pyroptotic cell death. Mesenchymal stem cell derived extracellular vesicles have been shown to suppress NLRP3 expression via miR-223-3p and to alleviate renal IRI by restoring impaired mitophagy [12].

There is evidence that the same axis can operate in the opposite direction. In a hepatic IRI model, exosomes were reported to mediate hippocampal and cortical neuronal injury by activating pyroptosis [23]. This finding diverges from the general trend of the literature in showing that exosomes may act not only protectively but also as carriers of injury, and it rests on a single study.

6.3. Inflammatory signalling: IRAK1/NF-κB

Interleukin-1 receptor associated kinase 1 (IRAK1) is a downstream component of Toll-like receptor signalling and participates in NF-κB activation. Exosomal miR-146a-5p has been reported to target IRAK1 and to reduce NF-κB dependent cytokine production [17,24]. This mechanism is not organ specific and has been described in more than one tissue.

6.4. Oxidative stress: Nrf2/HO-1

Nuclear factor erythroid 2 related factor 2 (Nrf2) dissociates from its cytosolic repressor under conditions of oxidative stress, translocates to the nucleus and increases expression of genes containing antioxidant response elements, including heme oxygenase-1. Exosome administration has been reported to activate this pathway and to reduce damage attributable to reactive oxygen species [8,27].

6.5. Mitochondrial quality control

Mitophagy is the selective removal of damaged mitochondria and becomes insufficient during IRI. Exosomes have been shown to restore this process [12] and to regulate AMPK/mTOR and Akt/mTOR dependent autophagy [8,27]. Preservation of mitochondrial integrity is decisive both for maintaining energy metabolism and for limiting reactive oxygen species production.

6.6. Cellular reprogramming: microglial polarization

In cerebral IRI models, exosome administration has been reported to shift microglia from the proinflammatory M1 phenotype toward the reparative M2 phenotype and to reduce neuronal pyroptosis [8,23]. Exosomes derived from human umbilical cord MSC have been shown to preserve blood-brain barrier integrity, although this finding is at preprint level [29].

Considered together, these six mechanisms reveal the following pattern: different miRNAs are reported in different organs, yet they converge on a limited number of shared pathways. This admits two interpretations. The first is that the pathogenesis of IRI has a common core independent of organ, and that exosomes act on this core. The second is that studies preferentially measure these pathways, so that what is found is what was sought. The available data are insufficient to distinguish between the two; distinguishing them would require simultaneous, hypothesis-independent screening of multiple pathways within the same model.

Findings by Organ System

7.1. Kidney. Exosomes derived from endothelial colony forming cells have been shown to home to the kidney after ischemic injury and to accumulate in the tissue through receptor-ligand interaction [20]. Mesenchymal stem cell derived vesicles confer protection through mitophagy [12], and exosomes obtained from splenic ischemic preconditioning models have been reported to attenuate renal injury [30]. When the human ex vivo perfusion study is added to these [31], the kidney emerges as the organ carried furthest from the preclinical setting toward human application.

7.2. Heart

Exosomes derived from cardiac progenitor cells protect the myocardium after acute ischemia/reperfusion [10,11]. In large animal models, exosomes from cardiosphere derived cells have been shown to reduce scarring and to limit ventricular remodelling [32]. Exosomes from adipose derived MSC

prevent cardiomyocyte apoptosis induced by oxidative stress [33]. Plasma exosomes in the late phase of remote ischemic preconditioning reduce injury through the RISK pathway [25]. Although the cardiac data comprise the most diverse profile of vesicle sources, they contain no human interventional evidence [24,34]. A meta-analysis of stem cell derived exosomes in animal models of acute myocardial infarction reports a consistent benefit at the preclinical level [35].

7.3. Brain and spinal cord.

Mesenchymal stem cell derived exosomes suppress neuroinflammation and shift microglial polarisation toward the M2 phenotype [8]. Exosomes enriched in miR-25 and derived from bone marrow have been shown to protect the spinal cord during transient ischemia [14]. Human data in this organ system are confined to the biomarker level [26].

7.4. Liver.

Extracellular vesicles derived from human umbilical cord MSC have been shown to alleviate hepatic IRI by suppressing oxidative stress and the neutrophil inflammatory response, with the mitochondrial antioxidant enzyme MnSOD identified within the vesicles [15]. Hepatic IRI also has systemic consequences beyond its local effects: exosomes have been shown to mediate injury in distant neuronal tissue by activating pyroptosis [23].

7.5. Testis.

Exosomes obtained from adipose derived MSC have been shown to prevent ischemia-reperfusion injury following torsion-detorsion in rat testes [16]. A further protective effect has been reported for bone marrow derived mesenchymal stem cell exosomes, although this source is a preprint [36].

Vesicle Distribution and Tissue Selectivity Following Systemic Administration

The homing of exosomes to the injured organ is partly explained by receptor-ligand interactions. In the ischemic kidney, the CXCR4-SDF-1α axis has been shown to direct vesicle uptake [20]. Following systemic administration, however, a substantial proportion of the vesicles accumulates in off-target organs, particularly the liver, spleen and lung [6,37]. Biodistribution has been shown to vary appreciably with cell source, route of administration and targeting strategy [37]. This precludes any definition of the relationship between the dose administered and the dose reaching the tissue.

Approaches aimed at improving targeting include surface modification, ligand conjugation, the use of carrier systems and genetic enrichment of the cargo [6]. The comparative superiority of these strategies has not yet been demonstrated. Moreover, the absence of a distinction between cargo specificity and the overall effect of the preparation makes rational design of engineering approaches difficult [8,19].

Data Obtained from Human Studies

9.1. Ex vivo perfusion studies in human organs

This design provides the most concrete link between experimental work and clinical application. Marginal kidneys procured from extended criteria donors and deemed unsuitable for transplantation were placed on machine perfusion and perfused with a cold, oxygenated solution. Addition of mesenchymal stromal cell derived extracellular vesicles to the perfusate arrested ischemic damage, prevented reoxygenation injury and preserved tissue integrity. Global renal ischemic damage score, renal ultrastructure, mitochondrial distress, apoptosis, cell proliferation index and mediators of energy metabolism were assessed together. The authors propose this approach as a novel organ preservation strategy for expanding the donor pool [31].

This design has three distinguishing features: the intervention took place in human tissue, it coincided with the reperfusion period, and there was no uncertainty regarding biodistribution. No other human model combining all three has been described in the existing literature.

Registered clinical trials

Therapeutic experience in patients is very limited. One early-phase study evaluates bone marrow derived mesenchymal stem cell exosomes transfected with miR-124 in acute ischemic stroke, with administration planned by stereotactic injection approximately one month after stroke onset [18]. A second early-phase study, in which exosomes derived from human induced pluripotent stem cells are given intravenously, is also registered [38].

Within the literature surveyed for this review, no publication reporting results was found for either study. The present situation is therefore not that clinical trials have never been conducted, but that those conducted have not progressed beyond registration.

9.2. Observational clinical studies

This is the level at which human data are strongest. In a study comparing 65 patients with acute ischemic stroke and 66 healthy individuals, serum exosome concentration and brain-specific exosomal miR-9 and miR-124 levels were significantly higher in the patient group ($p<0.01$), and these levels correlated positively with NIHSS scores and infarct volumes [26]. Serum exosomal metabolomic and proteomic profiles specific to remote ischemic preconditioning have also been characterised in humans [28].

Considered together, these three levels clarify the current position of the field. Exosomes already function in humans as a measurable marker and have yielded concrete results in the context of organ preservation, whereas as a systemically administered therapy they remain untested.

10. Methodological Limitations

The nature of the studies reviewed precludes calculation of a pooled effect size for three separate reasons.

First is the problem of the unit of analysis. The primary studies are distributed across five organ systems, with the number of studies per organ ranging widely (Table 2). Pooling at the organ level is therefore not statistically feasible.

Second is heterogeneity of outcome. Studies employ different measures, including infarct size, histological damage score, apoptotic index, biochemical markers and ultrastructural assessment. A standardised mean difference cannot be calculated without a common unit.

Third is heterogeneity of intervention. Vesicle source, isolation method and definition of dose vary from study to study. In the absence of a potency assay linked to the mechanism of action, standardisation based on protein content or particle number may not reflect biological activity [39,40]. Under these conditions it cannot be assumed that two studies have administered an equivalent dose.

Beyond these three constraints, the possibility of publication bias should not be disregarded. All of the primary studies surveyed report findings in the protective direction. Given the low likelihood of publication for negative or null results, part of the observed consistency may derive from this asymmetry.

11. Differences Between Experimental and Clinical Studies

The gap between experimental evidence and clinical application cannot be reduced to a single cause. Differences arise at four separate and mutually independent levels (Figure 2).

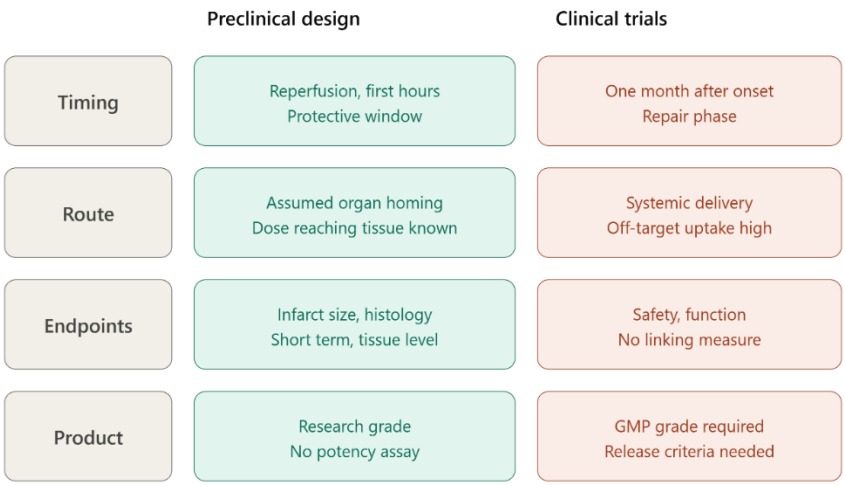


Figure 2. Four levels of mismatch between preclinical and clinical study design

11.1. Timing of administration All experimental studies focus on the moment of reperfusion and the hours that follow, the period in which activation of protective pathways is meaningful. In the most widely cited clinical study, by contrast, administration occurs approximately one month after stroke

onset [18]. That design targets tissue repair rather than reperfusion injury. Consequently, even a negative result would not have tested the hypothesis derived from the experimental work. This is a common form of error in the translational literature: the clinical trial does not reproduce the conditions on which the preclinical rationale rests [2,5].

11.2. Route of administration. Much of the protection observed in experimental models rests on the assumption that exosomes home to the injured organ [20]. A substantial proportion of the vesicles, however, accumulates in off-target organs [6]. The quantity reaching the tissue after systemic administration is unknown, which precludes determination of the effective dose [37]. The advantage of the machine perfusion design is that it removes this uncertainty entirely [31].

11.3. Outcome measures assessed. Experimental studies report results in terms of infarct size and histological damage scores, whereas clinical trials are designed around safety and functional outcome measures. No intermediate outcome measure that is mechanistically linked and measurable in humans has been defined to connect the two levels. Circulating exosomal miRNAs could serve this purpose [26], but have not yet been used in this way.

11.4. Product characteristics. The preparations used in experimental studies are produced under laboratory conditions for research purposes. A product intended for clinical use requires GMP-grade manufacture, scale-up, release criteria and batch-to-batch consistency [39]. This transition is not merely an increase in output but a redefinition of the product. Harmonisation of reporting standards is a precondition of this process [21,22].

12. Recommendations for Future Research

The foregoing assessment indicates that the priority for advancing the field is not further mechanistic study. The following order of priority may be proposed.

First, isolation and characterisation methods should be brought to a common standard. Reporting size distribution, surface markers and cargo content against uniform criteria would render studies mutually comparable; published minimal reporting requirements exist for this purpose [21,22].

Second, potency assays linked to the mechanism of action should be developed. Only in this way will the concept of dose acquire meaning, and only thereafter can dose-response and pharmacokinetic studies be conducted [40].

Third, machine perfusion should be considered a priority point of clinical entry. This design removes biodistribution uncertainty, places administration within the reperfusion period and permits direct measurement at the tissue level [31]. The transplant setting further offers the advantage of a predictable ischemic interval.

Fourth, early-phase trials in which administration is timed to the reperfusion period should be designed. The registered trials do not meet this condition [18,38].

Fifth, circulating exosomal markers should be validated as intermediate outcome measures. This step could resolve the difference in measurement between experimental and clinical studies [26].

Finally, the use of common outcome measures in at least three independent studies per organ is the minimum condition for a formal meta-analysis to become possible in the future.

13. Conclusion

Experimental data from five separate organ systems consistently indicate that exosomes exert a protective role in ischemia-reperfusion injury. This effect is mediated by anti-apoptotic, anti-inflammatory and mitochondria-supporting cargo acting at the level of PI3K/Akt, PTEN/Akt, RISK, Nrf2/HO-1, AMPK/mTOR, NF-κB and the NLRP3 inflammasome. Targeting is explained in part by CXCR4 and SDF-1 alpha dependent organ homing.

This consistency should not be interpreted without regard to the nature of the studies reviewed. The evidence on the topic comprises 19 primary studies, against which nine reviews on the same subject are available. Two of the primary studies are preprints that have not undergone peer review. The two studies conducted in patients remain at the stage of registration without reported results. All of the primary studies surveyed, moreover, report findings in the protective direction.

Human data show an uneven distribution across three levels. Exosomes have become a measurable marker at the diagnostic level and have produced concrete protection in ex vivo organ perfusion, whereas as a systemically administered therapy they have not progressed beyond registration.

The central argument of this review is that the gap does not arise from any demonstration that the treatment is ineffective. It arises at four levels: timing of administration, route of administration, outcome measures assessed, and product characteristics. The current early-phase trials are designed in such a way that, even if they returned negative results, they would not test the hypothesis derived from the experimental work.

Progress in the field therefore depends not on further mechanistic findings but on manufacturing standardisation, definition of potency criteria, validation of intermediate outcome measures, and study designs in which administration is placed within the reperfusion period. Ex vivo machine perfusion stands out as the only human model that currently satisfies these conditions and should be considered first as the point of clinical entry.

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BEYOND SCREEN TIME: MAPPING DIGITAL OVER-CONNECTEDNESS ONTO ADOLESCENT OCCUPATIONAL BALANCE THROUGH THE A-OBS FRAMEWORK

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Objective
This review aims to critically synthesize how digital over-connectedness—specifically nomophobia, phubbing, and the Fear of Missing Out (FoMO)—sabotages adolescent occupational balance by utilizing the multidimensional framework of the Adolescent Occupational Balance Scale (A-OBS), thereby transcending reductionist quantitative screen-time metrics.

Material and Methods
A comprehensive literature search was conducted across major electronic databases (PubMed, Scopus, CINAHL, and TR Dizin) spanning recent scientific evidence. Studies investigating tech-induced behavioral addictions, adolescent lifestyle disruptions, and pediatric nursing interventions were critically analyzed and conceptually mapped onto the four core subscales of the A-OBS framework.

Findings
The synthesized findings delineate a multi-layered destructive cascade across all four A-OBS dimensions: (1) Algorithmic reward architectures trigger continuous dopaminergic feedback loops, causing severe micro- and macro-level time compression (Temporality); (2) Bedtime device usage and short-wavelength blue-light exposure suppress nocturnal melatonin secretion, prolonging sleep latency and fragmenting slow-wave and REM sleep architecture (Rest and Sleep); (3) Excessive virtual immersion monopolizes daily schedules, displacing physical activities and serving as a sanctuary for maladaptive coping (Occupational Variations and Adaptation); and (4) Externalized digital validation loops degrade the subjective value adolescents assign to offline milestones and face-to-face relationships (Occupational Meaning and Value).

Conclusion
Digital over-connectedness induces a profound clinical occupational crisis. Pediatric nursing interventions must evolve beyond simplistic screen-time restrictions toward holistic lifestyle redesign, peer-inclusive counseling, and macro-level health policy advocacy. This paradigm empowers advanced clinicians to target the neurobiological and cognitive drivers of digital addiction, effectively reclaiming restorative occupations and safeguarding adolescent health.
Keywords: Adolescent Occupational Balance Scale (A-OBS); Pediatric Nursing; Digital Addiction; Nomophobia; Phubbing; Lifestyle Redesign.

Despite the burgeoning literature documenting the adverse psychosocial and physical correlates of adolescent digital over-connectedness, contemporary pediatric healthcare paradigms remain predominantly limited by a reductionist focus on quantitative screen-time metrics. This narrow analytical lens systematically fails to capture the profound qualitative disruption that complex digital behaviors—such as nomophobia, phubbing, and the Fear of Missing Out (FoMO)—inflict upon the intricate architecture of daily life. To address this conceptual gap, this review explicitly deploys the multidimensional framework of the Adolescent Occupational Balance Scale (A-OBS) to critically synthesize how modern digitalization sabotages the vital equilibrium between adolescent productivity, leisure, and restoration. By systematically mapping these contemporary digital pathologies across the four core dimensions of the A-OBS—Temporality, Rest and Sleep, Occupational Variations and

Adaptation, and Occupational Meaning and Value—this paper aims to transcend primitive, restriction-based clinical strategies. Ultimately, the purpose of this review is to formulate an advanced, evidence-based pediatric nursing framework for holistic lifestyle redesign, providing clinicians with the theoretical and practical tools necessary to restore developmental synchrony and safeguard adolescent health in a hyper-connected era.

1. TEMPORALITY

Digital Time Distortion and Sabotage of Developmental Routine

Temporality, within the conceptual framework of the Adolescent Occupational Balance Scale (A-OBS), transcends the mere chronological quantification of duration; it delineates the subjective perception, structuring, and qualitative management of time across daily occupational domains (Güney Yılmaz et al., 2023). Under conditions of normative occupational balance, temporality facilitates a harmonious integration of productivity, leisure, and restorative occupations (Güney Yılmaz et al., 2023). However, the pervasive infiltration of digital over-connectedness—manifesting as smartphone addiction, nomophobia, and the Fear of Missing Out (FoMO)—actively warps this temporal adaptation, precipitating a profound disruption in how adolescents experience, value, and allocate their daily routines (Lestari & Suratmini, 2024).

The architectural design of modern mobile applications and gaming platforms is explicitly engineered to maximize engagement through variable-ratio reinforcement schedules, a mechanism structurally analogous to the operant conditioning utilized in slot machines (Sachdeva et al., 2025). This unpredictable delivery of social validation and algorithmic rewards hyper-stimulates the adolescent's developing ventral striatum, precipitating a continuous dopaminergic feedback loop that bypasses the still-maturing prefrontal cortex responsible for executive inhibition (Mthembu et al., 2014; Sachdeva et al., 2025). Consequently, adolescents enter a maladaptive "flow state" characterized by severe temporal distortion. While empirical neurocognitive assessments indicate that social media addiction selectively impairs suprasecond perceptual timing—inducing significant time overestimation and diminished temporal sensitivity at a micro-level (Zhou et al., 2025)—this sensory deficit paradoxically manifests macroscopically as a severe compression of elapsed time during prolonged digital engagement. In this altered cognitive state, the subjective passage of hours is compressed into minutes, fundamentally compromising the adolescent's capacity for accurate temporal monitoring and subsequent occupational engagement (Christodoulou & Roussos, 2025; Zhou et al., 2025).

This dopaminergic hijacking directly sabotages the cohesion of adolescent developmental routines (Sachdeva et al., 2025). Driven by nomophobia—the pathological anxiety of being disconnected—and FoMO, adolescents are compelled to engage in continuous device checking, fracturing their daily schedules into disjointed digital episodes (Christodoulou & Roussos, 2025; Lestari & Suratmini, 2024). This perpetual state of online vigilance and the constant influx of push notifications systematically eradicate moments of "micro-boredom," which are neurodevelopmentally essential for cognitive rest, memory consolidation, and introspective thought (Li et al., 2025; Sachdeva et al., 2025). Instead of structured occupational engagement, the cognitive load imposed by digital multitasking exhausts limited attentional resources, culminating in ego depletion, heightened mind wandering, and pervasive cognitive failures (Li et al., 2025). Consequently, daily routines devolve from planned, meaningful occupational participation into fragmented, reactive behaviors that foster severe procrastination and systemic occupational imbalance (Aslanyürek et al., 2025; Güney Yılmaz et al., 2023).

From a pediatric nursing perspective, this pervasive digital hijacking constitutes a profound clinical occupational crisis defined by severe temporal desynchronization rather than a superficial failure of behavioral time-management (Yumru Menteş & Koç, 2025). Chronic psychological hyperarousal and prolonged screen exposure actively disrupt the alignment of the adolescent’s endogenous circadian rhythms with critical external constraints (Fatima et al., 2026; Sachdeva et al., 2025). This biological dysregulation desynchronizes the internal biological clock from essential social and developmental clocks, including family integration routines and rigid academic schedules (Li et al., 2025; Sachdeva et al., 2025). Within the A-OBS framework, such desynchronization undermines the foundational stability of daily temporality (Güney Yılmaz et al., 2023). Pediatric nursing interventions must, therefore, transcend primitive screen-time policing and pivot toward a holistic framework that targets the neurobiological and socio-temporal dimensions of digital behavior to restore developmental synchrony (Fatima et al., 2026; Yumru Menteş & Koç, 2025).

2. REST AND SLEEP

Physiological and Behavioral Sabotage of Restorative Occupations

Within the Adolescent Occupational Balance Scale (A-OBS) framework, "Rest and Sleep" is conceptualized not merely as a period of biological inactivity, but as an essential, restorative occupation required for physiological recovery, neurodevelopment, and the maintenance of holistic occupational balance (Güney Yılmaz et al., 2023). In normative development, this dimension serves as the primary energetic baseline that regulates the adolescent's capacity to effectively participate in other daily tasks (Güney Yılmaz et al., 2023; Li et al., 2025). However, modern digital over-connectedness acts as a multi-layered saboteur of this fundamental domain, precipitating a systemic collapse of both temporal adaptation and physiological homeostasis through distinct behavioral and neurobiological pathways (Fatima et al., 2026; Sachdeva et al., 2025).

The natural transition into restorative sleep is initially thwarted by bedtime behavioral displacement driven predominantly by the Fear of Missing Out (FoMO) and nomophobia (Aslanyürek et al., 2025; Lestari & Suratmini, 2024). The psychological urge to remain perpetually connected compels adolescents to engage in late-night device checking and compulsive notification monitoring, a pattern of problematic usage that fractures healthy wind-down routines (Fatima et al., 2026). Furthermore, the phenomenon of phubbing within the sleep environment—wherein the physical necessity of rest is compromised in favor of virtual engagement—induces a state of acute cognitive and emotional hyperarousal (Aslanyürek et al., 2025). Engaging with emotionally activating digital content elevates psychological rumination, directly prolonging sleep onset latency and eradicating the essential relaxation behaviors required for normative sleep initiation (Fatima et al., 2026; Oliveira Neto, 2026).

This behavioral latency is acutely compounded by profound photobiological disruptions. The short-wavelength blue light emitted by mobile devices directly interferes with the adolescent's developing circadian biology (Fatima et al., 2026). Specifically, photic exposure during nocturnal hours suppresses the endogenous synthesis and secretion of melatonin from the pineal gland (Fatima et al., 2026; Oliveira Neto, 2026). By shifting the circadian clock later into the night, this photobiological delay creates an institutional barrier to sleep onset, reinforcing the pre-existing cognitive arousal induced by the digital content itself (Oliveira Neto, 2026; Sachdeva et al., 2025).

While these factors delay sleep initiation, distinct concurrent mechanisms systematically fragment the macro- and micro-architecture of sleep after its onset. Nocturnal notification alerts and the residual urge to maintain online vigilance trigger frequent micro-arousals, leading to a critical reduction in both Slow-Wave Sleep (SWS) and Rapid Eye Movement (REM) phases, which are biologically imperative for brain maturation, memory consolidation, and physiological recovery (Fatima et al., 2026; Oliveira Neto, 2026). Macroscopically, this structural deficit manifests as severe daytime somnolence, chronic fatigue, and impaired executive functioning (Fatima et al., 2026; Li et al., 2025). Ultimately, this chronic sleep debt culminates in an absolute collapse of the adolescent's capacity to effectively engage in other vital daily occupational domains, precipitating attention deficits, diminished academic productivity, and systemic occupational imbalance (Demirci Güven et al., 2026; Fatima et al., 2026; Oliveira Neto, 2026).

From an advanced pediatric nursing perspective, this technologically mediated sleep disruption transcends poor lifestyle habits, warranting recognition as a distinct clinical diagnosis—such as severe sleep deprivation or disturbed sleep patterns—that requires targeted clinical care (Aslanyürek et al., 2025; Yumru Menteş & Koç, 2025). The chronic consequences of this deficit, ranging from immune suppression and hormonal metabolic dysregulation to profound cognitive failure, necessitate robust clinical intervention (Fatima et al., 2026; Li et al., 2025). Pediatric nursing frameworks must, therefore, evolve beyond dispensing generic sleep hygiene brochures. Clinicians must implement holistic, occupation-focused nursing interventions that address the underlying neurobiological and behavioral drivers of digital addiction, empowering adolescents to reclaim sleep as a sacred, active restorative occupation essential for their overall developmental synchrony and health (Güney Yılmaz et al., 2023; Yumru Menteş & Koç, 2025).

3. OCCUPATIONAL VARIATIONS AND ADAPTATION

Occupational Monopolization and Maladaptive Escapism

Within the Adolescent Occupational Balance Scale (A-OBS), the "Occupational Variations and Adaptation" dimension asserts that normative health and development are contingent upon a harmonious, diverse repertoire of daily occupations and the adaptive capacity to navigate environmental

demands (Güney Yılmaz et al., 2023). However, digital over-connectedness systematically obliterates this equilibrium, inducing a profound homogenization of the adolescent lifestyle. Excessive investment in singular digital activities—such as online gaming, continuous social media engagement, and compulsive smartphone use—monopolizes the adolescent's daily schedule, directly displacing essential face-to-face socialization, physical activities, and creative leisure pursuits (Demirci Güven et al., 2026; Sachdeva et al., 2025). Driven by phenomena like the Fear of Missing Out (FoMO) and nomophobia, adolescents become increasingly apathetic toward their physical surroundings, sacrificing real-world interpersonal development in favor of maintaining a perpetual virtual presence (Lestari & Suratmini, 2024). Consequently, the adolescent's activity portfolio contracts severely, devolving from a diverse set of meaningful roles into a rigid, sedentary digital routine that actively disrupts normative self-care and social obligations (Demirci Güven et al., 2026; Yumru Menteş & Koç, 2025).

This digital monopolization fundamentally paralyzes the adolescent's adaptive capacities, transforming technology into a mechanism for maladaptive escapism. Instead of developing resilient coping strategies to manage real-world stressors, academic burdens, or emotional dysregulation, vulnerable adolescents increasingly utilize digital environments as an avoidant sanctuary (Fatima et al., 2026; Goswami et al., 2025). Individuals presenting with elevated neuroticism, anxiety, or depressive symptoms frequently retreat into the anonymity of the internet or the endless consumption of algorithmically curated short-video platforms—such as TikTok and Instagram Reels—to bypass immediate emotional challenges and seek psychological solace (Goswami et al., 2025; Sachdeva et al., 2025). This avoidant behavior initiates a vicious clinical cycle: as adolescents rely more heavily on virtual distraction and digital gratification to self-soothe, they systematically fail to cultivate essential, real-world problem-solving skills and emotional resilience (Fatima et al., 2026). Over time, this chronic avoidance not only compounds their underlying psychological distress but completely compromises their capacity to adaptively cope with the foundational challenges of transitioning into adulthood (Goswami et al., 2025).

From a clinical pediatric nursing perspective, the profound loss of occupational variety and the reliance on digital escapism present severe physiological and psychosocial risks. The displacement of varied, active occupations precipitates significant physical deconditioning, with the resultant sedentary lifestyle driving increased rates of obesity, metabolic dysfunction, and musculoskeletal pathologies such as "text neck" and compromised posture (Fatima et al., 2026; Sachdeva et al., 2025). Concurrently, this digital immersion fosters severe social isolation and the deterioration of vital offline support networks, further endangering the adolescent's holistic health (Mthembu et al., 2014). To mitigate this destruction, pediatric nursing interventions must pivot toward structural lifestyle redesign—actively guiding the adolescent to diversify their daily activity portfolio and restore a balanced configuration of occupations (Demirci Güven et al., 2026; Mthembu et al., 2014). Clinicians must implement targeted, peer-inclusive, and hobby-centric strategies that expand the adolescent's repertoire of physical and social interests, replacing fragmented digital consumption with healthy, face-to-face engagements that foster genuine adaptive coping mechanisms in the physical world (Fatima et al., 2026; Yumru Menteş & Koç, 2025).

4. OCCUPATIONAL MEANING AND VALUE

The Illusion of Digital Validation and Devaluation of Reality

Within the Adolescent Occupational Balance Scale (A-OBS) framework, the dimension of "Occupational Meaning and Value" posits that normative health is maintained when an adolescent perceives their daily activities as intrinsically valuable, purpose-driven, and closely aligned with their developing identity (Güney Yılmaz et al., 2023). However, digital over-connectedness fundamentally shifts this meaning-making process away from real-world achievements toward external, virtual validations. The architectural design of social media platforms and gaming applications leverages variable-ratio reinforcement schedules—delivered through likes, comments, and algorithmic rewards—that directly stimulate the adolescent's dopaminergic reward system. Consequently, adolescents increasingly anchor their self-worth and occupational identity to this immediate, superficial digital validation (Fatima et al., 2026; Sachdeva et al., 2025). As digital engagement monopolizes the adolescent's cognitive appraisal of value, tangible real-world milestones—such as academic performance, skill acquisition, or physical hobbies—suffer a profound subjective devaluation. Empirical evidence explicitly demonstrates that higher severity of internet gaming disorder and smartphone addiction correlates directly with a diminished perception of meaning and value in daily offline

occupations, rendering physical-world tasks unrewarding by comparison (Demirci Güven et al., 2026; Mthembu et al., 2014).

This existential shift toward virtual validation inevitably precipitates the devaluation of interpersonal meaning in the physical world, most visibly manifested through the behavioral phenomenon of phubbing. Defined as the act of ignoring individuals in face-to-face environments in favor of a smartphone, phubbing severely diminishes the psychological and existential value of authentic human interaction (Aslanyürek et al., 2025; Goswami et al., 2025). Driven by underlying psychological constructs such as nomophobia and the Fear of Missing Out (FoMO), adolescents become increasingly apathetic toward their immediate surroundings, consistently prioritizing a virtual audience over physical presence (Lestari & Suratmini, 2024). This constant diversion of attention disrupts the fundamental face-to-face communication, eye contact, and shared attention required for normative socio-emotional development and empathy construction (Goswami et al., 2025; Sachdeva et al., 2025). By systematically choosing digital connectivity over immediate social engagement, adolescents erode the depth and quality of their real-world relationships. Paradoxically, the hyper-focused pursuit of this virtual connection cultivates profound feelings of social isolation, loneliness, and a distorted sense of social worth (Aslanyürek et al., 2025; Fatima et al., 2026).

From an advanced pediatric nursing perspective, this systemic recalibration of meaning constitutes a profound developmental threat to adolescent identity formation and self-esteem. Clinical interventions cannot be restricted to the simplistic monitoring and restriction of screen hours; instead, they must directly target the adolescent's cognitive appraisal of value (Žmavc et al., 2025). Pediatric nurses must spearhead lifestyle redesign approaches that empower adolescents to consciously evaluate and restructure their daily occupational portfolios. To counteract the illusion of digital validation, clinicians should implement peer-led, identity-centered interventions and meaning-centered cognitive-behavioral counseling strategies that foster genuine self-efficacy, autonomy, and resilience (Yumru Menteş & Koç, 2025; Žmavc et al., 2025). By guiding adolescents to invest their time in hobby-centric pursuits and meaningful face-to-face social engagements, nursing professionals can facilitate the reconstruction of a healthy, offline identity, enabling the adolescent to rediscover intrinsic value and authentic connection within the physical world.

5. CONCLUSION AND FUTURE IMPLICATIONS

5.1. Conclusion

This critical review demonstrates that modern digital over-connectedness—driven by interrelated behavioral and psychological constructs such as nomophobia, phubbing, and the Fear of Missing Out (FoMO)—constitutes a systemic developmental threat that dismantles the foundational pillars of adolescent occupational balance. When evaluated through the comprehensive architectural lens of the Adolescent Occupational Balance Scale (A-OBS), the impact of digital addiction is revealed not as a superficial time-management failure, but as a profound clinical crisis that simultaneously deconstructs the neurobiological, photobiological, behavioral, and existential dimensions of daily adolescent life.

The evidence synthesizes a destructive cascade: digital hyper-connectivity actively warps macro- and micro-temporal adaptation (**Temporality**), fragments the vital architecture of restorative sleep through neuroendocrine and behavioral sabotage (**Rest and Sleep**), homogenizes the daily activity portfolio into a rigid, sedentary digital monopoly while paralyzing real-world adaptive coping (**Occupational Variations and Adaptation**), and ultimately shifts the cognitive appraisal of life's value from intrinsic, tangible milestones to superficial, algorithmic validations (**Occupational Meaning and Value**). Consequently, the contemporary adolescent is left vulnerable to severe lifestyle desynchronization, physiological deconditioning, and profound identity fragmentation.

5.2. Implications for Pediatric Nursing Practice

Pediatric nursing professionals occupy a critical echelon in adolescent healthcare and must immediately pivot from obsolete, reductive "screen-time restriction" mandates toward a holistic, occupation-focused clinical paradigm.

- **Advanced Clinical Screening:** Pediatric and school health nurses must structurally integrate the A-OBS alongside smartphone and gaming addiction indices into routine clinical assessments to proactively identify adolescents undergoing early occupational drift and temporal desynchronization.

- **Holistic Lifestyle Redesign:** Interventions must abandon generic hygiene brochures. Instead, advanced clinicians must engineer peer-led, hobby-centric, and identity-centered lifestyle redesign protocols. These strategies should actively guide adolescents to restructure their daily schedules, expand their real-world social and physical repertoires, and restore sleep as a sacred restorative occupation.
- **Cognitive-Behavioral Resiliency Training:** Nurses should employ meaning-centered cognitive-behavioral counseling to address the underlying psychological drivers of digital escapism (such as anxiety and neuroticism), empowering adolescents to build authentic self-efficacy and resilience in the physical world.

5.3. Implications for Future Research and Health Policy

The complex matrix of technologically mediated occupational imbalance demands robust empirical tracking and systemic structural reform.

- **Longitudinal and Interventional Research:** Future research must transcend cross-sectional designs. Longitudinal studies utilizing the A-OBS framework are urgently required to track the long-term metabolic, cognitive, and social trajectories of digitally compromised adolescents. Moreover, randomized controlled trials (RCTs) must be conducted to evaluate the clinical efficacy of nurse-led digital detox and occupational restructuring models.
- **Macro-Level Health Policies:** At the institutional level, pediatric nursing leaders must collaborate with educational policy-makers to draft comprehensive "Digital Hygiene and Balance" curriculums within secondary education systems. Public health mandates must address the commercial determinism of persuasive app architectures, advocating for safer algorithmic designs that protect developing adolescent brains from dopamine-driven entrapment.

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ÇÖLYAK HASTALARINDA KAÇINGAN/KISITLI YİYECEK ALIM BOZUKLUĞU

AVOIDANT/RESTRICTIVE EATING DISORDER IN PATIENTS WITH CELIAC DISEASE

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ÖZET:

AMAÇ: Kaçıngan/kısıtlı yiyecek alım bozukluğu (ARFID); besinlerin duyusal özelliklerine karşı isteksizlik, yemeye ilgi azlığı veya yemenin olumsuz sonuçlarından korkma nedeniyle besin alımının miktar ve/veya çeşitlilik açısından kısıtlanmasıyla karakterizedir. ARFID riskinin, tedavi olarak kısıtlı diyetlerin uygulandığı kronik gastrointestinal sistem hastalıklarında daha yüksek olabileceği bildirilmektedir. Bilinen tek etkili tedavisi glutensiz diyet olan çölyak hastalığında diyetteki kısıtlamalar ile ARFID'e bağlı patolojik kaçınmanın ayırt edilmesi güçleşmektedir. Bu derlemede, çölyak hastalığı olan bireylerde ARFID riskinin ve ilişkili faktörlerin incelenmesi amaçlanmıştır.

MATERYAL VE YÖNTEM

Çölyak hastalığı olan bireylerde ARFID riski ve ilişkili faktörleri inceleyen güncel literatür değerlendirilmiştir. PubMed, Scopus ve Web of Science veri tabanlarında yer alan, 2016-2026 yılları arasında İngilizce olarak yayımlanan çalışmalar incelenmiştir.

BULGULAR

Çölyak hastalığının bilinen tek etkili tedavisi yaşam boyu glutensiz diyete uyumdur. Glutensiz diyetin kısıtlayıcı içeriği, gluten maruziyeti ve gastrointestinal semptomlara ilişkin kaygılar; bazı bireylerde diyetin tıbbi beslenme tedavisinin ötesinde sınırlandırılmasına ve kaçıngan/kısıtlı yeme davranışlarının gelişmesine zemin hazırlayabilmektedir. ARFID'de besin alımının kısıtlanması; besinlere karşı ilginin az olması, besinlerin duyusal özelliklerine yönelik hassasiyet veya boğulma, kusma, ağrı ve gastrointestinal semptomlar gibi yemenin olumsuz sonuçlarından korkma ile ilişkili olabilmektedir. Bu durum yetersiz enerji ve besin ögesi alımı, vücut ağırlığı kaybı, büyüme geriliği, düşük diyet kalitesi ve yaşam kalitesinde bozulma ile sonuçlanabilmektedir. ARFID küresel prevalansının yetişkin popülasyonunda yaklaşık %0,3–3,1 arasında değiştiği, kronik gastrointestinal hastalıklara sahip bireylerde bu oranın daha yüksek olduğu bildirilmektedir. Çölyak hastalarında yapılan çalışmalarda kullanılan ölçek, yaş grubu ve çalışma grubu özelliklerine bağlı olarak ARFID riskinin %14–57 arasında değiştiği bildirilmiştir.

SONUÇ

Mevcut bulgular, çölyak hastalarında ARFID riskinin yalnızca glutensiz diyet uygulanmasıyla açıklanamayacağını göstermektedir. Devam eden gastrointestinal semptomlar, gluten maruziyetine ilişkin korku, sosyal ortamlarda diyete uyumun zorlaşması ve psikiyatrik eş tanılar ARFID riskiyle ilişkili olabilecek faktörler arasında değerlendirilmektedir. Çölyaklı bireylerin ARFID riski açısından taranması ve multidisipliner olarak değerlendirilmesi önemlidir.

Anahtar Kelimeler: Çölyak hastalığı, kaçıngan/kısıtlayıcı yiyecek alım bozukluğu, glutensiz diyet

ABSTRACT

OBJECTIVE

Avoidant/restrictive food intake disorder (ARFID) is characterized by restriction in the amount and/or variety of food consumed because of sensory aversion, lack of interest in eating, or fear of adverse consequences. ARFID risk may be higher in chronic gastrointestinal diseases requiring restrictive diets. In celiac disease, whose only effective treatment is a lifelong gluten-free diet, distinguishing medically necessary restriction from pathological avoidance is difficult. This review aimed to examine ARFID risk and associated factors in individuals with celiac disease.

MATERIALS AND METHODS
Literature examining ARFID risk and associated factors in celiac disease was reviewed. English-language studies published between 2016 and 2026 and indexed in PubMed, Scopus, or Web of Science were evaluated.

RESULTS
The restrictive nature of a gluten-free diet, concerns about gluten exposure, and gastrointestinal symptoms may lead some individuals to restrict food intake beyond medical necessity and develop avoidant/restrictive eating behaviors. In ARFID, restriction may reflect low interest in food, sensory sensitivity, or fear of consequences such as choking, vomiting, pain, and gastrointestinal symptoms. These behaviors may cause inadequate energy and nutrient intake, weight loss, growth retardation, poor diet quality, and impaired quality of life. Global ARFID prevalence among adults ranges from 0.3% to 3.1% and is higher in individuals with chronic gastrointestinal diseases. Studies in celiac disease have reported ARFID risk ranging from 14% to 57%, depending on the assessment tool, age group, and study population.

CONCLUSION
Evidence suggests that ARFID risk in celiac disease cannot be explained solely by adherence to a gluten-free diet. Persistent gastrointestinal symptoms, fear of gluten exposure, difficulty following the diet in social settings, and psychiatric comorbidities may contribute to this risk. Screening individuals with celiac disease for ARFID and providing multidisciplinary evaluation are important components of the clinical care.
Keywords: Celiac disease, avoidant/restrictive food intake disorder, gluten-free diet

GİRİŞ
Çölyak hastalığı; buğday, arpa ve çavdarda bulunan protein komplekslerinden biri olan glutenin tüketimiyle tetiklenen otoimmün bir hastalıktır. Hastalık; glutene bağımlı çeşitli klinik belirtiler, spesifik otoantikorların varlığı, HLA-DQ2 ve HLA-DQ8 histouyumluluk antijenlerinin bulunması ve enteropati ile karakterizedir (Kowalski et al., 2025). Çölyak hastalığının küresel prevalansının incelenen popülasyona ve kullanılan metodolojiye bağlı olarak %0,3–5,6 arasında değiştiği bildirilmektedir (Singh et al., 2018). Çölyak hastalığının bilinen tek etkili tedavisi yaşam boyu sıkı bir glutensiz diyete uyumdur (Kowalski et al., 2025; Mearin et al., 2022). Glutensiz diyet; buğday, arpa ve çavdar gibi gluten içeren tahılların diyetten çıkarılmasının yanı sıra, besinlerin hazırlanması, depolanması ve servis edilmesi sırasında oluşabilecek çapraz bulaşın önlenmesini gerektiren bir tedavi yaklaşımıdır (White et al., 2016). Ürün seçeneklerinin sınırlı olması, besin etiketlerini düzenli olarak okuma gerekliliği, ev dışında güvenli besine erişimde yaşanan güçlükler ve sosyal ortamlarda yemek yemeye ilişkin kaygılar, bireylerin besin tercihlerini, yeme davranışlarını ve yaşam kalitesini olumsuz etkileyebilmektedir (Guennouni et al., 2024; Lee et al., 2021; White et al., 2016).
Kaçıngan/Kısıtlı Yiyecek Alım Bozukluğu (ARFID), ilk kez Ruhsal Bozuklukların Tanısal ve Sayımsal El Kitabı-5'te (DSM-5) ayrı bir tanı olarak tanımlanan ve tüketilen besinlerin miktarının ve/veya çeşitliliğinin kısıtlanması sonucunda bireyin enerji ve besin ögesi gereksinimlerinin karşılanamamasıyla karakterize bir yeme bozukluğudur (American Psychiatric Association, 2022). ARFID'de besin alımının kısıtlanması; yemeğe veya besine karşı ilginin azlığı, besinlerin duyusal özelliklerine yönelik hassasiyet veya boğulma, kusma, ağrı ve gastrointestinal semptomlar gibi yemenin olumsuz sonuçlarından korkma ile ilişkili olabilmektedir. Bu durum vücut ağırlığı kaybı, büyüme geriliği, besin ögesi yetersizlikleri, oral beslenme desteğine ihtiyaç ve psikososyal işlevsellikte bozulma ile sonuçlanabilmektedir. ARFID'de anoreksiya nervoza ve bulimiya nervozadan farklı olarak vücut ağırlığı veya beden şekline ilişkin bir algı bozukluğu bulunmamaktadır (American Psychiatric Association, 2022; Burton Murray et al., 2021; Kaul et al., 2025). Bu derlemenin amacı, çölyak hastalarında ARFID riskini ve ilişkili faktörleri incelemektir. Bu çalışmada PubMed, Scopus ve Web of Science veri tabanlarında 2016–2026 yılları arasında İngilizce yayımlanan çalışmalar incelenmiştir. Tarama sırasında "celiac disease", "coeliac disease", "ARFID", "avoidant/restrictive food intake disorder", "restrictive eating" ve "gluten-free diet" anahtar kelimeleri kullanılmıştır.

GELİŞME

ARFID'in küresel prevalansının çocuk ve adölesan popülasyonunda %0,35 ila %3,2 ve yetişkin popülasyonunda %0,3 ila %3,1 arasında değiştiği bildirilmektedir (Ramirez & Gunturu, 2024). Kronik gastrointestinal hastalıklara sahip bireylerde bu oranın daha yüksek olduğu belirtilmektedir (Fink et al., 2022; Kaul et al., 2025). Çölyak hastalarında yürütülen çalışmalarda ise kullanılan değerlendirme aracı, yaş grubu ve örneklemin özelliklerine göre ARFID riski %14–57 arasında değişmektedir (Kaul et al., 2025). Bununla birlikte, çalışmalarda bildirilen bu oranların tamamı DSM-5 tanı kriterlerine dayalı klinik ARFID prevalansını yansıtmamaktadır. Bazı oranlar tarama ölçekleriyle belirlenen ARFID riskini veya olası ARFID semptomlarının görülme sıklığını ifade etmektedir. ARFID semptomlarını değerlendirmek amacıyla yaygın olarak kullanılan araçlardan biri olan Dokuz Maddeli Kaçıngan/Kısıtlayıcı Yiyecek Alım Bozukluğu Tarama Ölçeği (NIAS) Zickgraf ve Ellis (Zickgraf & Ellis, 2018) tarafından geliştirilmiş bir ölçektir. Ölçek, seçici yeme, iştah ve boğulma, kusma, ağrı ve gastrointestinal semptomlar gibi yemenin olumsuz sonuçlarından korkma olmak üzere üç alt boyuttan oluşmaktadır. NIAS'ın özgün İngilizce formunun yanı sıra Çince, İspanyolca, Arapça, Türkçe ve Farsça dillerine ilişkin psikometrik geçerlik ve güvenirlik çalışmaları bulunmaktadır (Biglari et al., 2026; Fekih-Romdhane et al., 2023; He et al., 2021; Kaşak et al., 2024; Medina-Tepal et al., 2023).

Farklı gastrointestinal sistem hastalıklarına sahip yetişkin bireylerde yürütülen bir çalışmada, NIAS kullanılarak ARFID semptomları değerlendirilmiş ve katılımcıların %53,7'sinde ARFID semptomları saptanmıştır. Hastalık grupları arasında çölyak hastalığında ARFID semptomları açısından pozitif tarama oranı %48,7 olarak bildirilmiştir. Çölyak hastalarında NIAS alt boyutlarında korku %25, seçici yeme %17,1 ve iştahsızlık/yemeye ilgi azlığı %13,2 oranında saptanmıştır. Bununla birlikte, gastrointestinal hastalıklara özgü semptomların NIAS maddeleriyle örtüşebildiği ve özellikle gastrointestinal semptomlara ilişkin korkunun toplam NIAS puanının önemli bir bölümünü açıkladığı gösterilmiştir. Bu nedenle NIAS'ın kronik gastrointestinal hastalıklarda ARFID sıklığını olduğundan yüksek gösterebileceği ve tıbbi olarak uygun besin kısıtlaması ile patolojik kaçınmayı tek başına ayırt etmek için yeterli olmadığı bildirilmektedir. Ayrıca daha fazla ARFID semptomu bulunan bireylerde anksiyete ve depresyonun daha yüksek, sağlıkla ilişkili yaşam kalitesinin daha düşük olduğu; en belirgin ilişkinin sosyal işlevsellikte bozulma ile görüldüğü bildirilmektedir (Fink et al., 2022).

Çölyak hastalığında ARFID riskinin artmasında hastalığın ve tedavisinin doğasıyla ilişkili çeşitli faktörlerin rol oynayabileceği düşünülmektedir. Yaşam boyu sıkı glutensiz diyet uygulanması, glutenle çapraz bulaş riskine karşı dikkat gerekliliği ve gluten maruziyetinin olumsuz sağlık sonuçlarına ilişkin kaygı, bazı bireylerde tıbbi olarak gerekli kısıtlamaların ötesinde besinlerden kaçınmaya neden olabilmektedir (Kaul et al., 2025). Özellikle yeme sonrasında ortaya çıkan gastrointestinal semptomların gluten maruziyetiyle ilişkilendirilmesi, besin–semptom ilişkisine yönelik hipervijilansı artırarak daha önce semptom oluşturduğu düşünülen besinlerin diyetten çıkarılmasına ve zamanla besin çeşitliliğinin azalması ile diyet kalitesinde düşüşe yol açabilmektedir (Wolf et al., 2018). Bunun yanı sıra anksiyete düzeyinin yüksek olması, gastrointestinal semptomların varlığı, besinlerin olumsuz sonuçlarına ilişkin korku ve duyusal özelliklere bağlı seçici yeme davranışları çölyak hastalarında ARFID riskiyle ilişkili faktörler arasında yer almaktadır (Bennett et al., 2022; Kaul et al., 2025). Erişkin çölyak hastalarında yapılan bir çalışmada, katılımcıların %58'inin glutensiz diyetin gerekliliğinin ötesinde en az bir besini kısıtladığı ve bu davranışın daha düşük yaşam kalitesi ile daha yüksek anksiyete düzeyleriyle ilişkili olduğu bildirilmiştir. Buna karşın, ek besin kısıtlamalarının daha iyi glutensiz diyet uyumu ile ilişkili olmaması, aşırı kısıtlamanın hastalık kontrolü açısından ek bir yarar sağlamadığını düşündürmektedir (Lee et al., 2024). Bu nedenle çölyak hastalığında ARFID değerlendirilirken glutensiz diyetin gerektirdiği uygun kısıtlamalar ile tıbbi gerekliliğin ötesine geçen, diyet kalitesini ve psikososyal işlevselliği etkileyen kaçınma davranışlarının birbirinden ayrılması önem taşımaktadır.

Çocuk ve adölesan çölyak hastalarında yürütülen bir çalışmada, 8–17 yaş aralığında 101 çölyak hastası değerlendirilmiş ve ARFID tanısı çocuk ve ergen psikiyatristleri tarafından DSM-5 kriterlerine dayalı klinik görüşmeyle konmuştur. Çalışmada ARFID prevalansı %42,6 olarak saptanmıştır. ARFID tanısı bulunan bireylerde yaşa göre vücut ağırlığı ve yaşa göre beden kütle indeksi (BKİ) z-skorlarının daha düşük, osteopeni/osteoporoz ve mikro besin ögesi yetersizliklerinin daha sık olduğu belirlenmiştir. Ayrıca bu grupta anksiyete ve depresyon belirtilerinin daha yüksek, sağlıkla ilişkili yaşam kalitesinin daha düşük olduğu bildirilmiştir. Gastrointestinal semptomların varlığı ve daha yüksek anksiyete düzeyinin ARFID ile bağımsız olarak ilişkili olduğu gösterilirken, ARFID varlığının daha iyi glutensiz diyet uyumu veya serolojik kontrol ile ilişkili olmadığı bulunmuştur.

Bu bulgular, çölyak hastalığında tıbbi olarak gerekli gluten kısıtlamasının ötesine geçen yeme kısıtlamalarının özellikle büyüme, beslenme durumu ve psikososyal işlevsellik açısından klinik önem taşıdığını ve bu bireylerin multidisipliner olarak değerlendirilmesi gerektiğini düşündürmektedir (Teke et al., 2026).

Çölyak hastalığı ve çölyak dışı gluten duyarlılığı bulunan çocuk ve yetişkinlerde yürütülen bir çalışmada, çölyak hastalığı olan grupta DSM-5 kriterleri doğrultusunda ARFID prevalansı %18 olarak saptanmıştır. Kısıtlayıcı yeme davranışının en sık nedeni yemenin olumsuz sonuçlardan korkma %60, ikinci sıklıkta iştahsızlık/yemeye ilgi azlığı %37 olarak bildirilmiştir. Yaş grupları için yapılan değerlendirmede ARFID semptomları çocuk ve adölesanların %23'ünde, yetişkinlerin %15'inde görülmüştür. Ayrıca ARFID semptomları bulunan bireylerde BKİ ve yaşa göre BKİ persentilinin daha düşük, vücut ağırlığı kaybı veya yetersiz vücut ağırlığı artışı öyküsünün daha sık olduğu bildirilmiştir. Vücut ağırlığı kaybı veya yetersiz ağırlık artışı öyküsünün ARFID olasılığını yaklaşık üç kat artırdığı gösterilmiştir. Bir yıllık izlemde ARFID belirtilerinin %17 oranında devam ettiği belirlenmiştir. Bu sonuçlar, glutenle ilişkili hastalıklarda vücut ağırlığı kaybı, büyüme geriliği ve glutensiz diyetin ötesine geçen besin kısıtlamalarının ARFID açısından dikkatle değerlendirilmesi gerektiğini göstermektedir (Atkins et al., 2026).

Erişkin çölyak hastalarında yürütülen bir çalışmada, 137 hastanın %57'si hasta bildirimine dayalı anket yöntemi ile yapılan ARFID taramasına göre ARFID açısından riskli olarak sınıflandırılmıştır. ARFID riski olan ve olmayan gruplar arasında BKİ, mikro besin ögesi yetersizlikleri, osteopeni/osteoporoz, duodenal biyopsi bulguları ve glutensiz diyete uyum açısından anlamlı farklılık saptanmamıştır. Buna karşın, glutensiz diyetin besin seçimi ve sosyal yaşam üzerindeki yükünün ARFID ile ilişkili olduğu; kısıtlayıcı yemenin en sık bildirilen temel nedeninin gastrointestinal rahatsızlık yaşama korkusu olduğu gösterilmiştir. Bu bulgular, çölyak hastalarında tıbbi olarak gerekli gluten kısıtlaması ile gereksiz ve maladaptif besin kaçınmasının ayırt edilmesinin ve izlemde beslenme ile psikososyal yükün birlikte değerlendirilmesinin önemini ortaya koymaktadır (Bennett et al., 2022).

Bu çalışmalar birlikte değerlendirildiğinde, ARFID ile çölyak hastalığı arasındaki ilişkinin yalnızca beslenme yetersizliği veya düşük vücut ağırlığı ile açıklanamayacağı görülmektedir. Pediatrik örneklemlerde düşük vücut ağırlığı ve BKİ z-skorları, mikro besin ögesi yetersizlikleri ve kemik sağlığına ilişkin olumsuz bulgular bildirilirken, erişkinlerde benzer farklılıkların her çalışmada gösterilmediği görülmektedir (Bennett et al., 2022; Teke et al., 2026) Buna karşılık gastrointestinal semptomlardan korkma, anksiyete, beslenmeyle ilişkili sosyal güçlükler ve yaşam kalitesindeki azalma çalışmalar arasında daha tutarlı biçimde öne çıkmaktadır (Atkins et al., 2026; Bennett et al., 2022; Teke et al., 2026). Bu farklılıklar, çölyak hastalarında ARFID değerlendirilirken antropometrik ölçümlerin ve biyokimyasal parametrelerin yanında besin çeşitliliği, diyet kalitesi, yeme davranışları ve psikososyal işlevselliğin de dikkate alınması gerektiğini düşündürmektedir.

Çölyak hastalarının izleminde, glutensiz diyete uyumun değerlendirilmesinin yanında tıbbi beslenme tedavisinin gerektirdiği kısıtlamaların ötesine geçen besin kaçınmalarının da sorgulanması önem taşımaktadır. Bu kapsamda diyetisyenler, gluten dışında kaçınılan besin veya besin gruplarını, bu kısıtlamaların gerekçelerini ve hastanın diyet kalitesini düzenli olarak değerlendirmelidir. Özellikle gastrointestinal semptomların gluten maruziyeti veya belirli besinler ile ilişkilendirilmesinin sorgulanması, gelişebilecek hipervijilansın erken dönemde fark edilmesine katkı sağlayabilir. Bunun yanı sıra beslenmeyle ilişkili anksiyete, dışarıda yemek yeme veya sosyal ortamlardan kaçınma ve besin güvenliğine yönelik kaygı gibi psikososyal göstergeler de izlem kapsamında ele alınmalıdır. Glutensiz diyetin ötesine geçen kısıtlamalar, beslenme yetersizliği veya psikososyal işlev kaybı saptandığında hekim, diyetisyen, psikiyatrist ve psikologların yer aldığı multidisipliner bir yaklaşım benimsenmelidir. Bu yaklaşım, çölyak hastalığının etkin şekilde kontrol edilmesini sürdürürken gerekli olmayan besin kısıtlamalarının ve maladaptif yeme davranışlarının gelişmesini önlemeye yardımcı olabilir (Kaul et al., 2025).

SONUÇ

Mevcut bulgular, çölyak hastalığının bilinen tek etkili tedavisi olan glutensiz diyetin ötesine geçen besin kısıtlamalarının daha iyi glutensiz diyet uyumu veya hastalık kontrolü sağlamadığını göstermektedir. Buna karşılık, özellikle büyüme geriliği ve diyet kalitesinin düşmesi, artmış anksiyete ve depresyon belirtileri, sosyal işlevsellikte bozulma ve yaşam kalitesinde azalma gibi klinik ve psikososyal sonuçlarla ilişkili olabileceği bildirilmektedir.

Bu nedenle çölyak hastalarının izleminde glutensiz diyete uyumun sağlanmasının yanı sıra, tıbbi gerekliliğin ötesine geçen besin kısıtlamalarının erken dönemde tespit edilmesi hedeflenerek riskli bireyler beslenme durumu ve psikososyal işlevsellik açısından multidisipliner olarak değerlendirilmelidir.

Bununla birlikte, mevcut literatürün yorumlanmasında bazı metodolojik sınırlılıklar göz önünde bulundurulmalıdır. Çalışmalar arasında yaş grupları, örneklem özellikleri ve ARFID değerlendirme yöntemleri açısından belirgin farklılıklar bulunmaktadır. Bazı çalışmalarda ARFID tanısı DSM-5 kriterlerine dayalı klinik değerlendirmeyle konulurken, bazılarında öz-bildirim temelli tarama araçları kullanılmıştır. Ayrıca kronik gastrointestinal hastalıklarda hastalığın yönetimi için gerekli olan besin kısıtlamaları, gastrointestinal semptomlar ve bunlara ilişkin korkular ARFID tarama araçlarındaki bazı maddelerle örtüşebilmekte ve prevalansın olduğundan yüksek tahmin edilmesine yol açabilmektedir. Çalışmaların kesitsel nitelikte olması çölyak hastalığı, glutensiz diyet ve ARFID arasındaki ilişkinin yönünün belirlenmesini güçleştirmektedir. Bu nedenle özellikle çölyak hastalığına özgü klinik değerlendirme yaklaşımlarının kullanıldığı ve uzun dönem izlemin gerçekleştirildiği çalışmalara gereksinim bulunmaktadır.

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PHARMACOPHORE MAPPING FOR ANTI-LUNG-CANCER AGENTS

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Abstract
Pharmacophore mapping is a ligand and structure based computational strategy used to identify the spatial arrangement of chemical features required for effective anti-lung-cancer activity. In lung cancer drug discovery, models are commonly developed against oncogenic targets such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), mesenchymal–epithelial transition factor (MET), vascular endothelial growth factor receptor, and other resistance-associated kinases. Typical pharmacophoric elements include hydrogen-bond donors and acceptors, hydrophobic regions, aromatic rings, ionisable groups, and excluded volumes. These features are generated from active ligands, protein–ligand crystal structures, or molecular dynamics-derived conformations, then validated using known actives, decoys, enrichment factors, and receiver operating characteristic analysis.
Validated models enable rapid virtual screening of large chemical libraries and support scaffold hopping, lead optimisation, and drug repurposing. Candidate compounds are usually prioritised by pharmacophore fit, molecular docking, binding-energy estimation, molecular dynamics simulation, and predicted absorption, distribution, metabolism, excretion, and toxicity properties. For EGFR-mutant non-small-cell lung cancer, mapping can distinguish interactions needed for wild-type, sensitising, and resistance mutations such as L858R, T790M, and C797S. Multi-target pharmacophore models may also help identify compounds capable of suppressing parallel signalling pathways and delaying resistance. Nevertheless, computational hits require biochemical, cellular, and in vivo validation because model quality depends on ligand diversity, protein conformation, protonation state, and dataset balance. Integration with QSAR and machine learning can further improve activity prediction and prioritisation. Overall, pharmacophore mapping reduces experimental workload and guides the rational discovery of selective, potent, and safer anti-lung-cancer agents.
Keywords: Pharmacophore mapping; Lung cancer; EGFR inhibitors; Virtual screening; Molecular docking

INTRODUCTION

Lung cancer is not a single molecular disease. In NSCLC, tumour growth can be driven by alterations in EGFR, ALK, MET, ROS1, RET and other signalling proteins, and the dominant pathway may change as treatment applies selective pressure. Targeted inhibitors have therefore improved precision, but they have not removed the problem of acquired resistance. The attraction of pharmacophore mapping is that it does not require a new inhibitor to resemble an existing drug closely. Instead, it asks whether a molecule can reproduce the spatial features needed for recognition at a chosen binding site. This makes the method useful for virtual screening and scaffold hopping, especially when chemically distinct solutions are desired (Giordano et al., 2022).
A pharmacophore may be ligand based, structure based or hybrid. Ligand-based models identify features shared by active molecules, whereas structure-based models derive features from interactions observed in a receptor pocket. Hybrid approaches combine both sources of information. Early EGFR work showed that a relatively simple arrangement of one hydrogen-bond acceptor, an aromatic feature and hydrophobic regions could discriminate active inhibitors and support database screening (Gupta et al., 2011). More recent work has linked pharmacophore screening to docking and laboratory testing, showing how the approach can move from pattern recognition to experimentally testable leads (Weng et al., 2022).

RESEARCH AND FINDINGS

Building and validating pharmacophore models

Model quality depends as much on the input data as on the modelling software. Ligand-based training sets should contain credible activity data and enough structural diversity to avoid learning only one scaffold. Structure-based models require a biologically meaningful protein conformation, careful treatment of protonation and tautomeric states, and attention to crystallographic waters or mutations that reshape the pocket. Conformational sampling is equally important because the lowest-energy free ligand is not necessarily the bioactive conformation. Table 1 summarises the recurring features used in kinase-oriented models.

Validation should ask a practical question: can the model retrieve known actives from a background of non-active or decoy compounds? Sensitivity, specificity, receiver-operating-characteristic area under the curve and enrichment factors are useful for this purpose. Noor et al. (2024), for example, validated an allosteric EGFR pharmacophore with DeepCoy-generated decoys before screening more than 13 million ZINC molecules. Such testing does not prove that a future hit will inhibit the target, but it reduces the chance that the model is merely a visually convincing arrangement of features. Pharmacophore fit is therefore best interpreted as a ranking criterion, not as a biological endpoint.

Table 1. Core pharmacophoric features in anti-lung-cancer kinase inhibitor models

Feature	Functional meaning	Typical relevance in kinase models
H-bond acceptor	Accepts a hydrogen bond from the binding site.	Often represents hinge-region recognition in EGFR, ALK, MET or VEGFR2.
H-bond donor	Donates a hydrogen bond to a receptor residue.	Can reinforce ATP-site or allosteric-pocket contacts.
Aromatic feature	Represents an aromatic ring or planar π system.	Supports shape complementarity and aromatic interactions.
Hydrophobic region	Marks a non-polar interaction zone.	Frequently captures lipophilic subpockets and type-II kinase back-pocket binding.
Ionisable feature	Represents a positively or negatively ionisable centre.	Useful where electrostatic complementarity contributes to affinity or selectivity.
Excluded volume	Defines space occupied by receptor atoms.	Prevents sterically unrealistic matches in structure-based screening.

Target-focused applications

EGFR remains the most developed pharmacophore case study in lung cancer. Activating variants such as L858R alter kinase behaviour, whereas T790M and C797S are associated with resistance to successive generations of EGFR tyrosine kinase inhibitors. This has encouraged models that address both the ATP-binding site and alternative allosteric pockets. Structure-based screening against T790M/C797S EGFR identified putative allosteric ligands that remained stable in molecular-dynamics simulations, although the study itself was computational (Patel et al., 2021). Noor et al. (2024) similarly used an allosteric EGFR template, decoy validation, docking, ADMET filtering and dynamics to prioritise mutant-selective candidates. Pharmacophore screening of benzimidazole-1,2,3-triazole hybrids has also produced EGFR candidates supported by docking, dynamics and in-silico safety assessment, but these remain leads for experimental confirmation (Kumar et al., 2024).

A more persuasive level of evidence comes from studies that extend beyond computation. Weng et al. (2022) combined 3D-QSAR, common-feature and structure-based pharmacophores with docking, then tested selected compounds. NSC609077 inhibited EGFR activity and reduced growth and migration in gefitinib-resistant H1975 cells. By contrast, large commercial-library workflows that finish with docking, ADMET prediction and long molecular-dynamics simulations should be described as prioritisation studies rather than demonstrations of efficacy (Alanzi et al., 2024).

ALK provides a second important setting. Virtual screening and molecular dynamics have been used to search for candidates against crizotinib-resistant ALK (Kumar et al., 2016), while pharmacophore-guided repurposing has proposed approved drugs with compatible ALK-binding patterns (Faya Castillo et al., 2024). More recently, a multiscale ALK workflow combined pharmacophore screening, PAINS and ADMET filters, docking, dynamics and antiproliferative assays. One selected compound showed

moderate activity in A549 cells, illustrating both the promise and the need for further target-specific validation (Zhang et al., 2025).

MET is particularly relevant because bypass signalling can undermine EGFR-directed therapy. Cross-screening through EGFR-T790M and c-MET pharmacophores generated putative dual inhibitors that were subsequently examined by docking and dynamics (Singh & Silakari, 2017). Common-feature modelling has also been used to identify chemotypes compatible with both c-MET and ALK (Pirhadi et al., 2020). These studies are useful design exercises, but their conclusions should remain proportional to the evidence when biochemical inhibition has not been measured.

VEGFR2 modelling focuses on anti-angiogenic kinase recognition. Type-II inhibitors occupy the ATP site and an adjacent hydrophobic region, providing a distinctive feature arrangement for pharmacophore screening. A five-feature model was used to screen millions of molecules before docking, ADME analysis, dynamics and MM/GBSA calculations (Rathi et al., 2019). Receptor-based modelling has also guided the synthesis and biological evaluation of VEGFR2/FGFR1/BRAF inhibitors, giving a useful example in which computational design was followed by biochemical testing (Abdel-Mohsen et al., 2024). A broader review of VEGFR2 computer-aided design similarly argues for layered workflows rather than reliance on a single scoring method (Uba, 2025).

The same logic has been extended to polypharmacology. Structure-based mapping identified a natural-product scaffold predicted to engage c-MET, EGFR and VEGFR2 (Varma et al., 2023). Dual VEGFR2/c-MET studies have used cross-pharmacophore screening and structural filtering to prioritise candidates (Xie et al., 2024; Dong & Hao, 2025), while separate ligand-based models have been paired to search for EGFR/VEGFR2 inhibitors (Sangande et al., 2020). Beyond these major kinases, pharmacophore-based screening has generated computational ROS1 candidates (Vanajothi et al., 2022). RET offers a stronger translational example: an integrated pharmacophore, docking and dynamics workflow identified a repurposing candidate that was subsequently evaluated in a RET-specific lung-cancer cell model (Ramesh et al., 2021). Table 2 compares representative applications and their level of validation.

Table 2. Representative pharmacophore-guided applications and the strength of supporting evidence

Target/strategy	Model and follow-up	Evidence level	Representative finding
EGFR	Hybrid ligand-/structure-based; 3D-QSAR, docking and cell assays	Experimental cellular support	NSC609077 inhibited EGFR activity and reduced growth and migration in gefitinib-resistant H1975 cells (Weng et al., 2022).
Mutant EGFR	Allosteric pharmacophore; decoy validation, docking, ADMET and MD	Computational prioritisation	Large-scale screening produced mutant-selective allosteric candidates requiring experimental confirmation (Noor et al., 2024).
ALK	Structure/ligand-guided screening; PAINS/ADMET, docking, MD and cell assay	Computational plus antiproliferative assay	F1739-0081 showed moderate antiproliferative activity in A549 cells after multistage screening (Zhang et al., 2025).
EGFR-T790M/c-MET	Dual cross-pharmacophore; docking and MD	Computational	Cross-filtering produced putative dual inhibitors for resistant NSCLC (Singh & Silakari, 2017).
c-MET/ALK	Common-feature dual pharmacophore; docking and MD	Computational	A shared model identified chemotypes compatible with both kinase pockets (Pirhadi et al., 2020).

Target/strategy	Model and follow-up	Evidence level	Representative finding
VEGFR2	Five-feature pharmacophore; docking, ADME, MD and MM/GBSA	Computational	Million-scale screening prioritised type-II VEGFR2 candidates (Rathi et al., 2019).
c-MET/EGFR/VEGFR2	Structure-based polypharmacophore; docking, MD and ADMET	Computational	A natural-product scaffold was prioritised for three receptor tyrosine kinases (Varma et al., 2023).
RET	Pharmacophore/e-pharmacophore; docking, dynamics and cell assay	Experimental cellular support	A repurposing candidate identified in silico was evaluated in a RET-specific lung-cancer cell line (Ramesh et al., 2021).

Integration, limitations and future directions

In practice, pharmacophore mapping is most useful near the beginning of a staged discovery pipeline. A typical sequence is pharmacophore matching, physicochemical filtering, docking, binding-energy estimation, ADMET prediction, molecular dynamics and experimental testing. Each layer answers a different question. Docking proposes a plausible pose; molecular dynamics tests whether that pose remains stable under a chosen simulation model; and ADMET tools flag liabilities predicted from learned chemical patterns. Agreement across these methods can strengthen prioritisation, but it does not convert a virtual hit into a proven inhibitor.

Several limitations deserve explicit attention. Ligand-based models can inherit bias from narrow training sets, and a single receptor structure may miss active, inactive or allosteric conformations that matter for binding. Protonation, tautomer choice, water placement and dataset imbalance can also change the outcome. Ensemble pharmacophores derived from multiple structures or molecular-dynamics snapshots offer one route to handling receptor flexibility. Machine learning can add another layer by ranking large chemical spaces, while pharmacophore constraints retain a degree of mechanistic interpretability. Generative methods may eventually design molecules directly around mutation-specific or multi-target feature patterns. Even so, prospective biochemical, cellular and in-vivo validation will remain the point at which a computational hypothesis becomes pharmacological evidence.

CONCLUSION

Pharmacophore mapping is valuable in anti-lung-cancer drug discovery because it reduces a complex binding problem to a searchable three-dimensional hypothesis without locking discovery to one chemical scaffold. The evidence base is strongest for EGFR, including resistance-associated variants, but meaningful applications also exist for ALK, MET, VEGFR2, ROS1 and RET. The method is particularly suited to virtual screening, scaffold hopping, drug repurposing and multi-target design.

Its limitations are equally important. A high fit score, favourable docking pose or stable molecular-dynamics trajectory does not demonstrate inhibition, selectivity or therapeutic activity. The most informative studies are those that use pharmacophore mapping to narrow chemical space and then test the resulting candidates experimentally. Future ensemble, mutation-aware and machine-learning-assisted models should improve prioritisation, but their scientific value will continue to depend on transparent validation and careful distinction between predicted and experimentally demonstrated effects.

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GİRİŞİMSEL RADYOLOJİDE DEĞİŞEN İŞLEM PROFİLİ: BEŞ YILLIK TEK MERKEZ TREND ANALİZİ

EVOLVING PROCEDURAL PROFILE OF INTERVENTIONAL RADIOLOGY: A FIVE-YEAR SINGLE-CENTER TREND ANALYSIS

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ÖZET

Amaç

Merkezimizde gerçekleştirilen girişimsel radyoloji (GR) işlemlerinin sayı, dağılım ve zamansal değişimini değerlendirmek.

Gereç ve Yöntem

2019–2025 yılları arasında gerçekleştirilen GR işlemleri, COVID-19 dönemi (2020–2021) dışlanarak retrospektif olarak incelendi. Veriler hastane bilgi sisteminden elde edildi. Vasküler işlemler; nörovasküler (örn. karotis arter stentleme), santral vasküler (örn. renal arter stentleme), periferal vasküler (örn. femoral arter stentleme), santral venöz kateter/port ve transarteriyel kemoembolizasyon/radyoembolizasyon (TAKE/TARE) olarak sınıflandırıldı. Nonvasküler işlemler ise biyopsiler, termal ablasyonlar, drenaj işlemleri (örn. apse drenajı), hepatobiliyer girişimler (örn. biliyer drenaj) ve ürolojik girişimlerden (örn. nefrostomi) oluştu.

Bulgular

2019–2025 yılları arasında toplam işlem hacmi %49 artarken, bu artışın temel belirleyicisi %67 artan nonvasküler girişimler oldu. Nonvasküler işlemler arasında en yüksek oransal artış termal ablasyonda (%469) görülürken, bunu sırasıyla ürolojik girişimler (%148), drenaj işlemleri (%60), biyopsiler (%46) ve hepatobiliyer girişimler (%42) izledi. Mutlak işlem sayısındaki en büyük artış biyopsilerde (+720 işlem) ve ürolojik girişimlerde (+605 işlem) gerçekleşti. Vasküler girişimler içinde periferal (%−82), santral (%−50) ve nörovasküler (%−25) işlemler belirgin azalırken, santral venöz kateter/port (%51) ve TAKE/TARE (%64) işlemlerindeki artış sayesinde toplam vasküler işlem yükü büyük ölçüde sabit kaldı (%5).

Biyopsi tüm dönem boyunca en sık uygulanan işlem oldu (%31,5–37,4). Santral venöz kateter/port işlemleri, 2025 yılı dışında ikinci sırada yer alırken, 2025 yılında bu sırayı ürolojik girişimler aldı. Nörovasküler, santral vasküler ve periferal vasküler girişimlerin toplam payındaki azalmaya (%12,2'den %3,2'ye gerileme) bağlı olarak vasküler işlemlerin toplam payı %29,0'dan %20,3'e geriledi. Buna karşın nonvasküler işlemlerin payı, özellikle ürolojik girişimler, drenaj işlemleri ve termal ablasyonlardaki artışın etkisiyle %71,0'dan %79,7'ye yükseldi.

Sonuç

Merkez deneyimimiz, girişimsel radyolojide işlem profilinin nonvasküler girişimler lehine belirgin şekilde değiştiğini göstermektedir. Santral venöz kateter/port ve TAKE/TARE işlemlerindeki artışa rağmen, nörovasküler, santral vasküler ve periferal vasküler girişimlerdeki azalma nedeniyle toplam vasküler işlem yükü büyük ölçüde sabit kalmıştır.

Anahtar Kelimeler: Girişimsel radyoloji; nonvasküler girişimler; vasküler girişimler; işlem trendleri; işlem yükü.

Abstract

Purpose

To evaluate the number, distribution, and temporal changes of interventional radiology (IR) procedures performed at our center.

Materials and Methods

IR procedures performed between 2019 and 2025 were retrospectively reviewed, excluding the COVID-19 period (2020–2021). Data were obtained from the hospital information system. Vascular procedures were classified as neurovascular (e.g., carotid artery stenting), central vascular (e.g., renal artery

stenting), peripheral vascular (e.g., femoral artery stenting), central venous catheter/port procedures, or transarterial chemoembolization/radioembolization (TACE/TARE). Nonvascular procedures comprised biopsies, thermal ablations, drainage procedures (e.g., abscess drainage), hepatobiliary interventions (e.g., biliary drainage), and urological interventions (e.g., nephrostomy).

Results

Between 2019 and 2025, the overall procedural volume increased by 49%, primarily driven by nonvascular interventions, which increased by 67%. Among nonvascular procedures, thermal ablation showed the greatest relative increase (+469%), followed by urological interventions (+148%), drainage procedures (+60%), biopsies (+46%), and hepatobiliary interventions (+42%). In absolute numbers, biopsies (+720 procedures) and urological interventions (+605 procedures) accounted for the largest increases. Within vascular interventions, peripheral (−82%), central (−50%), and neurovascular (−25%) procedures declined markedly, whereas central venous catheter/port procedures (+51%) and TACE/TARE (+64%) increased, maintaining an overall stable vascular workload (+5%).

Biopsy was the most common procedure (31.5–37.4%). Central venous catheter/port placement ranked second except in 2025, when urological interventions became second. Vascular procedures declined from 29.0% to 20.3% as the combined share of neurovascular, central vascular, and peripheral vascular interventions fell from 12.2% to 3.2%. Conversely, nonvascular procedures increased from 71.0% to 79.7%, driven by urological interventions, drainage procedures, and thermal ablation.

Conclusion

Our experience demonstrates a marked shift toward nonvascular interventions. Although central venous catheter/port procedures and TACE/TARE increased, overall vascular workload remained stable because of declines in neurovascular, central vascular, and peripheral vascular interventions.

Keywords: Interventional radiology; nonvascular interventions; vascular interventions; procedural trends; workload

GİRİŞ

Girişimsel radyoloji (GR), görüntüleme kılavuzluğunda gerçekleştirilen minimal invaziv tanısal ve tedavi edici girişimleri kapsayan, teknolojik gelişmeler ve yeni tedavi yöntemlerinin katkısıyla uygulama alanı sürekli genişleyen bir uzmanlık dalıdır. Bununla birlikte girişimsel radyoloji pratiği yalnızca teknolojik gelişmelerden değil, aynı zamanda hasta yönlendirme alışkanlıkları, diğer girişimsel branşlarla olan etkileşim, kurumsal organizasyon ve sağlık sistemine bağlı faktörlerden de etkilenmektedir. Bu nedenle girişimsel radyoloji işlem profili ve işlem hacimleri merkezler arasında ve zaman içerisinde önemli değişkenlik gösterebilmektedir [1].

İşlem hacmi ve dağılımındaki zamansal değişimlerin ortaya konulması, klinik hizmet planlaması, eğitim gereksinimlerinin belirlenmesi ve gelecekteki altyapı ile insan gücü planlaması açısından önem taşımaktadır. Ancak literatürde girişimsel radyoloji uygulamalarındaki uzun dönemli değişimi vasküler ve nonvasküler alt gruplar temelinde değerlendiren çalışma sayısı sınırlıdır [2,3]. Bu çalışmada, merkezimizde gerçekleştirilen girişimsel radyoloji işlemlerinin sayı, dağılım ve zamansal değişiminin vasküler ve nonvasküler alt gruplar bazında değerlendirilmesi amaçlanmıştır.

Gereç Ve Yöntem

Bu retrospektif çalışmada, merkezimizde 2019–2025 yılları arasında gerçekleştirilen girişimsel radyoloji işlemleri değerlendirildi. COVID-19 pandemisinin sağlık hizmet sunumu, hasta başvuruları ve elektif girişim hacimleri üzerinde belirgin değişikliklere neden olması ve bu durumun uzun dönem işlem eğilimlerinin yanlış yorumlanmasına yol açabileceği düşünülerek 2020–2021 yılları analiz dışı bırakıldı. Veriler hastane bilgi yönetim sisteminden elde edildi. İşlemler vasküler ve nonvasküler olmak üzere iki ana gruba ayrıldı.

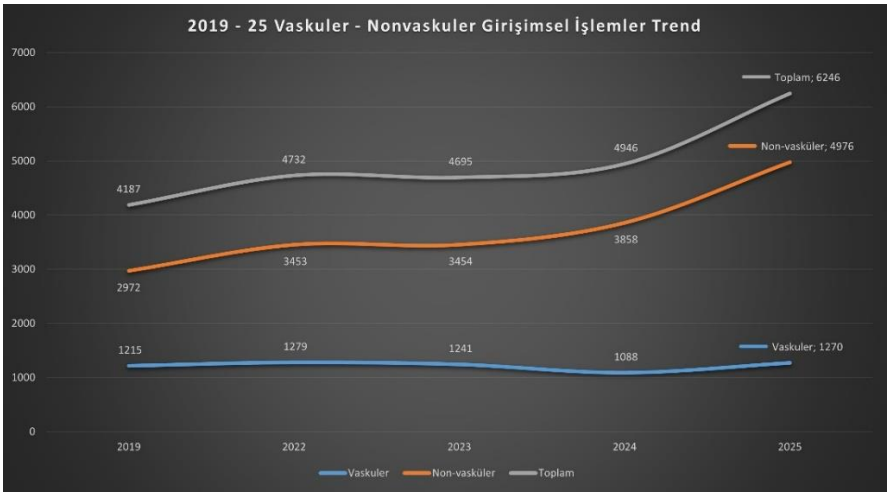
Vasküler girişimler; nörovasküler, santral vasküler, periferal vasküler, santral venöz kateter (SVK)/port ve transarteriyel kemoembolizasyon/radyoembolizasyon (TAKE/TARE) olmak üzere beş alt grupta değerlendirildi. Nörovasküler grup başta karotis arter stentleme, akut iskemik inmede mekanik trombektomi ve tanısal dijital subtraksiyon anjiyografi (DSA) olmak üzere ilgili kategorideki tüm girişimleri kapsamaktaydı. Santral vasküler grup renal arter stentleme, adrenal venöz örnekleme ve vena cava filtre uygulamaları gibi santral vasküler girişimleri; periferal vasküler grup ise yüzeyel femoral arter stentleme, infrapopliteal arterlere yönelik perkütan translüminal anjiyoplasti ve varis tedavileri

olmak üzere tüm periferal vasküler girişimleri içermekteydi. SVK/port grubuna geçici ve tünelli diyaliz kateterleri, santral venöz kateter ve venöz port implantasyonları; TAKE/TARE grubuna ise transarteriyel kemoembolizasyon ve radyoembolizasyon işlemleri dahil edildi.
Nonvasküler girişimler biyopsiler, termal ablasyonlar, drenaj işlemleri, hepatobiliyer girişimler ve ürolojik girişimler olmak üzere beş alt grupta incelendi. Biyopsi grubu karaciğer, böbrek ve kemik biyopsileri gibi tüm ince iğne aspirasyon ve tru-kut biyopsi işlemlerini; termal ablasyon grubu başta karaciğer tümörleri, renal hücreli karsinom ve tiroid/paratiroid nodül ablasyonları olmak üzere tüm termal ablasyon işlemlerini; drenaj grubu ise intraabdominal apse, ampiyem ve yüzeyel apse drenajları ile torasentez ve parasentez olmak üzere tüm drenaj işlemlerini kapsamaktaydı. Hepatobiliyer girişimler grubunda başlıca perkütan transhepatik biliyer drenaj, perkütan kolesistostomi ve biliyer stentleme; ürolojik girişimler grubunda ise perkütan nefrostomi, antegrad double J stenti takılması, nefrostomi kateter değişimi ve perkütan sistostomi işlemleri yer almaktaydı. İşlem grupları, girişimsel radyolojide yaygın kabul gören prosedür sınıflandırmaları esas alınarak oluşturuldu.
Her işlem kategorisi için yıllık işlem sayıları ve toplam işlemler içindeki yüzdesel dağılımlar hesaplandı. Ayrıca 2019 yılı başlangıç referansı alınarak 2025 yılına kadar olan mutlak ve oransal değişimler değerlendirildi.

Bulgular

Çalışma döneminde (2019–2025) merkezimizde gerçekleştirilen toplam girişimsel radyoloji işlem sayısı %49 artarak 4.187'den 6.246'ya ulaştı. Bu artışın temel belirleyicisi nonvasküler girişimler oldu. Nonvasküler girişim sayısı %67 artış göstererek 2.972'den 4.976'ya yükselirken, vasküler girişim sayısı 1.215'ten 1.270'e çıkarak yalnızca %5 oranında arttı (Tablo 1, Figür 1).

Figür 1. 2019 - 25 Vasküler ve Non-vasküler Girişimsel İşlemler Trend Analizi

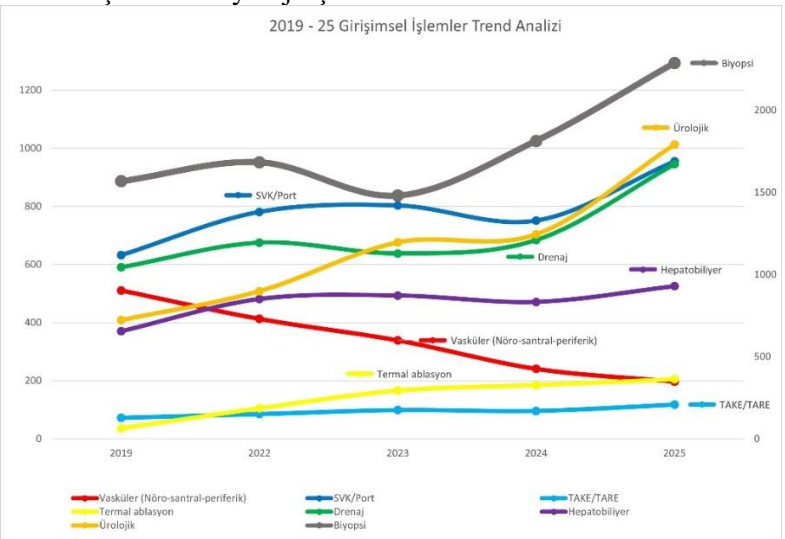


Nonvasküler girişimler içerisinde en yüksek oransal artış termal ablasyon grubunda izlendi. Termal ablasyon sayısı 36'dan 205'e yükselerek %469 artış gösterdi. Bunu sırasıyla ürolojik girişimler (%148; 408'den 1.013'e), drenaj işlemleri (%60; 590'dan 945'e), biyopsiler (%46; 1.568'den 2.288'e) ve hepatobiliyer girişimler (%42; 370'den 525'e) izledi. Mutlak işlem sayısındaki artış açısından ise en büyük katkıyı biyopsiler (+720 işlem) ve ürolojik girişimler (+605 işlem) sağladı (Tablo 1, Figür 2-3).
Vasküler girişimler değerlendirildiğinde, en belirgin azalma periferik vasküler girişimlerde gözlendi (%−82; 234'ten 41'e). Bunu santral vasküler (%−50; 209'dan 105'e) ve nörovasküler girişimler (%−25; 68'den 51'e) takip etti. Buna karşın santral venöz kateter/port işlemleri %51 (632'den 955'e), TAKE/TARE işlemleri ise %64 (72'den 118'e) arttı (Tablo 1, Figür 2-3). Nörovasküler, santral vasküler ve periferal vasküler girişimlerin toplamı 511'den 197'ye gerileyerek %61 oranında azalmasına rağmen, SVK/port ve TAKE/TARE işlemlerindeki artış sayesinde toplam vasküler işlem hacmi büyük ölçüde korunmuş oldu (+ %5; 1215'den 1270'e) (Tablo 1).

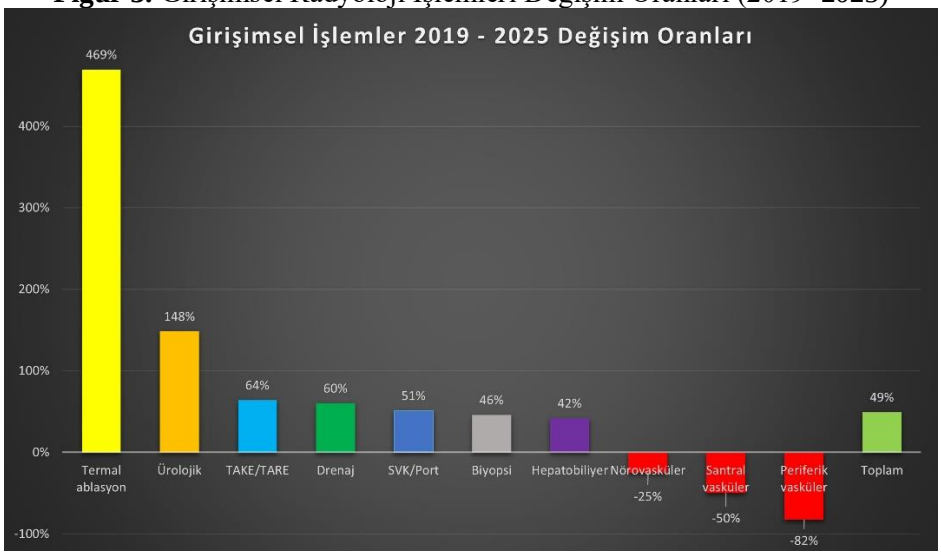
Tablo 1. Girişimsel Radyoloji İşlemlerinin Kategorilere Göre Yıllık İşlem Hacmi ve 2019–2025 Dönemindeki Değişim Oranları

Kategori	İşlem Sayıları					2019 - 25 % Değişim
	2019	2022	2023	2024	2025	
Nörovasküler	68	62	57	61	51	-25%
Periferik vasküler	234	176	104	63	41	-82%
Santral vasküler	209	175	178	117	105	-50%
Vasküler (Nöro - santral - periferik)	511	413	339	241	197	-61%
SVK/Port	632	781	803	751	955	51%
TAKE/TARE	72	85	99	96	118	64%
Vasküler - Alt toplam	1.215	1.279	1.241	1.088	1.270	5%
Termal Ablasyon	36	105	166	185	205	469%
Biyopsi	1.568	1.684	1.481	1.814	2.288	46%
Drenaj	590	675	638	684	945	60%
Hepatobiliyer	370	481	493	471	525	42%
Ürolojik	408	508	676	704	1.013	148%
Nonvasküler - Alt toplam	2.972	3.453	3.454	3.858	4.976	67%
Toplam	4.187	4.732	4.695	4.946	6.246	49%

Figür 2. Girişimsel Radyoloji İşlemlerinin 2019–25 Dönemi Trend Analizi



Figür 3. Girişimsel Radyoloji İşlemleri Değişim Oranları (2019–2025)



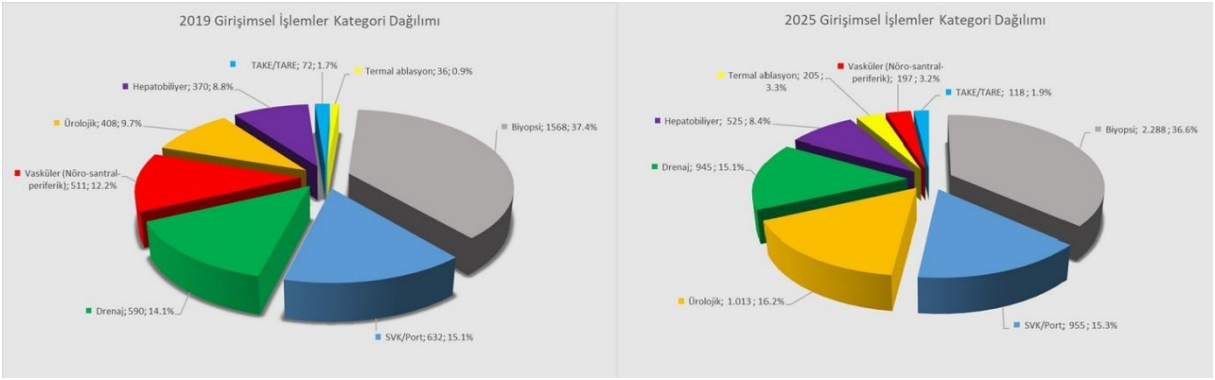
Toplam işlem dağılımı incelendiğinde biyopsiler tüm çalışma dönemi boyunca en sık uygulanan girişim olarak kaldı ve toplam işlemlerin %31,5–37,4'ünü oluşturdu. Santral venöz kateter/port işlemleri 2019–2024 yılları arasında ikinci sırada yer alırken (%15,1–17,1), 2025 yılında bu sırayı %16,2 ile ürolojik girişimler aldı. İşlem kategorilerinin toplam girişimler içindeki payları değerlendirildiğinde vasküler girişimlerin oranı %29,0'dan %20,3'e gerilerken, nonvasküler girişimlerin oranı %71,0'dan %79,7'ye yükseldi (Tablo 2).

Vasküler girişimler içerisinde en belirgin düşüş, nörovasküler, santral vasküler ve periferal vasküler girişimlerin toplam payında izlendi (%12,2'den %3,2'ye). Buna karşılık SVK/port (%15,1'den %15,3'e) ve TAKE/TARE (%1,7'den %1,9'a) işlemlerinin toplam işlem hacmi içerisindeki payı büyük ölçüde korundu. Nonvasküler girişimlerde ise özellikle ürolojik girişimler (%9,7'den %16,2'ye), termal ablasyon (%0,9'dan %3,3'e) ve drenaj işlemlerinin (%14,1'den %15,1'e) toplam işlem hacmi içerisindeki payında artış gözlenirken, biyopsiler yüksek oranını korudu (%37,4'ten %36,6'ya), hepatobiliyer girişimlerin payı ise büyük ölçüde stabil seyretti (%8,8'den %8,4'e) (Tablo 2, Figür 4).

Tablo 2. Girişimsel Radyoloji İşlemlerinin Kategorilere Göre Yüzdesel Dağılımı (2019–2025)

	İşlem Dağılımı ve Yüzdeleri				
Kategori	2019	2022	2023	2024	2025
Nörovasküler	1,6%	1,3%	1,2%	1,2%	0,8%
Periferik vasküler	5,6%	3,7%	2,2%	1,3%	0,7%
Santral vasküler	5,0%	3,7%	3,8%	2,4%	1,7%
Vasküler (Nöro-santral-periferik)	12,2%	8,7%	7,2%	4,9%	3,2%
SVK/Port	15,1%	16,5%	17,1%	15,2%	15,3%
TAKE/TARE	1,7%	1,8%	2,1%	1,9%	1,9%
Vasküler - Alt toplam	29,0%	27,0%	26,4%	22,0%	20,3%
Termal Ablasyon	0,9%	2,2%	3,5%	3,7%	3,3%
Biyopsi	37,4%	35,6%	31,5%	36,7%	36,6%
Drenaj	14,1%	14,3%	13,6%	13,8%	15,1%
Hepatobiliyer	8,8%	10,2%	10,5%	9,5%	8,4%
Ürolojik	9,7%	10,7%	14,4%	14,2%	16,2%
Non-vasküler - Alt toplam	71,0%	73,0%	73,6%	78,0%	79,7%

Figür 4. 2019 ve 2025 Yılları Girişimsel Radyoloji İşlemleri Alt Kategori Payları



Sonuç

Bu çalışma, merkezimizde girişimsel radyoloji işlem profilinin beş yıllık dönemde belirgin biçimde değiştiğini ve toplam işlem hacmindeki artışın esas olarak nonvasküler girişimlerden kaynaklandığını göstermektedir. Özellikle biyopsi, ürolojik girişimler, drenaj işlemleri ve termal ablasyonlardaki belirgin artış, nonvasküler girişimlerin toplam işlem yükü içindeki payını daha da artırmıştır.

Buna karşılık, nörovasküler, santral vasküler ve periferal vasküler girişimlerde belirgin azalma izlenmiş; santral venöz kateter/port ve TAKE/TARE işlemlerindeki artış ise toplam vasküler işlem hacminin büyük ölçüde korunmasını sağlamıştır. Bu bulgular, girişimsel radyoloji pratiğinin zaman içerisinde yalnızca niceliksel olarak büyümediğini, aynı zamanda uygulama alanları ve işlem dağılımı açısından da önemli bir dönüşüm geçirdiğini ortaya koymaktadır. İşlem eğilimlerinin düzenli olarak izlenmesi; klinik hizmetlerin organizasyonu, eğitim önceliklerinin belirlenmesi ve gelecekteki insan gücü ile altyapı gereksinimlerinin planlanması açısından önem taşımaktadır.

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CLIMATE CHANGE IMPACTS ON FRESHWATER ECOSYSTEMS IN THE KURDISTAN REGION, IRAQ

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ABSTRACT
Background: Climate change is an important environmental challenge for freshwater ecosystems, particularly in regions exposed to increasing temperature and water-resource stress. This study assessed recent air-temperature patterns in four major cities of the Kurdistan Region of Iraq and considered their potential implications for freshwater ecosystems. Material and methods: Monthly mean near-surface air temperature for Erbil, Sulaymaniyah, Duhok, and Halabja was evaluated from January to June 2026. Mean monthly temperatures were calculated from daily temperature values, and seasonal and spatial differences were compared. Results: All four locations showed a clear increase in mean air temperature from January to June. January was the coolest month, whereas June was the warmest. The January–June mean temperature was highest in Erbil (16.45 °C), followed by Halabja (16.08 °C), Sulaymaniyah (15.60 °C), and Duhok (13.88 °C). The observed spatial differences are consistent with differences in geographic position and local climatic conditions. Conclusion: The observed warming pattern may increase evaporation, contribute to freshwater loss, reduce dissolved-oxygen availability, and alter aquatic biological processes. Because the present study evaluates air temperature rather than direct ecosystem-response measurements, these effects should be regarded as potential implications. Continuous climate monitoring combined with water-temperature, hydrological, water-quality, and biological measurements is recommended.
Keywords:Air temperature; aquatic biodiversity; climate variability; freshwater management; lake ecosystems; water resources; warming; water quality

1. INTRODUCTION
Climate change has become one of the most significant environmental challenges of the twenty-first century, affecting freshwater ecosystems across the globe. Rising air temperatures, altered precipitation patterns, and increasing frequencies of extreme weather events can influence the physical, chemical, and biological characteristics of lakes, rivers, and wetlands. Freshwater ecosystems are particularly vulnerable because they support diverse aquatic organisms while providing essential ecosystem services, including drinking water, irrigation, fisheries, and recreation. Changes in climatic conditions can disrupt ecological balance, reduce biodiversity, and threaten water security for both humans and wildlife (Intergovernmental Panel on Climate Change [IPCC], 2023).
Air temperature is an important climatic variable controlling freshwater ecosystem processes. Increasing atmospheric temperatures can influence water temperature, thermal stratification, dissolved oxygen concentrations, nutrient cycling, and primary productivity. Warmer water generally contains less dissolved oxygen, which can place additional stress on aquatic organisms. Elevated temperatures may also promote algal growth and alter eutrophication processes, with consequences for water quality and ecosystem health (Moss, 2010; Woolway et al., 2020).
The Kurdistan Region of Iraq contains natural and artificial freshwater bodies, including Dukan Lake, Darbandikhan Lake, Duhok Lake, and several reservoirs that support water supply, agriculture, hydropower generation, fisheries, and other human activities. These resources are exposed to environmental pressures associated with climate variability, population growth, land-use change, and pollution. Rising temperatures together with drought and changing precipitation may alter hydrological processes and water availability, potentially affecting aquatic biodiversity (United Nations Environment Programme, 2021).
Remote sensing, satellite observations, and climate reanalysis datasets have improved the capacity to monitor environmental change across large areas. Such approaches complement field observations and can provide spatially and temporally continuous information relevant to freshwater assessment (Woolway & Merchant, 2019; Topp et al., 2020).
Previous studies have documented relationships between warming and freshwater ecosystem responses, including changes in thermal structure, lake warming, dissolved oxygen conditions, species composition, and algal-bloom risk (Adrian et al., 2009; O'Reilly et al., 2015; Woolway et al., 2020). However, regional assessments for the Kurdistan Region remain limited.

Therefore, the present study aimed to evaluate mean air-temperature patterns from January to June 2026 in Erbil, Sulaymaniyah, Duhok, and Halabja and to discuss their potential implications for freshwater ecosystems.

2. LITERATURE REVIEW

2.1. Effects of Rising Temperature on Freshwater Ecosystem Dynamics. Climate warming can alter freshwater ecosystems by changing water temperature, metabolic rates, seasonal cycles, species distributions, and community interactions. Warmer conditions can also increase evaporation and modify lake thermal structure. Adrian et al. (2009) identified lakes as sensitive indicators of climate change because physical and biological processes respond measurably to changing climatic conditions.

2.2. Climate Change Effects on Water Quality and Aquatic Biodiversity. Freshwater organisms are sensitive to changes in temperature and water quality. Increased temperature, altered precipitation, drought, pollution, and habitat degradation can interact to reduce habitat suitability and biodiversity. Climate-driven changes may also modify nutrient availability and increase the risk of algal blooms. Dudgeon et al. (2006) emphasized the vulnerability of freshwater biodiversity to multiple environmental pressures.

2.3. Climate Variability in Semi-Arid Regions. Semi-arid regions are especially sensitive to changes in temperature, precipitation, and evaporation. Higher atmospheric temperature can increase evaporative demand and contribute to water scarcity when precipitation is insufficient. The Middle East has experienced substantial drought and water-resource pressures, making climate monitoring important for regional water management (Trigo et al., 2010; Al-Ansari, 2019).

2.4. Climate Data and Freshwater Monitoring. Climate reanalysis and remote-sensing products provide important tools for evaluating environmental variability. ERA5 provides spatially and temporally consistent climate information suitable for environmental analyses (Hersbach et al., 2020). Remote sensing can complement field measurements of inland waters and support assessment of long-term ecosystem changes (Topp et al., 2020).

3. MATERIALS AND METHODS

3.1. Study Area. The study considered four major cities of the Kurdistan Region of Iraq: Erbil, Sulaymaniyah, Duhok, and Halabja. The selected locations represent different geographic and climatic settings. Erbil represents a central lowland environment, Duhok represents a northern mountainous environment, and Sulaymaniyah and Halabja represent eastern mountainous areas.

3.2. Climate Data. Monthly mean near-surface air temperature at approximately 2 m above the surface was evaluated for January–June 2026. The study used climate-monitoring information described in the original manuscript as including ERA5 reanalysis and available meteorological records. The analysis was designed to compare seasonal and spatial temperature variation among the four locations (Hersbach et al., 2020).

3.3. Temperature Analysis. Monthly mean temperature was calculated as the arithmetic mean of daily temperature values for each month: Mean temperature (°C) = Σ daily temperatures / Number of days. Monthly values were compared from winter (January–February) through spring and early summer (March–June). The six-month mean for each city was calculated from the six reported monthly means.

4. RESULTS

Mean monthly air temperature increased progressively from January to June in all four study locations. The lowest monthly values occurred in January, whereas June recorded the highest values. Duhok consistently had the lowest temperature among the four locations, while Erbil and Halabja generally recorded the highest values during the warmer months.

Erbil increased from 7.2 °C in January to 29.4 °C in June; Sulaymaniyah increased from 5.8 °C to 28.7 °C; Duhok increased from 4.4 °C to 27.2 °C; and Halabja increased from 6.5 °C to 29.0 °C.

Erbil had the highest January–June mean temperature (16.45 °C), followed by Halabja (16.08 °C), Sulaymaniyah (15.60 °C), and Duhok (13.88 °C).

5. DISCUSSION

The present study demonstrated a clear seasonal increase in mean air temperature from January to June 2026 across Erbil, Sulaymaniyah, Duhok, and Halabja. The observed pattern is consistent with the transition from winter to early summer. The spatial differences among the locations may reflect geographic position, elevation, and local climatic conditions.

The temperature pattern has potential implications for freshwater ecosystems. Increased air temperature can contribute to higher surface-water temperature and evaporation, while warmer water can reduce oxygen solubility. These mechanisms may increase ecological stress for temperature-sensitive aquatic organisms and influence biological processes. Previous research has documented broad freshwater responses to warming, including changes in thermal structure, mixing regimes, and lake-surface temperature (Williamson et al., 2009; Woolway & Merchant, 2019; O'Reilly et al., 2015).

Duhok recorded the lowest mean temperature over the study period, whereas Erbil recorded the highest. The difference is compatible with the contrasting geographic settings of the selected cities, although the present dataset does not permit attribution of the differences to elevation alone. Further analysis using station elevation, precipitation, humidity, wind speed, and radiation would be needed to quantify the contribution of individual climatic controls.

In the Kurdistan Region, potential warming-related effects are important because freshwater resources are also exposed to drought, pollution, population growth, and increasing water demand. Higher temperatures combined with limited water availability may increase pressure on lakes and reservoirs. Nevertheless, the present study does not directly measure water temperature, dissolved oxygen, nutrient concentrations, biological communities, or lake water levels. Therefore, relationships between the observed air temperatures and ecosystem responses should be interpreted as potential impacts rather than demonstrated causal effects.

Future studies should integrate long-term air- and water-temperature records with hydrological, water-quality, phytoplankton, and biodiversity measurements. Such integrated monitoring would provide stronger evidence for determining how climate variability is affecting freshwater ecosystems in the region.

6. CONCLUSION

1. Mean air temperature increased consistently from January to June 2026 in Erbil, Sulaymaniyah, Duhok, and Halabja.
2. Erbil had the highest January–June mean temperature (16.45 °C), while Duhok had the lowest (13.88 °C).
3. The observed spatial differences are consistent with variation in geographic position and local climatic conditions.
4. Increasing air temperature may contribute to higher evaporation, warmer freshwater, lower oxygen solubility, and changes in aquatic biological processes.
5. Because the study did not directly measure freshwater ecosystem responses, the reported ecological consequences should be regarded as potential implications requiring further field-based investigation.
6. Continuous climate monitoring integrated with hydrological, water-quality, and biological measurements is recommended to support freshwater ecosystem management and climate adaptation in the Kurdistan Region.

Table 1. Mean Monthly Air Temperature (°C) From January To June 2026

Month	Erbil (°C)	Sulaymaniyah (°C)	Duhok (°C)	Halabja (°C)
January	7.2	5.8	4.4	6.5
February	9.4	8.0	6.1	8.7
March	12.2	11.5	10.0	12.0
April	17.2	16.8	15.6	17.3
May	23.3	22.8	20.6	23.0
June	29.4	28.7	27.2	29.0

Table 2. Mean Air Temperature For January–June 2026

City	Mean temperature (°C)
Erbil	16.45
Sulaymaniyah	15.60
Duhok	13.88
Halabja	16.08

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INNOVATIONS IN MEDICAL BIOTECHNOLOGY, GENETICS, AND MOLECULAR BIOLOGY: A CRITICAL REVIEW OF CHALLENGES, LIMITATIONS, AND FUTURE DIRECTIONS

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Abstract
Medical biotechnology has become one of the most transformative scientific disciplines of the twenty-first century, reshaping disease diagnosis, prevention, treatment, and healthcare delivery through advances in genomics, molecular diagnostics, gene editing, regenerative medicine, and artificial intelligence (AI). This review critically synthesises international, African, and Nigerian literature published between 2019 and 2026, supplemented by seminal foundational studies, to examine innovations that have shaped contemporary medical biotechnology alongside the scientific, ethical, regulatory, economic, and infrastructural barriers that constrain their equitable diffusion. A narrative, thematic-analytic review method was applied to literature retrieved from PubMed, Scopus, Web of Science, and reports of leading international bodies, and the analysis was organised through an integrated theoretical lens combining Systems Theory, Human Capital Theory, and the Technology Acceptance Model. The review finds that while precision medicine, CRISPR-Cas gene editing, molecular diagnostics, and AI-assisted drug discovery have measurably improved diagnostic accuracy and treatment outcomes, substantial disparities persist between high-income and low- and middle-income countries in research funding, laboratory infrastructure, skilled workforce, regulatory capacity, and commercialization pathways. In Nigeria and much of Sub-Saharan Africa, these disparities are compounded by weak university–industry linkages, brain drain, and dependence on imported diagnostics and biologics. The review concludes that sustainable progress requires coordinated investment in research infrastructure, interdisciplinary human-capital development, ethical governance, and innovation-friendly policy frameworks, and it proposes an integrated biotechnology-innovation framework together with targeted recommendations for governments, universities, industry, and international development partners.
Keywords: medical biotechnology; genetics; molecular biology; precision medicine; gene editing; genomics; Nigeria; Africa

1. Introduction

The rapid advancement of biotechnology, genetics, and molecular biology has fundamentally transformed modern medicine, creating unprecedented opportunities for disease prevention, diagnosis, treatment, and healthcare innovation. Over the past three decades, discoveries in molecular genetics, recombinant DNA technology, genomics, proteomics, bioinformatics, and synthetic biology have expanded humanity's capacity to understand complex biological systems and to develop targeted therapeutic interventions, reshaping biomedical research, pharmaceutical development, and public health strategy worldwide [1].

Medical biotechnology denotes the application of biological systems, living organisms, cellular components, and molecular techniques to the development of products and technologies that improve human health. In contrast to conventional medicine, which is largely oriented toward symptomatic

treatment, medical biotechnology seeks to understand disease at the molecular and genetic level; thereby enabling personalised interventions tailored to individual genetic profiles an orientation that underlies the emergence of precision medicine in the management of cancer, diabetes mellitus, cardiovascular disease, inherited disorders, autoimmune conditions, and infectious disease [2].

The completion and continued refinement of the Human Genome Project laid the technical foundation for contemporary genome sequencing. The cost of sequencing a human genome fell from approximately US$100 million in the early 2000s to below US$500 for selected applications by 2025, a reduction that has enabled the routine integration of genomic information into clinical decision-making, disease-risk prediction, and therapy design [3].

Parallel advances in molecular biology polymerase chain reaction (PCR), real-time quantitative PCR, next-generation sequencing (NGS), digital PCR, fluorescence in situ hybridisation, and liquid biopsy have become indispensable for detecting infectious disease, identifying genetic abnormality, diagnosing cancer, and conducting epidemiological surveillance. The COVID-19 pandemic illustrated this indispensability directly: reverse-transcription PCR became the diagnostic gold standard, genomic surveillance tracked viral evolution, and mRNA vaccine platforms compressed a development cycle that historically took a decade into less than a year while preserving safety and efficacy standards [4,5].

A further breakthrough has been the maturation of CRISPR-Cas gene-editing systems, which permit precise modification of DNA sequences and have opened new possibilities for correcting inherited disorders such as sickle cell disease, β-thalassaemia, cystic fibrosis, and Duchenne muscular dystrophy [6]. The regulatory approval of the first CRISPR-based therapies for sickle cell disease and β-thalassaemia marks a significant milestone in translating genome editing from bench research into clinical practice, notwithstanding continuing concerns regarding safety, cost, and equitable access [7].

Artificial intelligence and machine learning have further accelerated discovery by enabling analysis of the large biological datasets generated through genomics, proteomics, and clinical research. AI-based platforms such as AlphaFold now predict protein structure with accuracy that previously required years of experimental crystallography, and comparable systems assist in drug-candidate identification, genomic-variant interpretation, and clinical-trial optimisation [8,9].

Despite these achievements, the global diffusion of biotechnology remains highly unequal. High-income countries continue to dominate biotechnology research, patenting, and commercialization because of sustained investment in infrastructure, education, and public–private partnership, whereas many low- and middle-income countries particularly in Sub-Saharan Africa continue to contend with inadequate funding, limited laboratory infrastructure, workforce shortages, fragmented regulation, and weak technology-transfer mechanisms [10,11]. Nigeria illustrates both the opportunity and the constraint: institutions such as the National Biotechnology Research and Development Agency (NBRDA), together with universities and research institutes, have initiated programmes in vaccine development, molecular diagnostics, genomics, and bioinformatics, yet inconsistent investment; unreliable infrastructure, brain drain, and weak academia–industry collaboration continue to limit national capacity [12].

Beyond the scientific and infrastructural domains, medical biotechnology raises complex ethical, legal, and social questions concerning gene editing, reproductive biotechnology, genetic privacy, data ownership, biobanking, and equitable access, all of which require deliberate governance if innovation is to retain public trust [13]. The sector's growth also bears directly on the United Nations Sustainable Development Goals, particularly SDG 3 (Good Health and Well-Being), SDG 4 (Quality Education), SDG 9 (Industry, Innovation and Infrastructure), and SDG 17 (Partnerships for the Goals).

1.1 Problem Statement

Although medical biotechnology has transformed global healthcare through genomics, molecular diagnostics, gene editing, regenerative medicine, and personalised medicine, its potential remains constrained by scientific, ethical, regulatory, financial, and infrastructural barriers whose severity is unevenly distributed. Disparities between developed and developing countries in research capacity, technology transfer, workforce development, and equitable access remain pronounced, and in Nigeria and comparable African contexts these are compounded by insufficient research investment, weak industry–academia collaboration, and fragile regulatory systems. Ethical controversies surrounding genome editing, genomic-data governance, AI-assisted diagnostics, and intellectual property add further complexity. These persistent challenges warrant a critical, integrative evaluation of current innovations and practical strategies for advancing biotechnology responsibly, sustainably, and equitably.

1.2 Significance of the Study

By integrating global evidence with African and Nigerian perspectives, this review contributes to scholarly discourse on healthcare innovation, research financing, ethical governance, and biotechnology commercialisation. It offers evidence-based guidance for researchers, healthcare professionals, policymakers, industry, and development partners seeking to strengthen biotechnology systems, and it is of particular value to low- and middle-income settings where the gap between scientific potential and practical translation remains widest. The study further situates biotechnology innovation within the framework of the United Nations Sustainable Development Goals notably SDG 3, SDG 4, SDG 9, and SDG 17 thereby linking scientific advancement to broader national-development and health-security priorities.

1.3 Research Gap

While a substantial body of literature addresses individual dimensions of medical biotechnology genomics, gene editing, molecular diagnostics, or artificial intelligence in isolation, few studies integrate these strands within a single theoretical and empirical account that spans global, African, and Nigerian contexts simultaneously. Existing reviews are also heavily concentrated on high-income settings, leaving the structural, regulatory, and workforce constraints that shape biotechnology translation in Sub-Saharan Africa comparatively under-examined. Moreover, the literature rarely combines Systems Theory, Human Capital Theory, and the Technology Acceptance Model into a unified explanatory framework capable of linking innovation inputs, enabling environment, and healthcare outcomes. This review addresses that gap by synthesising literature published between 2019 and 2026 through an integrated theoretical lens, and by proposing a consolidated input–process–environment–outcome framework applicable to both global and developing-country contexts.

2. Literature Review

A clear delineation of the concepts underpinning biotechnology, genetics, and molecular biology is essential to appreciating their combined role in modern healthcare. This section defines the core constructs, clarifies their interrelationship, sets out the theoretical framework guiding the review, and thematically synthesises the empirical literature on innovation in medical biotechnology.

2.1 Conceptual Review

2.1.1 Biotechnology and Medical Biotechnology

Biotechnology is a multidisciplinary field integrating biology, chemistry, genetics, molecular biology, engineering, computer science, and medicine to develop products and technologies that improve human life, through the manipulation of living organisms, biological systems, or their components [14]. The OECD defines biotechnology as the application of science and technology to living organisms, and to parts, products, and models thereof, in order to alter living or non-living materials for the production of knowledge, goods, and services a definition that frames biotechnology simultaneously as a scientific discipline and an innovation platform [15]. Although traditional biotechnological practice (fermentation, brewing) dates back millennia, modern biotechnology emerged after the elucidation of the DNA double helix and the subsequent development of recombinant DNA technology in the 1970s, since when it has diversified into agricultural, industrial, environmental, marine, pharmaceutical, and medical biotechnology [16].

Medical biotechnology is the application of biological knowledge, molecular technique, and genetic engineering to the development of diagnostics, therapeutics, vaccines, regenerative therapies, and personalised medicine [17]. It encompasses molecular diagnostics, recombinant DNA technology, monoclonal-antibody production, vaccine biotechnology, stem-cell therapy, regenerative medicine, pharmacogenomics, gene therapy, tissue engineering, precision medicine, synthetic biology, and bioinformatics. The rapid development of mRNA vaccines, CRISPR-based treatment of sickle cell disease, CAR-T cell immunotherapy, and AI-assisted drug discovery illustrate the field's transformative reach [2,7].

2.1.2 Genetics and Molecular Biology

Genetics is the branch of biological science concerned with heredity, genetic variation, and the transmission of traits through genes functional DNA units encoding the proteins that determine structure and function in living organisms [18]. Contemporary genetics extends well beyond classical Mendelian inheritance to encompass molecular, population, medical, cytogenetic, developmental, and quantitative

genetics, together with epigenetics and functional genomics. The Human Genome Project fundamentally advanced the field by providing the first complete sequence of the human genome, enabling identification of genes implicated in inherited disease, cancer, and complex disorders [19], and today underpins genetic counselling, prenatal diagnosis, cancer genomics, pharmacogenomics, and newborn screening. Identification of pathogenic BRCA1/BRCA2 variants, for instance, allows clinicians to assess hereditary breast and ovarian cancer risk and implement preventive intervention before disease onset [3].

Molecular biology is the study of biological processes at the molecular level principally the interactions among DNA, RNA, protein, and enzymes that regulate cellular function [20] and bridges genetics, biochemistry, microbiology, and cell biology. Its core techniques (PCR, qPCR, RT-PCR, DNA sequencing, NGS, Southern/Northern/Western blotting, CRISPR-Cas editing, DNA microarrays, and single-cell sequencing) are indispensable to infectious-disease diagnosis, cancer diagnosis, prenatal testing, molecular epidemiology, vaccine development, and drug discovery, and were central to the diagnostic and surveillance response to COVID-19 [5].

2.1.3 Precision Medicine and Gene Editing

Precision medicine tailors disease prevention, diagnosis, and treatment to an individual's genetic composition, environmental exposure, lifestyle, and clinical characteristics, replacing the traditional uniform treatment model with one informed by genomics, proteomics, metabolomics, bioinformatics, and AI [2]. Its applications span targeted cancer therapy, rare-disease treatment, pharmacogenomics, precision oncology, cardiovascular risk prediction, and neurodegenerative-disease research, and it has become one of the fastest-growing areas of medical biotechnology because it improves treatment effectiveness while reducing the costs associated with ineffective therapy.

Gene editing comprises technologies zinc-finger nucleases, transcription activator-like effector nucleases (TALENs), and CRISPR-Cas systems that enable precise, targeted modification of DNA. CRISPR-Cas9 has become the dominant platform because of its efficiency, accuracy, and comparative simplicity [6,7], and now supports correction of disease-causing mutation, disease modelling, drug-target discovery, immune-cell engineering for cancer therapy, and regenerative medicine, alongside continuing debate over germline modification, off-target effects, informed consent, and equitable access [13].

2.1.4 Interrelationship of the Core Disciplines

Biotechnology, genetics, and molecular biology are distinct yet tightly interconnected: genetics supplies knowledge of hereditary mechanism and gene function; molecular biology explains the processes governing gene expression and cellular activity; and biotechnology translates this scientific understanding into diagnostic kits, gene therapies, vaccines, and targeted medicines. Identification of a pathogenic mutation, for example, relies on molecular-biology techniques such as sequencing or PCR, while biotechnology converts that discovery into a clinical product a synergy that, reinforced by bioinformatics, AI, and systems biology, underlies the acceleration of precision medicine and individualised clinical care.

2.2 Theoretical Framework

The review is anchored in three complementary theories explaining how scientific knowledge in this field is generated, adopted, and translated into innovation. Systems Theory conceptualises biological and organisational entities as interconnected systems whose components function collectively [21]; applied here, it explains why successful biotechnology innovation depends on coordinated interaction among universities, healthcare providers, regulators, industry, funders, policymakers, and patients, and why weakness in any one component inadequate funding, ineffective regulation, limited research capacity, or poor technology transfer degrades the effectiveness of the whole ecosystem, a dynamic that is especially salient in low- and middle-income settings.

Human Capital Theory holds that investment in education, training, research, and skill development enhances productivity and innovation [22]; within medical biotechnology, this underscores the centrality of skilled scientists, clinicians, bioinformaticians, and regulatory experts, and clarifies why workforce shortage and professional migration constrain biotechnology development in many developing countries.

The Technology Acceptance Model explains adoption of new technologies through perceived usefulness and perceived ease of use, and has been widely applied to the uptake of electronic health records, genomic testing, and AI-assisted clinical decision support [23]. Applied here, it suggests that healthcare

professionals, policymakers, and patients adopt biotechnological innovation more readily when it is perceived as reliable, beneficial, and well-integrated into existing workflow, and that ethical concern, regulatory uncertainty, cost, and limited technical expertise reduce acceptance — underscoring the need for supportive policy, stakeholder engagement, and continuous training.

Integrating these three theories, the review's conceptual framework treats innovation in biotechnology, genetics, and molecular biology as the primary driver of improved healthcare outcomes, a relationship moderated by research funding, infrastructure, regulatory quality, ethical governance, human capital, and public acceptance: stronger enabling environments are expected to enhance translation of scientific discovery into accessible, sustainable healthcare innovation, whereas persistent infrastructural, ethical, and socioeconomic constraint limits that translation.

2.3 Thematic Review of Innovations in Medical Biotechnology

2.3.1 Global Perspective

Globally, biotechnology has evolved from a laboratory science into a major economic and healthcare enterprise, contributing substantially to pharmaceutical production, vaccine development, precision medicine, regenerative medicine, synthetic biology, and industrial innovation [11]. The Human Genome Project, completed in 2003, decoded approximately three billion DNA base pairs and remains the field's foundational achievement [19]; subsequent reductions in NGS cost have made genomic information integral to routine clinical practice, supporting mutation identification, cancer genomic profiling, rare-disease diagnosis, prenatal testing, pharmacogenomics, and population genomics [3]. Collins and Ashley argue that precision medicine constitutes one of modern biotechnology's greatest achievements precisely because it replaces generalised treatment protocols with genetically informed intervention [2].

CRISPR-Cas9 gene editing has similarly progressed from laboratory tool to clinical intervention: the 2023 regulatory approval of CRISPR-based therapy for sickle cell disease and β-thalassaemia demonstrates that genome editing has moved beyond experimental application into routine translational medicine [7]. mRNA vaccine technology achieved a comparable milestone during the COVID-19 pandemic, with Pfizer-BioNTech and Moderna compressing vaccine-development timelines from roughly a decade to under a year while sustaining safety and efficacy [4] a success that has since stimulated mRNA-platform research against HIV, malaria, tuberculosis, influenza, cancer, and autoimmune disease.

Artificial intelligence has become an indispensable component of biotechnology research: AlphaFold has been shown to predict protein structure with an accuracy previously requiring years of experimental investigation [8], and AI is now integral to drug discovery, medical imaging, genomic interpretation, clinical decision support, protein engineering, precision oncology, and biomarker discovery. Nonetheless, several scholars caution that biotechnology remains constrained by high research cost, ethical controversy surrounding genome editing, intellectual-property dispute, regulatory complexity, and unequal global distribution of scientific resource [13].

2.3.2 African Perspective

Africa possesses considerable biotechnological opportunity given its biodiversity, expanding research institutions, and growing disease burden, yet biotechnology development across the continent remains markedly lower than in Europe, North America, and parts of Asia. African countries collectively contribute less than 2% of global biotechnology patents despite accounting for approximately 17% of the world's population — a disparity attributable to inadequate research funding, limited infrastructure, shortage of trained scientists, dependence on imported equipment, weak university–industry collaboration, insufficient venture-capital investment, and inconsistent policy [10]. Continued reliance on imported vaccines, diagnostics, and biopharmaceuticals persists despite substantial underlying scientific potential [17]; the COVID-19 pandemic exposed this vulnerability directly through delayed vaccine access in many African states, prompting renewed government attention to pharmaceutical self-reliance.

South Africa has emerged as the continent's biotechnology leader, benefiting from advanced genomic-research centres, biotechnology incubators, strong university–industry collaboration, and substantial government investment, with notable contributions to HIV research, tuberculosis genomics, SARS-CoV-2 surveillance, cancer genomics, and vaccine development. Egypt, Kenya, Rwanda, Morocco, and Ghana have likewise expanded investment in molecular diagnostics, genomics, vaccine production, and biotechnology education [24]. African scholarship increasingly emphasises that strengthening the continental ecosystem requires regional collaboration, sustainable financing, harmonised regulation, and

enhanced postgraduate training [25], alongside sustained attention to genetic-data ownership, informed consent, benefit-sharing, and equitable access to biotechnological innovation.

2.3.3 Nigerian Perspective

Nigeria, as Africa's most populous nation and one of its largest scientific communities, possesses substantial potential to become a regional biotechnology hub. The National Biotechnology Research and Development Agency, together with universities, teaching hospitals, and research institutes, has expanded activity in molecular diagnostics, genomics, vaccine research, stem-cell biology, agricultural biotechnology, bioinformatics, and forensic genetics. During the COVID-19 pandemic, expanded PCR capacity and genomic surveillance conducted through the Nigeria Centre for Disease Control and Prevention (NCDC) and the African Centre of Excellence for Genomics of Infectious Diseases improved outbreak detection and variant monitoring [26].

Nonetheless, national research-and-development expenditure remains below internationally recommended levels, producing inadequate laboratory infrastructure, limited access to advanced sequencing platforms, and insufficient funding for translational research; persistent shortages of skilled personnel, brain drain, unreliable electricity, fragmented funding, and weak commercialisation pathways further constrain the sector [12]. Many innovations generated within Nigerian universities and research institutes fail to progress beyond laboratory or pilot stage because of weak intellectual-property management, limited venture-capital investment, and inadequate academia–industry collaboration, sustaining continued reliance on imported diagnostics, vaccines, and biopharmaceuticals. Recent policy initiatives — including the National Biotechnology Policy and renewed emphasis on local vaccine production, genomics, and bioeconomy development nonetheless indicate growing recognition of biotechnology as a strategic sector for national health security and economic diversification.

2.3.4 Synthesis of Empirical Evidence

Recent empirical work corroborates these thematic patterns. Genomic-guided therapy has significantly improved treatment effectiveness in oncology, cardiovascular disease, and rare genetic disorder by enabling individualised therapeutic decision-making [2]. Evaluation of the first clinical implementation of CRISPR-based therapy found durable clinical benefit in patients with sickle cell disease and β-thalassaemia, while also highlighting unresolved concerns over treatment cost, long-term safety monitoring, and equitable access [7]. AI-based protein-structure prediction has been shown to substantially reduce the time and cost of experimental structural biology, with downstream benefit for drug discovery and vaccine development [8]. In the African context, growing interest in genomic research has been documented alongside uneven regulatory capacity, public engagement, and genomic literacy, with calls for stronger ethical frameworks and regional collaboration [25]. Within Nigeria, post-pandemic assessments document improvement in molecular-diagnostic laboratory infrastructure and workforce training, but continue to identify inadequate funding, equipment-maintenance challenges, and dependence on imported reagents as persistent constraints on sustainable development [12,26]. Collectively, this evidence indicates that medical biotechnology is generating measurable healthcare benefit, even as the translation of discovery into widespread clinical practice remains bounded by financial, institutional, and regulatory limitation.

2.3.5 Domain-Specific Innovations

Genomics and precision medicine. Advances in whole-genome and whole-exome sequencing and genome-wide association studies have deepened understanding of the genetic basis of rare and common disease, enabling precision medicine to reshape management of breast, colorectal, and lung cancer, diabetes, cardiovascular disorder, and inherited metabolic disease [3]. In oncology, genomic profiling of mutations in genes such as EGFR, BRAF, HER2, and BRCA1/2 has improved outcomes while reducing adverse effects associated with conventional chemotherapy, and pharmacogenomics supports individualised medication selection by predicting drug metabolism and therapeutic response [27]. Persistent limitations include the cost of genomic testing, unequal access to sequencing technology, underrepresentation of African populations in genomic databases, and limited integration of genomic services into routine care [25].

Molecular diagnostics. PCR, qPCR, RT-PCR, fluorescence in situ hybridisation, DNA sequencing, and NGS enable rapid, sensitive identification of infectious pathogens, genetic mutations, chromosomal abnormalities, and molecular biomarkers [20]. RT-PCR became the global diagnostic standard for SARS-CoV-2 infection, while sequencing supported surveillance of viral evolution and informed vaccine

design [5]; in oncology, liquid biopsy and circulating tumour DNA analysis have improved early cancer detection, and prenatal molecular testing has enhanced detection of chromosomal and inherited abnormality. Successful implementation nonetheless depends on sustained investment in laboratory infrastructure, quality assurance, and specialised personnel — investment that remains inadequate across much of the developing world [17].

Gene editing. Beyond the sickle cell and β-thalassaemia approvals discussed above, ongoing trials are evaluating CRISPR-based intervention for inherited blindness, muscular dystrophy, haemophilia, and selected cancers. Off-target mutation, long-term genomic stability, germline modification, informed consent, and equitable access remain the field's principal unresolved concerns, prompting recommendations for stringent ethical oversight, transparent governance, and international cooperation [13].

Regenerative medicine and stem-cell therapy. Combining biotechnology, tissue engineering, stem-cell biology, and biomaterials, regenerative medicine supports treatment of haematological malignancy through bone-marrow transplantation and experimental therapy for spinal-cord injury, Parkinson's disease, diabetes, myocardial infarction, and cartilage regeneration [28]. Advances in induced pluripotent stem cells have expanded opportunity for disease modelling, drug testing, and personalised regenerative therapy, though embryonic stem-cell ethics, tumour-formation risk, high cost, and limited long-term clinical evidence continue to shape regulatory decision-making and public acceptance.

Artificial intelligence and digital biotechnology. Machine-learning algorithms now support genomic interpretation, protein-structure prediction, medical imaging, drug discovery, and clinical decision support; AlphaFold remains the field's landmark achievement [8], and AI-assisted platforms increasingly integrate genomic, radiological, and clinical data to improve precision-oncology diagnosis and treatment planning, while accelerating pharmaceutical discovery by predicting candidate efficacy and toxicity ahead of laboratory testing [9]. Algorithmic bias, data privacy, cybersecurity risk, limited model transparency, and unequal digital-infrastructure access remain significant constraints.

2.3.6 Ethical, Legal, and Social Implications

Rapid innovation has generated ethical, legal, and social questions that extend beyond science: genetic privacy, informed consent, ownership of genomic data, genetic discrimination, equitable access, and intellectual-property rights remain central to contemporary debate [13]. Germline genome editing raises particular concern because resulting modification would be heritable, in contrast to somatic editing, which is confined to the treated individual; the ethical, evolutionary, and social-justice implications of germline intervention accordingly warrant continued international scrutiny. Public trust further depends on transparent communication, effective regulation, stakeholder engagement, and culturally sensitive ethical frameworks, and countries with robust governance systems are generally better positioned to advance biotechnology responsibly while sustaining public confidence.

3. Objectives and Research Hypotheses

3.1 Aim and Objectives

This review aims to critically synthesise contemporary innovations in medical biotechnology, genetics, and molecular biology and to evaluate the barriers that limit their equitable translation into healthcare practice, with particular attention to global, African, and Nigerian contexts. Specific objectives are to:

- (i) examine the conceptual evolution of medical biotechnology, genetics, and molecular biology;
- (ii) analyse the innovations transforming contemporary healthcare;
- (iii) evaluate the scientific, ethical, regulatory, and socioeconomic challenges limiting biotechnology development;
- (iv) synthesise recent empirical evidence across global, African, and Nigerian contexts;
- (v) identify emerging trends and future directions; and
- (vi) propose evidence-based recommendations for research, innovation, and policy.

3.2 Research Hypotheses

Derived from the review's research questions and its integrated theoretical framework (Section 2.2), the following propositions guide the synthesis and are advanced as working hypotheses for future empirical validation:

- **H1:** Recent innovations in genomics, molecular diagnostics, gene editing, and artificial intelligence are positively associated with improved diagnostic accuracy and treatment outcomes in medical biotechnology.
- **H2:** The strength of a country's enabling environment research funding, laboratory infrastructure, regulatory capacity, and skilled workforce positively moderates the translation of biotechnological innovation into equitable healthcare delivery.
- **H3:** Disparities in research investment and infrastructure between high-income and low- and middle-income countries are associated with correspondingly unequal access to genomic, diagnostic, and gene-editing technologies.
- **H4:** In Nigeria and comparable Sub-Saharan African contexts, weak university–industry linkages and workforce migration (brain drain) are negatively associated with the commercialisation and clinical translation of locally generated biotechnology innovation.
- **H5:** Ethical governance and regulatory clarity are positively associated with public acceptance and adoption of biotechnological innovation, consistent with the Technology Acceptance Model.

4. Methodology

This review adopts a qualitative, narrative analytical-review design grounded in systematic content and thematic analysis of contemporary scholarly literature [29,30]. Rather than generating primary data, it synthesises evidence from peer-reviewed journal articles, books, policy documents, and reports of international organisations to critically evaluate innovation in biotechnology, genetics, and molecular biology alongside the scientific, ethical, regulatory, and socioeconomic conditions that shape its application.

Literature was drawn primarily from publications dated 2019–2026, supplemented by seminal works that established the field's theoretical and technological foundations including the Human Genome Project, recombinant DNA technology, and the CRISPR-Cas system. Sources were retrieved from PubMed, Scopus, Web of Science, SpringerLink, ScienceDirect, Wiley Online Library, and Nature Portfolio, and from reports of the WHO, the OECD, NASEM, and the NHGRI. The analytical framework integrates Systems Theory, Human Capital Theory, and the Technology Acceptance Model (Section 2.2) to explain how biotechnological innovation is generated, adopted, and translated into healthcare outcomes. Through thematic analysis, the literature was organised around biotechnology innovation, genomics, molecular diagnostics, gene editing, regenerative medicine, artificial intelligence, ethics, commercialisation, and policy, providing the structure for the discussion that follows.

5. Findings and Emerging Issues

Synthesis of the reviewed literature yields seven principal findings. *First*, biotechnology has shifted healthcare from a reactive, symptom-oriented model toward one that is proactive, predictive, preventive, and personalised, with whole-genome sequencing, PCR, NGS, liquid biopsy, molecular imaging, and pharmacogenomics now integral to routine clinical practice and no longer merely a supporting discipline within medicine [2].

Second, precision medicine is increasingly displacing generalised treatment across oncology, cardiology, neurology, rare genetic disorder, infectious disease, and pharmacogenomics, reducing unnecessary prescription, minimising adverse drug reaction, and lowering long-run healthcare cost despite relatively high initial investment [27], even as unequal access to genomic technology continues to widen disparity between developed and developing countries.

Third, artificial intelligence has become one of biotechnology's fastest-growing components, with machine-learning systems analysing large genomic datasets, predicting protein structure, and supporting drug design and clinical decision-making [8], though algorithmic bias, explainability, cybersecurity, and data privacy remain unresolved concerns [9].

Fourth, gene editing represents a genuine paradigm shift in therapeutic medicine: CRISPR-based therapy for sickle cell disease and β-thalassaemia demonstrates that inherited disorders once considered incurable may now be treatable [7], with ongoing research extending to cancer, haemophilia, muscular dystrophy, inherited blindness, HIV infection, and neurodegenerative disorder, subject still to unresolved questions of long-term safety, off-target mutation, germline modification, and affordability.

Fifth, molecular diagnostics have measurably improved early disease detection, from pandemic surveillance [5] to prenatal and neonatal screening, cancer diagnosis, antimicrobial-resistance

surveillance, and HIV and tuberculosis monitoring, with earlier molecular diagnosis substantially improving treatment outcomes while reducing expenditure associated with delayed diagnosis.

Sixth, substantial global inequality persists: high-income countries dominate biotechnology patenting, genomic databases, pharmaceutical research, financing, infrastructure, and commercialisation, while many African countries, including Nigeria, continue to experience inadequate infrastructure, insufficient funding, workforce shortage, equipment dependence, limited venture capital, and weak regulation — inequalities that materially restrict translation of scientific discovery into practical healthcare intervention.

Seventh, ethical governance has become an increasingly central concern spanning genome editing, embryonic stem-cell research, reproductive technology, genetic discrimination, data ownership, informed consent, privacy, and equitable access, reinforcing the position that responsible biotechnology innovation must balance scientific advancement against protection of human rights, and should therefore be evaluated on ethical acceptability and societal benefit alongside scientific achievement [13].

These findings point toward several emerging trajectories: deepening convergence of AI with precision medicine, molecular diagnostics, genomic interpretation, protein engineering, and digital pathology [9]; expansion of personalised medicine through pharmacogenomics, epigenetics, transcriptomics, and metabolomics; growth of synthetic biology for vaccine, insulin, antibody, enzyme, and biofuel production, with attendant benefit for pandemic preparedness [1]; an increasing centrality of bioinformatics to genome analysis, molecular modelling, and clinical genomics; expansion of regenerative medicine through stem-cell biology, tissue engineering, organoid technology, and three-dimensional bioprinting [28]; and, in the wake of pandemic-era supply disruption, rising government prioritisation across Africa including Nigeria of domestic vaccine production, genomic surveillance, biotechnology education, pharmaceutical manufacturing, and biotechnology entrepreneurship.

6. Challenges and Limitations of Medical Biotechnology

Notwithstanding substantial scientific progress, medical biotechnology continues to face interrelated barriers across seven domains.

- **Scientific and technical:** rapid technological advance frequently outpaces understanding of long-term biological effect, including off-target genome editing, genomic complexity, incomplete characterisation of gene–environment interaction, and reproducibility limitations [6].
- **Financial:** biotechnology research is highly capital-intensive, requiring investment in sequencing platforms, gene-editing technology, bioreactors, high-performance computing, and specialised laboratories, and limited research funding remains a principal obstacle in developing countries [11].
- **Infrastructural:** many low- and middle-income countries lack modern laboratories, reliable electricity, cold-chain systems, high-speed connectivity, and equipment-maintenance capacity, restricting both research productivity and clinical implementation.
- **Human resources:** the field requires expertise spanning molecular biology, genetics, bioinformatics, computational biology, clinical medicine, and regulatory science; workforce shortage and the international migration of trained scientists continue to weaken biotechnology ecosystems in developing countries.
- **Regulatory:** weak regulatory institutions can delay trials, approvals, and commercialization, while overly restrictive regulation can discourage innovation and investment, leaving countries to negotiate a persistent tension between safety and innovation.
- **Ethical:** controversy surrounding gene editing, stem-cell research, cloning, synthetic biology, and AI-assisted healthcare requires continuous governance review as technological capability evolves.
- **Commercialization:** many promising discoveries fail to reach market because of inadequate technology-transfer mechanisms, weak intellectual-property management, limited venture capital, and insufficient academia–industry collaboration.

7. Discussion: Practical and Policy Implications

The findings carry distinct implications for the principal stakeholders in the biotechnology ecosystem. Healthcare systems should integrate genomic medicine, molecular diagnostics, and personalised treatment into routine clinical practice while strengthening laboratory capacity and workforce training. Governments should substantially increase investment in biotechnology research, establish dedicated innovation funds, modernise laboratory infrastructure, and strengthen regulatory institutions. Universities and research institutions should promote interdisciplinary education spanning

biotechnology, genetics, molecular biology, artificial intelligence, bioinformatics, and biomedical engineering, and should deepen collaboration with industry to facilitate commercialisation of research output. The biotechnology industry should increase investment in research partnerships, technology transfer, vaccine manufacturing, genomic diagnostics, and local pharmaceutical production. Policymakers should ensure that biotechnology policy prioritises ethical governance, equitable access, intellectual-property management, biosafety regulation, and sustainable financing.

For Nigeria and Africa specifically, the review indicates that considerable scientific potential remains underutilized because of structural constraints rather than any deficit of underlying capability. Strengthening the sector will require increased government funding for research and development, modernization of biotechnology laboratories, expansion of postgraduate biotechnology programmes, stronger university–industry partnership, improved intellectual-property protection, enhanced regulatory capacity, deliberate retention of skilled scientists, and regional collaboration in genomics and vaccine manufacturing interventions that would jointly advance national health security, pharmaceutical self-reliance, and economic diversification, and that align directly with SDG 3, SDG 4, SDG 9, and SDG 17.

8. An Integrated Medical Biotechnology Innovation Framework

Building on the evidence synthesised above, this review proposes an integrated conceptual framework linking the inputs, processes, enabling environment, and outcomes of sustainable biotechnology innovation. Government investment, research funding, human-capital development, advanced laboratory infrastructure, digital technology, international collaboration, and regulatory support constitute the input factors that drive core innovation processes: genomics, molecular biology, artificial intelligence, gene editing, precision medicine, synthetic biology, bioinformatics, and translational research. These processes are, in turn, mediated by an enabling environment comprising ethical governance, intellectual-property protection, public acceptance, university–industry collaboration, technology transfer, and biotechnology entrepreneurship, which together determine whether innovation translates into the intended outcomes: improved disease diagnosis, personalized healthcare, better treatment outcomes, vaccine innovation, pharmaceutical self-reliance, increased research productivity, economic diversification, and sustainable healthcare systems. This input–process–environment–outcome structure offers a holistic reference model for future empirical validation and cross-country comparison.

9. Conclusion

The evolution of biotechnology, genetics, and molecular biology has established medical biotechnology as among the most influential scientific disciplines of the twenty-first century. Advances in genomics, molecular diagnostics, gene editing, regenerative medicine, synthetic biology, artificial intelligence, and precision medicine have collectively shifted healthcare toward a model that is predictive, preventive, personalised, and participatory, improving both patient outcomes and the evidence base for clinical decision-making [2]. The compressed development of mRNA vaccines during the COVID-19 pandemic exemplifies biotechnology's strategic importance to global health security and pandemic preparedness [17].

At the same time, the review confirms that biotechnology continues to face substantial scientific, ethical, financial, regulatory, and infrastructural constraint. Incomplete understanding of gene–environment interaction, off-target genome-editing effects, and the complexity of clinical translation remain significant scientific challenges; germline editing, genetic privacy, equitable access, informed consent, and genomic-data ownership remain significant ethical challenges; and regulators worldwide continue to negotiate the tension between promoting innovation and ensuring patient safety [13]. Disparity between high-income and developing countries in research capacity, commercialisation, and pharmaceutical manufacturing remains pronounced [11], and Nigeria notwithstanding its considerable scientific potential remains constrained by inadequate research investment, limited commercialisation, unreliable infrastructure, weak academia–industry collaboration, and persistent brain drain.

The review concludes that the future of medical biotechnology will depend increasingly on interdisciplinary integration across molecular biology, genetics, bioinformatics, artificial intelligence, nanotechnology, and computational science, and that realising the opportunity this integration presents will require sustained investment in research, human capital, digital infrastructure, ethical governance, and international collaboration. Biotechnology should accordingly be understood not merely as a

scientific enterprise but as a strategic instrument for national development, economic diversification, public-health improvement, and global competitiveness one whose benefits must be pursued in a manner that is ethically responsible, socially just, and consistent with the broader ambitions of the Sustainable Development Goals.

10. Recommendations

Addressing the challenges identified in this review requires coordinated, evidence-based action across government, academia, healthcare, industry, regulation, and international partnership.

10.1 Governments

- Increase sustained budgetary investment in biotechnology research and development, including competitive national grants that encourage collaboration among universities, research institutes, hospitals, and industry.
- Develop and periodically update comprehensive national biotechnology policy addressing funding, technology transfer, commercialisation, biosafety, ethical governance, and international collaboration.
- Strengthen national biotechnology infrastructure, including genomics centres, molecular diagnostic laboratories, biorepositories, digital infrastructure, and reliable electricity supply.

10.2 Universities and Research Institutions

- Redesign curricula to integrate molecular biology, genetics, artificial intelligence, bioinformatics, computational biology, and biomedical engineering, with emphasis on practical laboratory skill and innovation management.
- Deepen university–industry collaboration to accelerate technology transfer, patent development, and commercialisation of research output.
- Expand international research collaboration through joint grants, staff exchange, and multinational clinical trials, particularly to strengthen capacity in low- and middle-income countries.

10.3 Healthcare Institutions

- Progressively integrate genomic medicine, pharmacogenomics, and personalised treatment into routine clinical service through multidisciplinary precision-medicine units.
- Expand molecular-diagnostic capacity — PCR, qPCR, digital PCR, NGS, and biomarker analysis to strengthen infectious-disease surveillance, cancer diagnosis, and early detection of inherited disorders.

10.4 Researchers

- Prioritize translational research capable of converting laboratory discovery into clinical intervention, with attention to implementation science.
- Expand genomic research involving African populations to improve understanding of genetic diversity, disease susceptibility, and pharmacogenomics, and to strengthen the applicability of precision medicine globally [25].

10.5 Industry, Regulators, and Development Partners

- Invest in local pharmaceutical manufacturing of vaccines, monoclonal antibodies, recombinant proteins, diagnostic kits, and biosimilars to reduce import dependence and strengthen health security.
- Establish biotechnology innovation funds supporting start-ups, incubators, and venture capital to facilitate commercialization of university research.
- Strengthen transparent ethical-oversight mechanisms governing genome editing, stem-cell research, genomic-data management, and AI application, and periodically modernise biotechnology regulation to accommodate emerging technology.
- Sustain international capacity-building support prioritising local ownership, and promote equitable global access to genomic technology, vaccines, molecular diagnostics, and gene therapy.

10.6 Nigeria-Specific Priorities

- Strengthen a coordinated national biotechnology innovation system linking the Federal Ministry of Science, Technology and Innovation, the Federal Ministry of Health, universities, research institutes, industry, and regulators.

- Progressively increase research funding toward internationally recommended benchmarks, targeted at genomics, molecular diagnostics, vaccine development, precision medicine, and AI in healthcare.
- Improve research funding, laboratory facilities, remuneration, and career development to reduce brain drain and retain skilled biotechnology professionals.
- Invest in public-education campaigns to improve understanding of biotechnology, gene editing, genetic testing, and vaccine biotechnology, thereby strengthening acceptance and reducing misinformation.

10.7 Priorities for Future Research

- Long-term safety and effectiveness of CRISPR-based therapy.
- Ethical governance of artificial intelligence in biotechnology.
- Commercialisation pathways for biotechnology innovation in Africa, and comparative biotechnology-policy analysis across African countries.
- Economic evaluation of precision medicine and sustainable financing models for biotechnology research.
- Public perception of genome editing, and integration of biotechnology into universal health coverage and primary healthcare systems.

11. Contribution to Knowledge

This review contributes to existing scholarship in several respects. Theoretically, it integrates Systems Theory, Human Capital Theory, and the Technology Acceptance Model into a single explanatory framework for biotechnology innovation, demonstrating that successful development depends on interaction among institutional, economic, and social systems rather than on scientific discovery alone. Conceptually, it clarifies the interrelationships among genomics, molecular biology, gene editing, artificial intelligence, bioinformatics, and precision medicine that are frequently examined in isolation elsewhere in the literature. Empirically, it synthesises evidence published between 2019 and 2026, supplemented by foundational studies, into a single, current account of the field's trajectory. Geographically, it addresses an identifiable imbalance in the literature, which remains heavily concentrated on Europe, North America, and parts of Asia, by explicitly examining African and Nigerian biotechnology capacity, constraint, and opportunity. Practically and in terms of policy, it translates these findings into evidence-based guidance for healthcare institutions, universities, industry, regulators, and government, and proposes an integrated input–process–environment–outcome framework intended to support future empirical validation and cross-country comparison.

12. Limitations of the Review

As a narrative, qualitative synthesis rather than a systematic review conducted to PRISMA protocol, this study does not report a formal, replicable search strategy, quality-appraisal scoring, or meta-analytic effect estimate, and its conclusions should be read as an integrative account of the literature rather than as a quantitatively pooled result. The evidence base also remains unevenly distributed geographically, with African and Nigerian sources comparatively fewer than those from high-income settings, which may understate country-level heterogeneity within the developing-country literature. Future work employing a systematic or scoping-review methodology, and incorporating primary empirical data from African biotechnology institutions, would usefully extend and test the framework proposed.

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REPURPOSING OF EXISTING DRUGS FOR NSAID-INDUCED GASTRIC ULCERS: INSIGHTS FROM RECENT EXPERIMENTAL STUDIES

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Abstract

Aim

Nonsteroidal anti-inflammatory drug (NSAID)-induced gastric ulceration is a multifactorial disorder involving prostaglandin depletion, oxidative stress, inflammation, apoptosis, impaired microcirculation, and defective mucosal repair. This complexity has increased interest in repurposing existing drugs with established therapeutic indications as potential gastroprotective agents. This study aimed to evaluate recent experimental evidence from a unified perspective by examining the pharmacological rationale for drug repurposing in NSAID-induced gastric ulcer models and identifying the common mechanistic trends emerging from these studies.

Materials and Methods

Original experimental studies published between 2021 and 2026 were identified through the PubMed database. Studies investigating metformin, olmesartan, perindopril, rivastigmine, tadalafil, topiramate, felodipine, liraglutide, nifuroxazide, and alogliptin in experimental NSAID-induced gastric injury models were included. The studies were comparatively evaluated according to drug selection rationale, mechanisms of action, and the biological pathways involved in gastroprotection.

Results

Despite belonging to different pharmacological classes, the investigated drugs demonstrated convergent gastroprotective effects through complementary biological mechanisms. Protective effects were associated with reduced oxidative stress, suppressed inflammation and apoptosis, preservation of prostaglandin-mediated mucosal defense, improved endothelial function and microcirculation, and enhanced tissue repair. Frequently implicated pathways included ACE2/Ang-(1-7), DDAH-1/ADMA, Nrf2/HO-1, HMGB1/TLR4/NF-κB, GDNF/PI3K/Akt, SDF-1/CXCR4, and VEGF signaling. These findings indicate that current drug repurposing strategies increasingly target coordinated mechanisms supporting both mucosal protection and regeneration.

Conclusion

Recent experimental evidence suggests that exploiting the pleiotropic properties of existing drugs represents a promising strategy for NSAID-induced gastric ulceration. Rather than focusing solely on acid suppression, drug repurposing targets multiple biological processes involved in ulcer pathogenesis and healing. Further translational and clinical studies are needed to determine the clinical applicability of these experimental findings.

Keywords: Drug repurposing; NSAID-induced gastric ulcer; Gastroprotection; Experimental pharmacology

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antipyretic, and anti-inflammatory effects. However, their therapeutic utility is limited by gastrointestinal adverse effects ranging from superficial mucosal injury to ulceration, bleeding, and perforation. NSAID-associated gastric injury results from an imbalance between aggressive factors and mucosal defense mechanisms. Inhibition of cyclooxygenase activity and the consequent reduction in protective prostaglandins weaken mucus and bicarbonate secretion, mucosal blood flow, epithelial restitution, and other homeostatic responses. Direct epithelial damage, reactive oxygen species generation, inflammatory signaling, apoptosis, and microvascular dysfunction further contribute to gastric mucosal injury.[1,2]

Current preventive and therapeutic approaches include limiting NSAID exposure when clinically possible, assessing individual gastrointestinal risk, selecting cyclooxygenase-2-selective agents in appropriate patients, and using acid-suppressive or mucosal-protective treatments. Proton pump inhibitors remain a principal gastroprotective option, while histamine-2 receptor antagonists and

prostaglandin analogues may be considered in selected clinical settings. Nevertheless, acid suppression does not directly target all biological components involved in NSAID-induced mucosal damage. The multifactorial nature of this injury has therefore encouraged experimental investigation of agents that can modulate oxidative stress, inflammation, apoptosis, endothelial function, and tissue repair.[1-3]

Drug repurposing, also termed drug repositioning, involves identifying new therapeutic applications for existing or previously investigated compounds. Compared with de novo drug development, this strategy can draw on existing knowledge concerning pharmacological targets, formulation, pharmacokinetics, and safety. However, previous clinical use does not by itself establish efficacy or safety for a new indication, particularly when repurposing requires different doses, routes, treatment durations, or target populations. At the preclinical stage, drug repurposing should therefore be regarded as a strategy for identifying and prioritizing mechanistically plausible candidates rather than as a substitute for rigorous translational and clinical evaluation.[4,5]

Recent animal studies have investigated drugs originally used for metabolic, cardiovascular, neurological, and infectious or inflammatory conditions in NSAID-induced gastric injury models. Although these agents differ considerably in their established indications and primary pharmacological targets, their reported gastroprotective effects frequently converge on oxidative balance, inflammatory and apoptotic signaling, mucosal perfusion, prostaglandin-mediated defense, and tissue repair. A comparative consideration of their shared mechanistic patterns may provide a more integrated perspective on this emerging experimental literature. Accordingly, this review aimed to compare 10 recent experimental studies, relate the established pharmacological characteristics of the investigated drugs to their reported gastroprotective actions, and identify common mechanistic trends and translational limitations.

Main text

Review approach and scope

This article presents a narrative review and comparative mechanistic evaluation rather than a systematic review. The principal evidence set consisted of 10 original experimental articles published between 2021 and 2026 and identified through PubMed during the preparation of the congress presentation on which this full text is based. Studies were included when they investigated an established drug whose principal clinical indication lies outside conventional anti-ulcer therapy, used an NSAID-induced gastric injury or ulcer model, and reported macroscopic, histopathological, biochemical, immunohistochemical, or molecular outcomes relevant to gastroprotection. The investigated agents were metformin, liraglutide, alogliptin, perindopril, olmesartan, tadalafil, felodipine, rivastigmine, topiramate, and nifuroxazide.[6-15] The studies were compared according to drug class, experimental injury model, tissue-level findings, and proposed biological mechanisms. Additional review articles identified through Web of Science and Google Scholar were used to contextualize NSAID-induced gastric injury, current treatment approaches, and the general principles of drug repurposing but were not included in the comparative experimental evidence set. Because no registered protocol, exhaustive multidatabase search, formal study-quality appraisal, or risk-of-bias assessment was undertaken, this synthesis is intended to identify mechanistic patterns and research directions rather than provide a systematic estimate of therapeutic efficacy.

Pathophysiological rationale for multi-target gastroprotection

NSAID-induced gastric injury reflects the interaction of impaired mucosal defense with oxidative, inflammatory, vascular, and apoptotic processes. Cyclooxygenase inhibition and the resulting reduction in protective prostaglandins compromise mucus and bicarbonate secretion, mucosal perfusion, epithelial restitution, and maintenance of the gastric barrier. At the same time, mitochondrial dysfunction and reactive oxygen species increase lipid peroxidation and weaken endogenous antioxidant defenses. Pro-inflammatory cytokines and nuclear factor kappa B-related signaling promote leukocyte recruitment and epithelial disruption, whereas pro-apoptotic pathways reduce epithelial survival. Effective mucosal repair therefore depends not only on limiting acid-related injury but also on preserving blood flow, controlling inflammation and oxidative stress, supporting cell survival, and restoring epithelial and angiogenic responses.[1-3]

Consistent with this multifactorial pathophysiology, the included experimental studies assessed overlapping outcome domains rather than a single therapeutic target. These outcomes included macroscopic lesion or ulcer scores, histopathological damage, oxidative stress and antioxidant markers,

inflammatory cytokines, prostaglandin E2, apoptosis-related proteins, and indicators of vascular or regenerative signaling. Some studies additionally examined endothelial, neuroimmune, antioxidant-response, and tissue-repair pathways. This range of outcomes enables comparison of shared mechanistic patterns across pharmacologically distinct drugs. However, differences in NSAID type, animal characteristics, treatment schedules, outcome measures, and laboratory methods preclude direct comparisons of effect magnitude or a definitive ranking of the investigated agents.

Antidiabetic agents

Metformin was evaluated in both ethanol- and indomethacin-induced gastric injury models, although only the indomethacin model directly falls within the scope of the present review. In nondiabetic, normoglycemic Sprague-Dawley rats, oral metformin pretreatment reduced macroscopic and histopathological gastric injury, attenuated oxidative stress-related chemiluminescence, decreased TUNEL-positive apoptotic cells, and improved gastric mucosal blood flow. Because metformin did not alter fasting blood glucose in this experimental setting, the findings suggest that its gastroprotective activity was independent of its glucose-lowering action and was instead associated with antioxidant, anti-apoptotic, and perfusion-preserving effects.[6] Nevertheless, the study used a high experimental dose and a short pretreatment protocol, which should be considered when evaluating its translational relevance.

Liraglutide was investigated in streptozotocin-induced diabetic rats exposed to indomethacin. This model is particularly relevant to impaired tissue repair because persistent hyperglycemia can promote oxidative stress, inflammation, and defective angiogenic responses. Liraglutide reduced gastric ulceration and apoptosis, increased superoxide dismutase-1, glutathione, epidermal growth factor, vascular endothelial growth factor A, and prostaglandin E2, and decreased malondialdehyde, interleukin-6, and tumor necrosis factor-alpha.[7] These findings associate GLP-1 receptor agonism with antioxidant, anti-inflammatory, anti-apoptotic, and repair-supporting effects. However, liraglutide also reduced blood glucose in a dose-dependent manner. Its observed gastroprotection may therefore reflect a combination of improved metabolic control and direct pleiotropic effects. Moreover, the diabetic model limits direct comparison with studies conducted in metabolically healthy animals.

Alogliptin, a dipeptidyl peptidase-4 inhibitor, was evaluated in rats with diclofenac-induced gastric ulceration. Alogliptin reduced the ulcer index and preserved gastric mucosal architecture. These effects were accompanied by restoration of GDNF/PI3K/Akt signaling, increased phosphorylation of GSK3beta and CREB, enhanced COX-2/PGE2 expression, and recovery of SDF-1/CXCR4 signaling. The treatment also reduced NF-kappa B/TNF-alpha-associated inflammation and oxidative stress and shifted Bax/Bcl-2 expression toward cell survival.[8] Among the included studies, this investigation provided particularly detailed evidence concerning pathways associated with mucosal defense and regeneration. Nevertheless, these molecular associations do not establish that each pathway was individually necessary for the observed gastroprotective effect.

Renin-angiotensin system modulators

Perindopril, an angiotensin-converting enzyme inhibitor, was evaluated in rats receiving a single ulcerogenic dose of indomethacin. Seven-day oral pretreatment with perindopril reduced the ulcer index and attenuated histopathological gastric injury. These effects were accompanied by increased glutathione content and superoxide dismutase activity and decreased tumor necrosis factor-alpha, nitric oxide, and asymmetric dimethylarginine levels. Perindopril also increased DDAH-1, ACE2, Ang-(1-7), COX-2, and prostaglandin E2 expression.[9] Collectively, these findings associate its gastroprotective action with improved antioxidant defense, suppression of inflammation, regulation of the DDAH-1/ADMA pathway, and enhancement of the protective ACE2/Ang-(1-7) axis. The concurrent reduction in total nitric oxide and improvement in DDAH-1/ADMA signaling indicate that the findings should be interpreted as regulation of nitric oxide-related homeostasis rather than a nonspecific increase in nitric oxide availability.

Olmesartan, an angiotensin II type 1 receptor blocker, was investigated in both conventional and niosomal formulations. Pretreatment reduced macroscopic and histopathological gastric injury and improved indices of oxidative balance, inflammation, COX-1 activity, and prostaglandin E2-mediated mucosal defense. These effects were accompanied by reduced p38-MAPK activation and increased Nrf2/HO-1 signaling, linking the observed protection with suppression of inflammatory and oxidative

injury and reinforcement of endogenous antioxidant responses.[10] The niosomal formulation generally produced stronger effects than conventional olmesartan. This finding suggests that drug delivery and bioavailability influenced the observed gastroprotection; however, it also complicates interpretation because the enhanced formulation represents an additional intervention beyond repurposing of the unchanged drug. Consequently, the performance of niosomal olmesartan cannot be attributed solely to the established pharmacological properties of conventional olmesartan.

Vasoactive agents

Tadalafil, a phosphodiesterase-5 inhibitor, was evaluated in rats receiving a single ulcerogenic dose of indomethacin. Seven-day oral pretreatment reduced the ulcer index and attenuated histopathological abnormalities while increasing glutathione, superoxide dismutase activity, COX-2, and prostaglandin E2. Tadalafil also decreased tumor necrosis factor-alpha, asymmetric dimethylarginine, and total gastric nitric oxide levels and increased DDAH-1 expression. At the protein level, it reduced inducible nitric oxide synthase and increased endothelial nitric oxide synthase expression.[11] These findings suggest that its gastroprotective effect was associated with antioxidant and anti-inflammatory activity, prostaglandin-mediated mucosal defense, and differential regulation of nitric oxide synthase pathways. The simultaneous reduction in total nitric oxide and opposing changes in iNOS and eNOS support regulation of nitric oxide homeostasis rather than generalized enhancement of nitric oxide production. However, the pathway measurements were associative, and the study did not employ pathway-specific inhibition to establish causal mediation.

Felodipine, a dihydropyridine L-type calcium channel blocker, was examined in an acute indomethacin-induced gastric injury model, with famotidine used as a reference treatment. A single dose of felodipine administered before indomethacin substantially reduced both the number of ulcers and the ulcerated area. It also counteracted the indomethacin-associated increase in malondialdehyde and partially restored glutathione, superoxide dismutase, and catalase. Felodipine preserved COX-1 activity but did not significantly restore COX-2 activity.[12] The results therefore support an association between its experimental gastroprotection, antioxidant defense, and maintenance of constitutive COX-1 activity. Nevertheless, the study was limited to macroscopic and biochemical outcomes, included a small number of animals, and used a short-term preventive design. Evidence regarding histological protection, ulcer healing, and longer-term safety was not provided.

Neurological agents

Rivastigmine, an acetylcholinesterase and butyrylcholinesterase inhibitor used in the treatment of Alzheimer's disease, was evaluated as a two-week pretreatment in rats with indomethacin-induced gastric injury. Rivastigmine reduced the ulcer index and histopathological damage and decreased malondialdehyde, tumor necrosis factor-alpha, interleukin-6, nuclear factor kappa B, and caspase-3. It also increased superoxide dismutase, glutathione, total nitrite/nitrate, heme oxygenase-1, and proliferating cell nuclear antigen expression.[13] These findings associate its gastroprotective activity with improved antioxidant defense, suppression of inflammatory and apoptotic signaling, and enhanced epithelial proliferative responses. Notably, protection occurred despite increases in gastric acidity and pepsin, suggesting that the observed effect was not mediated by acid suppression. The authors interpreted these findings in relation to the cholinergic anti-inflammatory pathway and alpha7 nicotinic acetylcholine receptor signaling. However, alpha7nAChR activity was not directly measured or pharmacologically blocked; therefore, its mediating role remains a mechanistic hypothesis rather than a demonstrated causal pathway.

Topiramate, an antiseizure medication, was examined in an acute indomethacin-induced gastric injury model. A single intraperitoneal dose administered one hour before indomethacin reduced the macroscopic ulcerated area and attenuated histopathological injury. Topiramate also decreased malondialdehyde and increased glutathione, ferric reducing antioxidant power, superoxide dismutase, catalase, and glutathione peroxidase activity.[14] The consistency of the macroscopic, histological, and biochemical findings supports an association between topiramate-induced gastroprotection and restoration of gastric redox balance. In contrast to studies investigating multiple inflammatory, apoptotic, or regenerative pathways, the mechanistic evidence for topiramate was largely restricted to oxidative stress and antioxidant defense.

Furthermore, the high intraperitoneal dose, administration shortly before ulcer induction, and short observation period limit direct extrapolation to its conventional clinical use or to the treatment of established ulcers.

Nifuroxazide

Nifuroxazide, a nitrofuran derivative used primarily as an intestinal anti-infective agent, was evaluated at three oral doses in rats pretreated for 14 days before the administration of a single ulcerogenic dose of indomethacin. Famotidine was used as the reference treatment. Nifuroxazide dose-dependently reduced the ulcer index, preserved gastric mucin content, and attenuated histopathological injury. It also decreased malondialdehyde and increased glutathione, catalase, superoxide dismutase, Nrf2, and heme oxygenase-1. Its anti-inflammatory profile included reductions in HMGB1, TLR4, NF-kappa B p65, interleukin-1beta, tumor necrosis factor-alpha, STAT3, and serum C-reactive protein. Reduced caspase-3 immunoexpression additionally indicated attenuation of apoptotic activity.[15] Collectively, these findings associate nifuroxazide with reinforcement of the gastric mucosal barrier, activation of endogenous antioxidant responses, and suppression of inflammatory and apoptotic signaling. The breadth and dose responsiveness of these changes make nifuroxazide one of the more extensively characterized candidates in the present evidence set. However, the study used a preventive rather than therapeutic design, and no pathway-specific inhibitor, activator, or genetic intervention was employed. The Nrf2/HO-1, HMGB1/TLR4/NF-kappa B, and STAT3 findings should therefore be considered mechanistic associations rather than definitive evidence of causal mediation.

Comparative mechanistic synthesis

Across the 10 studies, the reported gastroprotective effects converged on five interrelated biological domains. First, modulation of oxidative stress was the most frequently observed pattern, generally reflected by reduced malondialdehyde or oxidative chemiluminescence and restoration of glutathione, superoxide dismutase, catalase, glutathione peroxidase, or related antioxidant responses. Second, several agents reduced inflammatory mediators, particularly tumor necrosis factor-alpha, interleukins, and NF-kappa B-associated signaling. Third, attenuation of apoptosis was reported for metformin, liraglutide, alogliptin, rivastigmine, and nifuroxazide. Fourth, perindopril, olmesartan, tadalafil, felodipine, liraglutide, alogliptin, and metformin influenced prostaglandin-dependent defense, endothelial regulation, mucosal perfusion, angiogenic signaling, or related regenerative processes. Finally, some studies extended beyond conventional oxidative and inflammatory markers to examine integrated repair pathways, including EGF/VEGF-A, GDNF/PI3K/Akt, SDF-1/CXCR4, DDAH-1/ADMA, ACE2/Ang-(1-7), and Nrf2/HO-1 signaling.[6-15]

These shared findings do not indicate pharmacological equivalence or establish the superiority of candidates evaluated with a larger number of biomarkers. The apparent mechanistic breadth of each drug partly reflects the outcomes selected by the investigators. For example, topiramate was examined predominantly through redox-related measures, whereas alogliptin and nifuroxazide were assessed using broader molecular panels. The absence of an inflammatory, apoptotic, vascular, or regenerative measurement in a study cannot be interpreted as evidence that the corresponding drug had no effect on that domain. Similarly, simultaneous changes in multiple signaling proteins may identify biologically plausible pathways but do not demonstrate that every measured pathway was necessary for gastroprotection. Direct comparisons based on the number or magnitude of altered biomarkers would therefore be inappropriate.

Substantial methodological heterogeneity further limits cross-study comparison. The investigations differed in animal strain, metabolic condition, ulcerogenic NSAID, NSAID dose and route, candidate-drug dose, duration of exposure, reference treatment, timing of tissue collection, and outcome selection. Indomethacin was used in most studies, usually as a single acute ulcerogenic challenge, whereas alogliptin was evaluated during repeated diclofenac exposure. Liraglutide was examined in streptozotocin-induced diabetic animals, metformin in normoglycemic rats, and olmesartan in both conventional and niosomal formulations. These differences may materially influence lesion severity, pharmacokinetic exposure, inflammatory and oxidative responses, and the apparent magnitude of gastroprotection.[6-15]

A further common feature was the predominance of preventive experimental designs. Most candidate drugs were administered before, or beginning before, NSAID exposure; consequently, the studies primarily demonstrate prophylactic gastroprotection rather than healing of an established ulcer. This distinction is clinically important because a drug capable of reducing acute experimental injury may not necessarily accelerate ulcer healing, prevent bleeding, or remain safe during prolonged coadministration with an NSAID. Taken together, the evidence supports several mechanistically plausible candidates for further investigation, but it does not permit direct efficacy ranking or clinical treatment recommendations.

Table 1. Comparative summary of the included experimental studies

Drug	Experimental model	Principal findings and mechanistic focus
Metformin[6]	Indomethacin; normoglycemic Sprague-Dawley rats	Reduced macroscopic and histopathological injury, oxidative stress-related chemiluminescence, and TUNEL-positive apoptosis; improved gastric mucosal blood flow.
Liraglutide[7]	Indomethacin; STZ-diabetic Wistar rats	Reduced ulceration, oxidative stress, inflammation, and apoptosis; increased EGF, VEGF-A, and PGE2. Glucose lowering may have contributed to protection.
Alogliptin[8]	Repeated diclofenac exposure; rats	Preserved mucosal architecture; restored GDNF/PI3K/Akt and SDF-1/CXCR4 signaling; increased COX-2/PGE2 and reduced NF-kappa B/TNF-alpha-associated inflammation and apoptosis.
Perindopril[9]	Indomethacin; Wistar rats	Reduced ulcer index and histopathological injury; improved antioxidant defense; increased PGE2 and modulated DDAH-1/ADMA and ACE2/Ang-(1-7) signaling.
Olmesartan[10]	Indomethacin; Sprague-Dawley rats; conventional and niosomal formulations	Reduced macroscopic and histopathological injury; increased Nrf2/HO-1 and COX-1/PGE2-related responses and reduced p38-MAPK and inflammatory markers.
Tadalafil[11]	Indomethacin; Wistar rats	Reduced ulceration, oxidative and inflammatory injury; increased PGE2 and differentially regulated DDAH-1/ADMA and iNOS/eNOS signaling.
Felodipine[12]	Indomethacin; Wistar rats	Reduced ulcer number and ulcerated area; improved antioxidant defense and preserved COX-1 activity. Histopathology was not assessed.
Rivastigmine[13]	Indomethacin; rats	Reduced inflammatory, oxidative, and apoptotic markers; increased HO-1 and PCNA. Findings were interpreted in relation to cholinergic anti-inflammatory signaling.
Topiramate[14]	Indomethacin; Wistar rats	Reduced ulcerated area and histopathological injury; decreased lipid peroxidation and strengthened enzymatic and nonenzymatic antioxidant defenses.
Nifuroxazide[15]	Indomethacin; Sprague-Dawley rats; three doses	Produced dose-dependent protection, preserved mucin, increased Nrf2/HO-1, and reduced HMGB1/TLR4/NF-kappa B, STAT3, inflammatory, and apoptotic markers.

Note: All included studies were conducted in rats and predominantly employed preventive treatment designs. The table summarizes the principal reported outcomes rather than every measured variable.

Changes in signaling markers indicate mechanistic associations unless causal pathway validation was performed. STZ, streptozotocin; EGF, epidermal growth factor; VEGF-A, vascular endothelial growth factor A; PGE2, prostaglandin E2; GDNF, glial cell line-derived neurotrophic factor; SDF-1, stromal cell-derived factor-1; ADMA, asymmetric dimethylarginine; DDAH-1, dimethylarginine dimethylaminohydrolase-1; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; PCNA, proliferating cell nuclear antigen.

Translational implications and limitations

The attraction of repurposing in this field lies in the availability of prior pharmacological knowledge, but the present evidence remains several steps removed from clinical application. All 10 studies were conducted in rats, and most used short pretreatment schedules followed by acute, high-dose NSAID injury. Such designs are useful for detecting biological protection but do not reproduce the heterogeneous exposures, comorbidities, polypharmacy, age distribution, or chronic risk encountered in clinical practice. The doses producing protection in animals may not correspond to approved human exposure, and a drug that reduces gastric biomarkers may still introduce cardiovascular, metabolic, neurological, or interaction-related risks that are unacceptable for prophylactic use.

The studies also primarily tested prevention rather than treatment of an established ulcer. Repurposing language should therefore remain cautious: the findings identify candidates and pathways for further investigation, not alternatives to evidence-based gastroprotection. Head-to-head comparisons under standardized conditions, replication by independent groups, pharmacokinetic assessment of gastroprotective exposure, evaluation of sex and comorbidity effects, and longer-duration safety studies would strengthen the preclinical evidence. Subsequent clinical investigation would require a clear target population and comparison with accepted preventive strategies.[3-5]

A further limitation concerns the present review itself. The evidence set was intentionally restricted to 10 recent studies selected for comparative presentation and was not generated through a registered systematic-review process. Publication bias, selective outcome reporting, and methodological variation were not formally assessed. The synthesis is consequently best interpreted as a structured map of emerging experimental mechanisms rather than a comprehensive or quantitative evaluation of drug efficacy.

Conclusion

Recent experimental studies show that established drugs from diverse therapeutic classes can attenuate NSAID-induced gastric injury through convergent yet complementary mechanisms. Across the reviewed models, gastroprotection involved restoration of redox balance, suppression of inflammatory and apoptotic signaling, preservation of prostaglandin-associated defense, improvement of endothelial or mucosal perfusion, and activation of tissue-repair pathways. Metformin, liraglutide, alogliptin, perindopril, olmesartan, tadalafil, felodipine, rivastigmine, topiramate, and nifuroxazide therefore provide mechanistically plausible examples of drug repurposing in experimental gastroprotection. However, heterogeneity among models and the exclusively preclinical nature of the evidence preclude conclusions regarding comparative superiority or clinical effectiveness. These findings should guide hypothesis generation and standardized translational research rather than immediate therapeutic adoption.

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ACCESS TO CENTRAL-LEVEL HOSPITALS AMONG OLDER ADULTS IN RURAL VIETNAM

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ABSTRACT
Based on secondary data of Institute of Sociology, Vietnam Academy of Social Sciences on the 2013 Population Health Survey in Thai Nguyen, Khanh Hoa and Vinh Long provinces, the study analyzes the patterns of utilization of central level hospitals of the elderly in rural areas. The results indicate that, for older adults living in rural areas, the use of central level hospitals generally increases with the severity of the illness, reaching relatively high and stable levels among those with chronic conditions, whether newly diagnosed or pre-existing, compared to those with acute illnesses or minor injuries. Importantly, most older adults do not consider the geographical distance to central-level hospitals as too far, but they have serious problems with the actual travel time, with most of them having to travel more than one hour to reach these institutions. Also the study reveals obvious differences between social groups. Among those that are ill acutely, women are more likely than men to seek care at central-level hospitals rather than lower-level facilities, but this gender difference largely disappears among those with newly diagnosed chronic conditions. Age and physical health also are significant barriers to access. The lowest access rate to hospitals at the central level was observed in the age group of 80 years and over, compared to a higher tendency to seek care at these hospitals among those aged 60–69 years. The overall study confirms the obvious gap between the great demand for specialized healthcare and the logistical difficulties of travel time and physical limitations that elderly people in rural areas experience.
Keywords: central-level hospitals; older adults; rural areas; healthcare access.

INTRODUCTION
The problem of the elderly today has become a global concern and an international priority. This is driven by their rising share of the world's population and an increasing growth trend from falling fertility rates and increasing life expectancy. In 1950 there were about 200 million people in the world over the age of 60. In 2000, this group accounted for 550 million people (about 10% of the total population) and is projected to reach 1.2 billion (almost 20%) by 2025. According to the Population and Housing Census in 2009 (as of April 1, 2009), there were about 9 million elderly people in Vietnam. The percentage of older persons in the total population increased from 6.9% in 1979 to 7.2% in 1989, 8.2% in 1999 and 9.47% in 2009. The aging of population in Vietnam is taking place at an increasing rate and on a broader scale (Bui, 2005). Like many other developing nations, Vietnam is aging fast, with few support services for the elderly other than traditional family care. Furthermore, modern elderly people are vulnerable due to their past experiences of war and social upheavals in their youth. Health agencies are trying to increase the services suited to the elderly, but often do not have reliable empirical data on the status and living conditions of this population.

The threat of population aging is the impending entry of the working-age population into old age in the coming years. Provision of elderly healthcare and establishment of strategic plans to help Vietnam cope with the increasingly serious population aging situation in the current context are some urgent issues that need to be solved. Over the years, Vietnam has implemented many policies and reached noteworthy milestones in its efforts to achieve universal access to healthcare services. By 2010, the rate of medical examination and treatment had increased, and the health insurance coverage rate reached 61%. The overall objective of developing the health system of Vietnam up to 2015 was: "Continuously building the health system of Vietnam toward equity, efficiency and development; improving the quality of health services to meet the increasing and diverse needs of the population in health protection, care and promotion; reducing morbidity, disability and mortality rates; increasing life expectancy" (Report on

Research Findings: For Growth and an Equitable Society at the Franco-Vietnamese Economic and Financial Forum, 2004). In recent years, the aging of the population has been accompanied by an increasing demand for medical examination, treatment and health care services among the elderly, especially those living in rural areas. However, poor infrastructure and limited access to healthcare services for older adults persist in many rural localities.

As people age naturally thru biological processes they also face greater risk for chronic illness, gradual loss of the ability to care for themselves, and greater need for assistance with activities of daily living. It therefore raises the need for health care and social support from family and society. The main institution of social care for the elderly in traditional society was the family. However, in today's society, with low birth rates, increasing nuclear families, and a higher percentage of older adults living separately from their children, families are increasingly finding it difficult to offer this traditional care (Luong, 2001). Therefore, the improvement of the availability and accessibility of elderly care services, especially health care, has become an urgent necessity at the present and future period of population aging. Filial piety, a cultural value, will not be sufficient to meet the unprecedented demands that Vietnamese families will soon face that may limit their capacity to care for an aging population. The rising burden of dependent elderly in developed Asian economies such as Japan and South Korea, combined with smaller families and more women in the migrant labor force, has increased family stress and made a rapid change in traditional family care models necessary. As Vietnam continues to develop economically, it is foreseeable that the combination of an aging population and changes in family structures will begin to put pressure on traditional caregiving practices (Din & Nguyen, 2010). This study describes the current situation of access to health care services for the elderly living in rural areas considering the above current challenges in elderly health care. Actionable policy recommendations are put forward to enhance the quality of health care services for the rural elderly population based on the findings.

METHODOLOGY

The 2013 Population Health Survey was carried out by the Institute of Sociology, Vietnamese Academy of Social Sciences in collaboration with the Social Science Research Council (USA), using a quantitative structured questionnaire with nearly 2,000 respondents in three provinces – Thai Nguyen, Khanh Hoa and Vinh Long. The questionnaire contained a number of key research modules including: demographic characteristics of the sample population; use of health insurance; household characteristics, spatial distance and social capital; morbidity patterns; pharmaceutical utilization; accessibility of health facilities; health-seeking behavior; health-related behaviors and perceptions; utilization of commune health centers; knowledge on reproductive health and HIV/AIDS; health status and educational attainment of children; and pregnancy history and related maternal health issues. This study extracts variables specifically pertaining to healthcare facility access from these questionnaire modules. Quantitative analytical methods were applied to examine cross-variable correlations by using SPSS (version 20.0), which empirically tested the study's objectives and hypotheses. These variables provide descriptive statistics of the study and generate preliminary hypotheses related to access to health care services among the rural elderly.

RESEARCH AND FINDINGS

ACCESSIBILITY TO CENTRAL-LEVEL HOSPITALS AMONG THE ELDERLY: CURRENT STATUS AND DETERMINANTS

Currently, hospitals at the central level are provided with the best conditions, including the most modern medical equipment and highly qualified medical staff. Based on the public opinion, these medical institutions in the central level are the medical institutions with the largest number of patients and treatments of all medical institutions. The present study examined the general situation of accessibility to healthcare services for the elderly, including access to central-level hospitals, but there were differences among sub-groups of elderly patients seeking care at these tertiary facilities, depending on their health status. For this research, health conditions are grouped into three general categories: acute illness/injury, new chronic condition, and pre-existing chronic condition. The empirical results are reported in the following tables:

Table 1. Distribution of Acute Illness and Injury Patients Accessing Healthcare Facility Types

Type of healthcare facility	*Percentage (%)*
Central-level hospital	3,8
District-level hospital	9,5
Commune health station	42,4
Private healthcare facility	12,7
Pharmacy	31,6
Total	100

Source: Author's survey data

As the data in Table 1 show, the percentage of rural elderly people who go to a central-level (national, provincial, and sector-specific) hospital is 3.8%, which is the lowest of all health facility types. In contrast, other types of medical services have higher utilization rates. This pattern can be explained by several hypotheses: spatial constraints, for example, the large geographical distance to tertiary healthcare facilities, or physical mobility limitations among older adults may be significant barriers hindering their access to central-level medical services. Alternatively, it can be hypothesized that for minor health issues (such as acute illnesses or minor injuries), rural older adults may choose not to visit central-level hospitals but rather choose alternative healthcare facilities that provide greater accessibility and lower financial burden. To further examine the utilization of healthcare services according to health status, the following table presents the types of medical facilities utilized by older adults with newly diagnosed chronic conditions.

Table 2. Distribution of Patients with Newly Diagnosed Chronic Conditions Accessing Healthcare Facility Types

Type of healthcare facility	*Percentage (%)*
Central-level hospital	23,3
District-level hospital	19,0
Commune health station	26,7
Private healthcare facility	26,7
Pharmacy	4,3
Total	100

Source: Author's survey data

As shown in Table 2, the percentage of rural older adults seeking hospital care for newly diagnosed chronic conditions in hospitals at the central level (23.3%) is higher than that of their counterparts with acute illnesses or injuries. The more severe and early stage of the disease may be associated with higher-level hospital utilization by rural older adults. In addition, hospitals at the central level are equipped with better medical infrastructures than those at the lower levels, so older adults are more likely to go to the tertiary hospitals for medical examination and treatment. The following analysis should also consider the use of healthcare services at the central level among the rural older adults with pre-existing chronic conditions.

Table 3. Distribution of Patients with Pre-existing Chronic Conditions Accessing Healthcare Facility Types

Type of healthcare facility	*Percentage (%)*
Central-level hospital	24,3
District-level hospital	16,2
Commune health station	27,0
Private healthcare facility	16,2
Pharmacy	16,2
Total	100

Source: Author's survey data

As shown in Table 3, a moderate proportion of older adults with pre-existing chronic conditions seek care from central-level hospitals (24.3%). Older adults continue to prefer seeking care at tertiary healthcare facilities during the long-term management phase of chronic illness. This may be explained, at least partly, by the fact that patients are first introduced to the treatment regimens at the central-level hospitals when they first develop their chronic disease, and they continue to seek care at the same facilities in the later stages of their illness.

It can be seen from the three analytical tables on the use of central hospitals that the proportion of rural elderly people using tertiary hospitals increases with the severity of the disease. Only a small proportion of the rural elderly with acute illness or minor injury use the central level hospitals (3.8%). Conversely, those with early or new diagnoses of chronic conditions, on the basis of the pattern of recurrent symptoms, display a considerably higher rate of use of central-level care (23.3%). This rate stabilizes as patients adapt to ongoing care at these tertiary facilities (24.3%). These results suggest that the health status of the rural elderly systematically influences the volume of the rural elderly seeking medical examination and treatment in the hospitals at the central level.

The following section provides a general overview of healthcare access at the central level facilities by discussing socio-demographic differentials in the use of healthcare services among the rural elderly social groups.

Table 4. Geographical Distance from Older Adults' Residences to Central-Level Hospitals

Geographical Distance	*N*	*%*
Near	356	59,4
Moderate	219	36,6
Far	24	4,0
Total	599	100

Source: Author's survey data

Geographical distance plays a significant role in determining access to health care facilities among older adults. Table 4. Measurement scale of spatial distance from older adults' residences to central-level hospitals. The majority of respondents live relatively close and with easy access to tertiary facilities (59,4%). Conversely, the share of older people living at a far distance – where physical access is considered challenging – stays low (4%).

Table 5. Travel Duration from Older Adults' Residences to Central-Level Hospitals

Travel Duration	N	%
Short	15	2,2
Moderate	79	11,8
Long	574	85,9
Total	1152	100

Source: Author's survey data

The vast majority of the elderly (85.9%) reported that they spent a lot of time on travel to seek medical examination and treatment in central level hospitals. For instance, in this study, the travel time metric "time-consuming" is defined as a travel time of more than one hour from the respondent's residence to the nearest central level hospital.

SOCIO-DEMOGRAPHIC DISPARITIES IN ACCESS TO CENTRAL-LEVEL HOSPITALS AMONG OLDER ADULTS

In addition to the general picture of healthcare service utilization, a more detailed analysis of demographic factors (e.g., gender and age cohorts) is needed to better identify the barriers and opportunities for access to central level hospitals among the rural elderly. Understanding these group-specific differences across socio-demographic categories is an important empirical basis for assessing equity and efficiency in healthcare access among today's older adults.

Table 6. Correlation Between Gender, Age, and the Distance Scale from Older Adults' Residences to Central-Level Hospitals (%)

		Geographical Distance		
		Near	*Moderate*	*Far*
Gender	Male	55,1	39,0	5,8
	Female	60,9	37,3	1,8
Age	60-69	60,1	36,8	3,1
	70-79	57,8	35,5	6,6
	80+	60,0	37,4	2,6

Source: Author's survey data

As can be seen from the table above, gender does not play an important role in the geographical distance between the residences of older adults and central-level hospitals. The closeness to home gives easy physical access to tertiary facilities to vast majority of both male and female respondents. Similarly, spatial distance has not been a substantial barrier to access to hospitals at the central level for the elderly in all the age groups.

Table 7. Correlation Between Gender, Age, and the Travel Duration Scale from Older Adults' Residences to Central-Level Hospitals (%)

		Travel Duration		
		Short	*Moderate*	*Long*
Gender	Male	1,9	10,8	87,3
	Female	1,9	12,2	85,9
Age group	60-69	0,3	12,9	86,8
	70-79	4,2	7,8	88,0
	80+	4,4	14,8	80,7

Source: Author's survey data

The elderly have more difficulty in reaching the central-level hospitals, because the distance from their homes to the tertiary facilities is far and the trip is usually over one hour. Interestingly, males report time-consuming travel more often than females (87.3% vs. 85.9%). The travel time from home to central-level hospitals is high for all age cohorts. The age group with the highest percentage of time spent for transportation is the oldest age group (80 years and over) (88.0%).

Table 8. Association Between Gender and the Number of Older Adults with Acute Illnesses or Injuries Seeking Care at Central-Level Hospitals (%)

Type of healthcare facility	*Gender*	
	Female	*Male*
Central-level hospital	5,7	1,5
District-level hospital	12,9	7,6
Commune health station	41,7	42,4
Cơ sở tư nhân	14,3	10,6
Pharmacy	20,0	37,9

Source: Author's survey data

Based on the data in the above table, the commune health center is the first place of care for both male and female older adults who need examination and treatment of acute illnesses, accounting for 41.7% of males and 42.4% of females. Women are more likely than men to seek treatment at formal health care facilities for the management of acute conditions. Men, however, are more likely than women to use retail pharmacies. This pattern leads to the hypothesis that the elderly men are less likely than the women to consult medical professionals for their ailments and more likely to self-medicate with over-the-counter drugs without prescription from a doctor.

Table 9. Association Between Age Groups and the Number of Older Adults with Acute Illnesses or Injuries Seeking Care at Central-Level Hospitals (%)

Type of healthcare facility	*Age group*		
	60-69	*70-79*	*80+*
Central-level hospital	5,6	0	4,0
District-level hospital	14,4	2,3	4,0
Commune health station	38,9	48,8	44,0
Private healthcare facility	11,1	16,3	12,0
Pharmacy	30,0	32,6	26,0

Source: Author's survey data

From the data in the above table, the proportion of the elderly who go to the central level hospital for medical examination and treatment in the age groups of 60-69 and 80 and above is 5.6% and 4.0% respectively. These data represent a small proportion relative to other types of healthcare facility, indicating that there are significant barriers to rural older adults accessing care in central-level hospitals. Furthermore, for these age groups, central-level hospitals had the lowest utilization rate among all healthcare institutions. It is also important to note that these respondents suffer from acute illnesses or injuries. This further supports the premise that the utilization of health care facilities varies depending on the severity and nature of the health condition.

Table 10. Association Between Gender and the Number of Older Adults with Newly Diagnosed Chronic Conditions Seeking Care at Central-Level Hospitals (%)

Type of healthcare facility	*Gender*	
	Female	*Female*
Central-level hospital	23,4	25,0
District-level hospital	23,4	16,1
Commune health station	23,4	30,4
Cơ sở tư nhân	23,4	26,8
Pharmacy	6,4	1,8

Source: Author's survey data

Data show that the percentages of male and female older adults with newly diagnosed chronic conditions who seek hospital care at the central level are almost the same, 25.0% and 23.4%, respectively. This pattern may be due to the similar demand of both genders for health care services at the first identification of a chronic illness. Therefore, there is no significant gender difference in the choice of central-level hospitals for the examination and treatment of newly diagnosed chronic diseases.

Table 11. Association Between Age Groups and the Number of Older Adults with Newly Diagnosed Chronic Conditions Seeking Care at Central-Level Hospitals (%)

Type of healthcare facility	*Age group*		
	60-69	*60-69*	*80+*
Central-level hospital	23,9	22,2	22,7
District-level hospital	19,4	18,5	18,2
Commune health station	22,4	25,9	40,9
Private healthcare facility	26,9	33,3	18,2
Pharmacy	7,5	0	0

Source: Author's survey data

The 60–69 age cohort has the highest utilization rate for central-level hospitals (23.9%), as shown in the above table. In addition, the trend of older adults with newly diagnosed chronic conditions seeking care at central-level facilities is increasing across all age groups. With the increase of newly diagnosed chronic diseases among people aged 70–79, the likelihood of seeking medical treatment in hospitals at the central level (22.2%) is higher, while people with acute illness or injury are less likely to go to tertiary hospitals for medical examination and treatment.

Table 12. Association Between Gender and the Number of Older Adults with Pre-existing Chronic Conditions Seeking Care at Central-Level Hospitals (%)

Type of healthcare facility	*Gender*	
	Female	*Female*
Central-level hospital	16,2	15,0
District-level hospital	24,3	20,3
Commune health station	29,0	30,8
Cơ sở tư nhân	18,8	20,7
Pharmacy	11,6	13,2

Source: Author's survey data

The use of central-level hospitals for the management of chronic diseases in rural older adults did not differ significantly between sexes (male: 16.2%; female: 15.0%). However, a slightly higher proportion of males uses hospitals at the central level, possibly on account of the higher prevalence and longer duration of chronic conditions among elderly males as compared to females. The following table presents the detailed age composition of rural elderly people who go to tertiary medical institutions for examination and treatment.

Table 13. Association Between Age Groups and the Number of Older Adults with Pre-existing Chronic Conditions Seeking Care at Central-Level Hospitals (%)

Type of healthcare facility	*Age group*		
	60-69	*60-69*	*80+*
Central-level hospital	18,3	17,4	7,0
District-level hospital	21,8	21,0	21,0
Commune health station	26,5	30,4	35,7
Private healthcare facility	20,4	19,6	20,3
Pharmacy	13,0	11,6	16,1

Source: Author's survey data

As can be seen from the above table, the 60–69 age group is the most demanding group for medical consultations in central level hospitals (18.3%), followed by a moderate use rate of the 70–79 age group (17.4%), whereas the oldest group (80 and above) has the lowest rate of visits to central level hospitals (7.0%). The physical health and the burden of advanced illnesses among the elderly are deteriorating and this can explain a big part of this gap. It limits their physical access to the central facilities. In contrast, individuals in the age group of 60–69 years are at the beginning of old age, thus, they are less likely to have physical limitations, which makes access to tertiary healthcare institutions easier than their older counterparts.

CONCLUSION

This study on access to central level hospitals among older people in rural Vietnam reveals important patterns and barriers when considering rapid population aging in Vietnam. There has been a continuous increase in the demand for medical examination, treatment and utilization of health care services among the rural elderly, especially for specialized tertiary health care. The empirical evidence shows that the share of access to central-level hospitals systematically rises with disease severity, reaching a relatively high and stable level among older adults suffering from chronic conditions (both newly diagnosed and pre-existing) compared to individuals with acute illnesses or mild injuries. While the majority of respondents do not consider geographical distance to be a major obstacle, the actual duration of travel (longer than one hour) represents a serious structural barrier to accessibility. Further, age and physical limitations remain significant barriers, as the oldest-old group (80+ years) has the lowest rate of central hospital utilization relative to the 60–69 group. Gender-based disparities are pronounced in acute illness management but nearly vanish among those with newly diagnosed chronic conditions. To summarize, this study emphasizes a serious mismatch between the demand for specialized health care and the logistical, temporal, and physical barriers faced by the elderly in rural areas.

Given the mounting pressure on traditional family caregiving models from modern socioeconomic changes, it is an urgent imperative to refine healthcare policies for equity, efficiency, and improved medical access for older adults.

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BİMAKSİLLER PROGNATİ, GUMMY SMILE VE İSKELETSEL SINIF II MALOKLÜZYONUN ÇİFT ÇENE ORTOGNATİK CERRAHİ VE GENİOPLASTİ İLE YÖNETİMİ: OLGU SUNUMU

MANAGEMENT OF BIMAXILLARY PROGNATHISM, GUMMY SMILE, AND SKELETAL CLASS II MALOCCLUSION WITH BIMAXILLARY ORTHOGNATHIC SURGERY AND GENIOPLASTY: A CASE REPORT

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Özet

Amaç: Maksiller vertikal fazlalık, sagittal iskeletsel uyumsuzluk ve belirgin gingival görünüm (gummy smile), erişkin bireylerde estetik ve fonksiyonel problemlere neden olan, multidisipliner yaklaşım gerektiren dentofasiyal deformitelerdir. Bu vaka raporunun amacı, iskeletsel Sınıf II maloklüzyon, dudak yetersizliği, konveks profil, artmış overjet ve gummy smile şikâyetleri bulunan erişkin kadın hastanın ortodontik tedavi ile kombine çift çene ortognatik cerrahi ve genioplasti tedavisinin sonuçlarını sunmaktır.

Materyal ve Yöntem

Tedavi öncesinde üst ve alt keserlerin ileri derecede protrüziv ve prokline konumlanmasına bağlı gelişen alveoler kompanzasyon nedeniyle, ideal keser pozisyonunun sağlanması, cerrahi hareket miktarının optimize edilmesi ve postoperatif stabilitenin artırılması amacıyla üst ve alt çenede 14, 24, 34 ve 44 numaralı dişler çekilerek ortodontik dekompanzasyon gerçekleştirilmiş ve hasta cerrahiye hazırlanmıştır. Cerrahi aşamada Le Fort I osteotomisi ile maksillaya impaksiyon uygulanarak vertikal maksiller fazlalık düzeltilmiş, gingival görünüm azaltılmış ve maksilla üç boyutlu olarak yeniden konumlandırılmıştır. Ardından bilateral sagittal split ramus osteotomisi (BSSRO) ile mandibular ilerletme yapılarak sagittal iskeletsel uyumsuzluk giderilmiş, yüz profilini ve alt yüz estetiğini iyileştirmek amacıyla eş zamanlı genioplasti uygulanmıştır. Postoperatif ortodontik tedavi ile oklüzyon detaylandırılmış ve tedavi tamamlanmıştır.

Bulgular

Tedavi sonunda Sınıf I oklüzyon, ideal overjet ve overbite ilişkisi, düzelmiş yüz profili, azalmış gingival görünüm, uyumlu dudak kapanışı ve dengeli fasiyal estetik elde edilmiştir.

Sonuç: Bu vaka, erişkin bireylerde sagittal iskeletsel uyumsuzluk ve gummy smile tedavisinde çekimli ortodontik dekompanzasyonun, maksiller impaksiyon, çift çene ortognatik cerrahisi ve genioplasti ile kombine edilmesinin hem fonksiyonel hem de estetik açıdan başarılı ve öngörülebilir sonuçlar sağlayan etkili bir tedavi yaklaşımı olduğunu göstermektedir.

Anahtar Kelimeler

Bimaksiller prognati, Gummy smile, Ortognatik cerrahi, Genioplasti, İskeletsel Sınıf II maloklüzyon

Abstract

Purpose

Vertical maxillary excess, sagittal skeletal discrepancy, and excessive gingival display (gummy smile) are dentofacial deformities that cause esthetic and functional impairments in adult patients and often require a multidisciplinary treatment approach.

The aim of this case report was to present the treatment outcomes of an adult female patient with skeletal Class II malocclusion, lip incompetence, a convex facial profile, increased overjet, and excessive gingival display who was treated with a combination of orthodontic treatment, bimaxillary orthognathic surgery, and genioplasty.

Materials and Methods
Before surgery, orthodontic decompensation was performed by extracting the maxillary and mandibular first premolars (14, 24, 34, and 44) to eliminate the dentoalveolar compensation associated with severely protrusive and proclined maxillary and mandibular incisors. This approach was intended to establish optimal incisor positioning, optimize the magnitude of surgical correction, and enhance postoperative stability, thereby preparing the patient for orthognathic surgery. During the surgical phase, vertical maxillary excess was corrected by means of a Le Fort I osteotomy with maxillary impaction, resulting in reduced gingival display and three-dimensional repositioning of the maxilla. Subsequently, bilateral sagittal split ramus osteotomy (BSSRO) was performed to advance the mandible and correct the sagittal skeletal discrepancy. Simultaneous genioplasty was carried out to further improve the facial profile and lower facial esthetics. Following surgery, postoperative orthodontic treatment was completed to refine the occlusion and finalize the treatment.

Results
Treatment resulted in a stable Class I occlusion, ideal overjet and overbite relationships, an improved facial profile, reduced gingival display, competent lip closure, and harmonious facial esthetics.

Conclusion
This case demonstrates that extraction-based orthodontic decompensation combined with maxillary impaction, bimaxillary orthognathic surgery, and genioplasty is an effective and predictable treatment approach for adult patients with sagittal skeletal discrepancy and excessive gingival display, providing successful functional and esthetic outcomes.
Keywords: Bimaxillary prognathism, Gummy smile, Orthognathic surgery, Genioplasty, Skeletal Class II malocclusion

1. GİRİŞ
Ortognatik cerrahi, büyümesini tamamlamış bireylerde yalnızca ortodontik tedavi ile yeterli düzeyde düzeltilemeyen şiddetli dentofasiyal deformitelerin tedavisinde kullanılan etkili ve öngörülebilir bir tedavi yaklaşımıdır. Özellikle belirgin iskeletsel Sınıf II maloklüzyonlarda sagittal çene uyumsuzluğuna vertikal maksiller fazlalık, artmış gingival görünüm, konveks profil ve dudak yetersizliği gibi estetik ve fonksiyonel problemlerin eşlik etmesi, ortodontik kamuflaj tedavisinin sınırlarını aşabilmektedir. Bu tür erişkin hastalarda ortodontik tedavinin ortognatik cerrahi ile kombine edilmesi; iskeletsel çene ilişkilerinin düzeltilmesi, fonksiyonel oklüzyonun oluşturulması ve dengeli bir dentofasiyal estetiğin sağlanması açısından önemli bir tedavi seçeneğidir.[1–3]
Vertikal maksiller fazlalık; artmış alt yüz yüksekliği, dudak yetersizliği ve istirahat veya gülümseme sırasında artmış maksiller diş ve diş eti görünümü ile ilişkili olabilen önemli bir dentofasiyal deformitedir. Gülümseme sırasında aşırı miktarda gingivanın görünür olması olarak değerlendirilen "gummy smile", gülümseme ve yüz estetiğini olumsuz yönde etkileyebilen önemli klinik bulgulardan biridir. Gummy smile etiyolojisi multifaktöriyel olup vertikal maksiller fazlalığın yanı sıra üst dudak uzunluğu ve hipermobilitesi, dentoalveoler faktörler ve değişmiş pasif erüpsiyon gibi çeşitli faktörlerle ilişkili olabilmektedir. Bu nedenle doğru tedavi yaklaşımının belirlenebilmesi için aşırı gingival görünümün etiyolojisinin doğru şekilde ortaya konulması önem taşımaktadır.[4]
Vertikal maksiller fazlalığa bağlı belirgin gingival görünümün bulunduğu erişkin bireylerde, iskeletsel problemin yalnızca ortodontik veya dentoalveoler yaklaşımlarla düzeltilmesi yeterli olmayabilmektedir. Bu olgularda Le Fort I osteotomisi ile maksillanın superior yönde yeniden konumlandırılması, diğer bir ifadeyle maksiller impaksiyon, vertikal maksiller fazlalığın düzeltilmesinde kullanılan temel cerrahi yaklaşımlardan biridir. Maksiller impaksiyon ile vertikal maksiller yükseklik ve gingival görünüm azaltılırken, maksillanın üç boyutlu olarak yeniden konumlandırılması sagittal ve vertikal çene ilişkilerinin eş zamanlı olarak düzenlenmesine olanak sağlamaktadır.

Maksillanın superior yönde yeniden konumlandırılması aynı zamanda ortognatik cerrahide stabilitesi yüksek cerrahi hareketlerden biri olarak bildirilmektedir.[5]

Ortognatik cerrahi öncesinde uygulanan preoperatif ortodontik tedavinin temel amaçlarından biri, iskeletsel deformiteye karşı gelişmiş dentoalveoler kompanzasyonların ortadan kaldırılması ve dişlerin kendi bazal kemikleri üzerinde cerrahi düzeltmeye uygun konumlara getirilmesidir. Keser dekompanzasyonu, gerçek iskeletsel uyumsuzluğun ortaya çıkarılması ve planlanan cerrahi hareketlerin dental kompanzasyonlar tarafından sınırlandırılmaması açısından cerrahi-ortodontik tedavinin önemli bir aşamasıdır. Bununla birlikte dekompanzasyon miktarının maloklüzyon tipine ve başlangıçtaki keser pozisyonlarına bağlı olarak değişebildiği gösterilmiştir.[6]

Preoperatif ortodontik dekompanzasyon sırasında gerçekleştirilen keser hareketleri yalnızca dental ilişkileri değil, cerrahi öncesi yumuşak doku profilini de etkileyebilmektedir. İskeletsel Sınıf II olgularda keserlerin başlangıçtaki kompanzasyon miktarı ve dekompanzasyon sırasında gerçekleştirilen hareketlerin cerrahi planlamayla birlikte değerlendirilmesi gerekmektedir. Cerrahi öncesi keser dekompanzasyonuna bağlı dental ve yumuşak doku değişikliklerinin farklı maloklüzyon gruplarında farklılık gösterebildiği bildirilmiştir.[7]

Özellikle üst ve alt keserlerin ileri derecede protrüziv ve prokline olduğu olgularda mevcut dentoalveoler kompanzasyonların giderilmesi için ark içerisinde yeterli alanın oluşturulması önem taşımaktadır. Bu nedenle uygun endikasyona sahip hastalarda premolar çekimleri, keserlerin bazal kemikler üzerindeki sagittal ve açısal konumlarının düzenlenmesine olanak sağlayarak cerrahi öncesi dekompanzasyonun gerçekleştirilmesine yardımcı olabilmektedir. Cerrahi öncesinde yeterli keser dekompanzasyonunun elde edilmesi, iskeletsel deformitenin gerçek boyutlarının ortaya çıkarılması ve planlanan cerrahi hareketlerin gerçekleştirilebilmesi açısından önemlidir.[8]

İskeletsel Sınıf II deformitelerinde sagittal ve vertikal problemlerin birlikte bulunduğu olgularda tek çeneye yönelik cerrahi girişim tüm dentofasiyal uyumsuzlukların düzeltilmesinde yeterli olmayabilir. Vertikal maksiller fazlalığın Le Fort I osteotomisi ve maksiller impaksiyon ile düzeltilmesi, mandibular yetersizliğin eşlik ettiği olgularda bilateral sagittal split ramus osteotomisi (BSSRO) ile mandibular ilerletme ile kombine edilebilmektedir. Böylece sagittal maksillomandibular ilişkinin düzeltilmesinin yanı sıra vertikal yüz boyutları, oklüzal ilişkiler ve yüz profili üzerinde daha kapsamlı bir kontrol sağlanabilmektedir. Maksiller impaksiyon ve mandibular ilerletmenin, uygun cerrahi planlama ve rijit fiksasyon ile stabilitesi yüksek ortognatik cerrahi hareketler arasında olduğu bildirilmiştir.[5]

Ortognatik cerrahi ile maksilla ve mandibulanın konumlarının düzeltilmesi yüz profilinde önemli değişiklikler oluşturmakla birlikte, çene ucunun morfolojisi ve sagittal-vertikal konumu alt yüz estetiğinin belirlenmesinde önemli rol oynamaktadır. Bu nedenle gerekli olgularda ortognatik cerrahiye eş zamanlı genioplasti eklenmesi; çene ucu projeksiyonunun düzenlenmesine, alt yüz oranlarının iyileştirilmesine ve daha dengeli bir yumuşak doku profilinin oluşturulmasına katkıda bulunabilmektedir. Güncel ortognatik cerrahi planlamasında çene ucunun maksillofasiyal profilin önemli bir bileşeni olduğu ve mevcut genial uyumsuzlukların bağımsız olarak değerlendirilerek gerektiğinde cerrahi olarak düzeltilmesi gerektiği vurgulanmaktadır.[9,10]

Bu vaka sunumunda, iskeletsel Sınıf II maloklüzyon, vertikal maksiller fazlalık, belirgin gingival görünüm, konveks profil, dudak yetersizliği ve artmış overjet ile birlikte üst ve alt keserlerde belirgin protrüzyon ve proklinasyon bulunan erişkin kadın hastanın ortodontik-cerrahi tedavisi sunulmaktadır. Üst ve alt keserlerin bazal kemikler üzerinde cerrahiye uygun konumlara getirilmesi ve mevcut dentoalveoler kompanzasyonların giderilmesi amacıyla 14, 24, 34 ve 44 numaralı dişlerin çekimini takiben preoperatif ortodontik dekompanzasyon gerçekleştirilmiştir. Cerrahi aşamada Le Fort I osteotomisi ile maksiller impaksiyon ve üç boyutlu maksiller yeniden konumlandırma, BSSRO ile mandibular ilerletme ve eş zamanlı genioplasti uygulanarak sagittal ve vertikal iskeletsel uyumsuzluğun düzeltilmesi, gingival görünümün azaltılması, fonksiyonel oklüzyonun sağlanması ve dengeli bir dentofasiyal estetiğin elde edilmesi amaçlanmıştır.

2. VAKA SUNUMU

Erişkin kadın hasta, gülümseme sırasında aşırı diş eti görünümü, konveks yüz profili, alt çene ve çene ucunun geride olması nedeniyle yüz estetiğinden duyduğu memnuniyetsizlik şikâyetiyle ortodonti kliniğine başvurmuştur. Hastanın sistemik sağlık durumu iyi olup herhangi bir kronik hastalık veya düzenli ilaç kullanım öyküsü bulunmamaktadır.

Klinik incelemede belirgin gingival görünüm (gummy smile), vertikal maksiller fazlalık, artmış alt yüz yüksekliği, mandibular retrognati, retrüziv çene ucu ve konveks yüz profili tespit edilmiştir. Dental değerlendirmede artmış overjet ile birlikte üst ve alt kesici dişlerde belirgin protrüzyon ve proklinasyon gözlenmiştir. Periodontal dokuların sağlıklı olduğu ve oral hijyen düzeyinin ortodontik tedavi için kabul edilebilir sınırlar içerisinde bulunduğu belirlenmiştir.
Sefalometrik analiz sonucunda hastanın belirgin iskeletsel Sınıf II ilişkiye sahip olduğu (SNA: 79,3°, SNB: 70,8°, ANB: 8,6°; Wits: +7,7 mm) ve hiperdiverjan vertikal büyüme paterni gösterdiği (FMA: 39,1°, SN-GoGn: 47,8°) belirlenmiştir. PFH/AFH oranının %56,1 ve alt anterior yüz yüksekliğinin 103 mm olması artmış vertikal yüz boyutunu desteklemiştir. Maksillanın sagittal konumu A-N Perp: +1,3 mm değeriyle yaklaşık normal sınırlar içerisinde bulunurken, Pog-N Perp: −21,4 mm değeri mandibula ve çene ucundaki belirgin retrüzyonu ortaya koymuştur.
Dental sefalometrik değerlendirmede üst ve alt kesici dişlerde ileri derecede protrüzyon ve proklinasyon saptanmıştır. Başlangıçta U1-NA 28,5°/10,8 mm, L1-NB 37,5°/16,2 mm ve IMPA 96° olarak ölçülmüş; interinsizal açının 105,5° olması keserlerin belirgin protrüziv ve prokline konumunu desteklemiştir. Panoramik radyografik değerlendirmede diş kökleri, alveolar kemik seviyeleri ve periodontal destek dokularında tedaviye engel oluşturacak herhangi bir patolojik bulguya rastlanmamıştır.

Tedavi planlamasında öncelikli hedefler:

- Üst ve alt kesici dişlerdeki ileri derecede protrüzyon ve proklinasyonun giderilerek cerrahi öncesi dental dekompanzasyonun sağlanması,
- İskeletsel Sınıf II maksillomandibular uyumsuzluğun düzeltilmesi,
- Vertikal maksiller fazlalığın ve artmış gingival görünümün azaltılması,
- Artmış anterior yüz yüksekliğinin kontrol altına alınması,
- Mandibular retrognati ve yetersiz çene ucu projeksiyonunun düzeltilmesi,
- Fonksiyonel, dengeli ve uzun dönem stabil bir oklüzyon elde edilmesi,
- Yüz profili ve gülümseme estetiğinin iyileştirilmesi olarak belirlenmiştir.

Hastaya mevcut dentofasiyal deformitenin özellikleri ve tedavi alternatifleri ayrıntılı olarak açıklanmıştır. Vakanın sagittal ve vertikal yönlerde belirgin iskeletsel düzensizlik göstermesi ve mevcut dentoalveoler protrüzyonun yalnızca ortodontik kamuflaj ile yeterli düzeyde düzeltilemeyecek olması nedeniyle kombine ortodontik ve cerrahi tedavi planlanmıştır. Üst ve alt kesici dişlerin ileri derecede protrüziv ve prokline konumlarının düzeltilmesi ve planlanan cerrahi hareketler için yeterli dentoalveoler dekompanzasyonun sağlanması amacıyla 14, 24, 34 ve 44 numaralı birinci premolar dişlerin çekimi gerçekleştirilmiştir. Sabit ortodontik tedavi ile çekim boşlukları kullanılarak kesici dişlerin retraksiyonu ve dikleştirilmesi, arkların hizalanması ve koordinasyonu ile cerrahi öncesi dental dekompanzasyon sağlanmıştır.
Ortodontik hazırlığın tamamlanmasının ardından çift çene ortognatik cerrahisi ve genioplasti uygulanmıştır. Cerrahi aşamada Le Fort I osteotomisi ile vertikal maksiller fazlalığın ve artmış gingival görünümün düzeltilmesi amacıyla maksilla anterior bölgede 7 mm, posterior bölgede 4,5 mm impakte edilmiş ve yüksek miktardaki maksiller impaksiyona eşlik edecek şekilde 2 mm öne konumlandırılmıştır. Diferansiyel maksiller impaksiyon ile vertikal yüz boyutlarının azaltılması, oklüzal düzlemin yeniden düzenlenmesi ve gülümseme sırasında aşırı diş eti görünümünün azaltılması hedeflenmiştir.
Mandibular retrognati ve iskeletsel Sınıf II ilişkinin düzeltilmesi amacıyla BSSRO ile mandibula 9 mm öne alınmıştır. Ayrıca yetersiz çene ucu projeksiyonunun düzeltilmesi ve daha dengeli bir yüz profilinin oluşturulması amacıyla ilerletici genioplasti uygulanarak çene ucu 3–4 mm anteriora konumlandırılmıştır. Böylece sagittal ve vertikal iskeletsel uyumsuzlukların düzeltilmesi, gingival görünümün azaltılması ve daha dengeli bir yüz profilinin elde edilmesi amaçlanmıştır. Cerrahi sonrasında ortodontik tedaviye devam edilerek oklüzyonun detaylandırılması, interkuspidasyonun optimize edilmesi ve tedavi sonuçlarının stabilizasyonu sağlanmıştır.
Tedavi sonunda sefalometrik olarak belirgin iskeletsel ve dentoalveoler değişiklikler elde edilmiştir. SNB 70,8°'den 77,8°'ye yükselirken ANB 8,6°'den 3,4°'ye gerilemiş ve başlangıçtaki belirgin iskeletsel Sınıf II ilişki önemli ölçüde düzeltilmiştir. Pog-N Perp değeri −21,4 mm'den −2,9 mm'ye değişerek mandibular ilerletme ve genioplasti sonrasında çene ucu projeksiyonunda elde edilen belirgin iyileşmeyi ortaya koymuştur.

Vertikal yönde FMA 39,1°'den 33,5°'ye, SN-GoGn 47,8°'den 40,1°'ye ve alt anterior yüz yüksekliği 103 mm'den 97,5 mm'ye gerilemiştir. Bu değişiklikler diferansiyel maksiller impaksiyon ve mandibular yeniden konumlandırma sonucunda vertikal yüz boyutlarında belirgin bir iyileşme sağlandığını göstermiştir.

Dental değerlendirmede U1-NA değeri 28,5°/10,8 mm'den 17°/4,3 mm'ye, L1-NB değeri 37,5°/16,2 mm'den 17,5°/6,1 mm'ye ve IMPA 96°'den 76°'ye gerilerken, interinsizal açı 105,5°'den 142,1°'ye yükselmiştir. Bu değişiklikler, çekimli ortodontik tedavi sonucunda başlangıçtaki ileri derecede dentoalveoler protrüzyonun azaltıldığını ve kesici dişlerde belirgin retraksiyon ve dikleşme sağlandığını göstermiştir.

Tedavi sonucunda iskeletsel Sınıf II ilişki ve vertikal maksiller fazlalık belirgin ölçüde düzeltilmiş, gingival görünüm azaltılmış, mandibula ve çene ucu projeksiyonu artırılmış ve daha dengeli bir yüz profili elde edilmiştir. Ortodontik dekompanzasyon ile ortognatik cerrahinin birlikte uygulanması sonucunda fonksiyonel ve estetik açıdan tatmin edici bir oklüzal ve dentofasiyal sonuç sağlanmıştır.

Klinik Görseller

Resim 1. Tedavi öncesi intraoral ve ekstraoral kayıtlar
Resim 2. Cerrahi öncesi ortodontik dekompanzasyon aşamasına ait intraoral görüntüler
Resim 3. Çift çene ortognatik cerrahisi ve genioplasti sonrası intraoral ve ekstraoral görüntüler
Resim 4. Tedavi öncesi ve tedavi sonrası lateral sefalometrik radyografilerin karşılaştırılması
Resim 5. Tedavi öncesi ve tedavi sonrası cephe, profil ve gülümseme fotoğraflarının karşılaştırılması



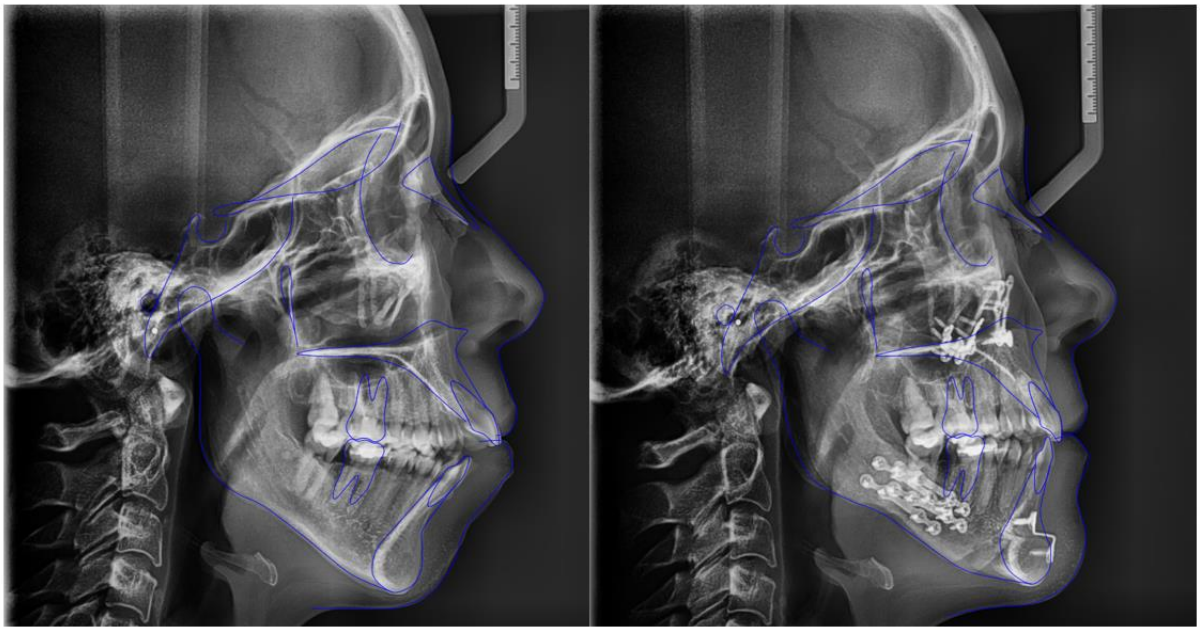
Resim 1. Tedavi öncesi intraoral ve ekstraoral kayıtlar



Resim 2. Cerrahi öncesi ortodontik dekompanzasyon aşamasına ait intraoral görüntüler



Resim 3. Çift çene ortognatik cerrahi ve genioplasti sonrası intraoral ve ekstraoral görüntüler



Resim 4. Tedavi öncesi ve tedavi sonrası lateral sefalometrik radyografilerin karşılaştırılması



Resim 5. Tedavi öncesi ve tedavi sonrası cephe, profil ve gülümseme fotoğraflarının karşılaştırılması

3. TARTIŞMA

Bu vaka raporunda, vertikal maksiller fazlalık, gummy smile, hiperdiverjan iskeletsel patern, mandibular retrognati ve iskeletsel Sınıf II maloklüzyona sahip erişkin bir hastanın çekimli ortodontik dekompanzasyon, çift çene ortognatik cerrahisi ve genioplasti ile tedavisi sunulmuştur. İskeletsel ve dentoalveoler problemlerin birlikte bulunduğu bu tür erişkin olgularda ortodontik ve cerrahi tedavinin birlikte planlanması, fonksiyonel oklüzyonun sağlanması ve yüz estetiğinin iyileştirilmesi açısından önem taşımaktadır.[3,5]

Ortognatik cerrahi öncesinde dental dekompanzasyon, keserlerin iskeletsel kaidelerine göre uygun konuma getirilmesi ve planlanan cerrahi hareketlerin gerçekleştirilebilmesi açısından önemlidir. Presürjikal dönemde yeterli dekompanzasyon sağlanamamasının cerrahi düzeltme miktarını sınırlayabileceği bildirilmiştir.[11] Sunulan vakada üst ve alt keserlerdeki ileri derecede protrüzyon ve proklinasyon nedeniyle 14, 24, 34 ve 44 numaralı birinci premolarlar çekilmiş ve keserlerin retraksiyonu ile cerrahi öncesi dekompanzasyon sağlanmıştır. Tedavi sonunda U1-NA değerinin 28,5°/10,8 mm'den 17°/4,3 mm'ye, L1-NB değerinin ise 37,5°/16,2 mm'den 17,5°/6,1 mm'ye gerilemesi elde edilen dentoalveoler değişimi göstermektedir.

Vertikal maksiller fazlalık ve buna bağlı aşırı gingival görünümün tedavisinde Le Fort I osteotomisi ile maksiller impaksiyon etkili bir cerrahi yaklaşımdır.[12] Maksillanın superior yönde yeniden konumlandırılması aynı zamanda ortognatik cerrahinin stabil hareketlerinden biri olarak bildirilmiştir.[5] Sunulan vakada maksilla anterior bölgede 7 mm, posterior bölgede 4,5 mm impakte edilmiş ve 2 mm ilerletilmiştir. Tedavi sonunda FMA'nın 39,1°'den 33,5°'ye ve alt anterior yüz yüksekliğinin 103 mm'den 97,5 mm'ye azalması vertikal yüz boyutlarında belirgin iyileşme sağlandığını göstermektedir.

İskeletsel Sınıf II olgularda maksiller impaksiyon ile mandibular ilerletmenin birlikte uygulanmasının sagittal ve vertikal iskeletsel ilişkinin düzeltilmesinde etkili olduğu ve kabul edilebilir stabilite gösterdiği bildirilmiştir.[13] Sunulan vakada mandibular retrognatinin düzeltilmesi amacıyla BSSRO ile mandibula 9 mm ilerletilmiştir. Bunun sonucunda SNB 70,8°'den 77,8°'ye yükselirken ANB 8,6°'den 3,4°'ye gerilemiş ve sagittal iskeletsel ilişki belirgin şekilde iyileşmiştir.

Güncel bir sistematik derlemede de iskeletsel Sınıf II olgularda mandibular ilerletme ve bimaksiller cerrahinin genel olarak yüksek stabilite gösterdiği, ancak mevcut kanıtların sınırlı olduğu bildirilmiştir.[14] Mandibular ilerletmeye ek olarak çene ucu projeksiyonunun artırılması amacıyla ilerletici genioplasti uygulanması, alt yüz ve profil estetiğinin iyileştirilmesine katkı sağlamaktadır. Sunulan vakada 9 mm mandibular ilerletmeye ek olarak çene ucu 3–4 mm öne alınmış ve Pog-N Perp değeri −21,4 mm'den −2,9 mm'ye ulaşmıştır. Bu değişim mandibular ilerletme ve genioplastinin kombine etkisiyle çene ucu projeksiyonunda belirgin iyileşme sağlandığını göstermektedir. Genioplastinin uzun dönem takiplerinde de ilerletme sonrası iskeletsel ve yumuşak doku sonuçlarının genel olarak stabil olduğu bildirilmiştir.[15] Sonuç olarak, çekimli ortodontik dekompanzasyon ile diferansiyel maksiller impaksiyon, mandibular ilerletme ve genioplastinin birlikte uygulanması sonucunda sagittal ve vertikal iskeletsel uyumsuzluk düzeltilmiş, gingival görünüm azaltılmış ve daha dengeli bir yüz profili elde edilmiştir. Bununla birlikte tek bir olgunun sunulması ve uzun dönem takip verilerinin bulunmaması çalışmanın temel kısıtlılıklarını oluşturmaktadır.

4. SONUÇ

Vertikal maksiller fazlalık, gummy smile, mandibular retrognati ve iskeletsel Sınıf II maloklüzyonun birlikte görülmesi, erişkin hastalarda multidisipliner yaklaşım gerektiren kompleks dentofasiyal deformitelerdendir. Sunulan olguda çekimli ortodontik dekompanzasyon ile üst ve alt keserlerdeki belirgin protrüzyon azaltılmış; ardından uygulanan diferansiyel maksiller impaksiyon, mandibular ilerletme ve genioplasti ile sagittal ve vertikal iskeletsel uyumsuzluk başarılı şekilde düzeltilmiştir. Tedavi sonunda gingival görünümde azalma, mandibula ve çene ucu projeksiyonunda artış, daha dengeli yüz profili ve fonksiyonel oklüzal ilişkiler elde edilmiştir. Bu vaka, uygun hasta seçimi ve disiplinler arası tedavi planlaması ile çekimli ortodontik dekompanzasyon ve çift çene ortognatik cerrahisinin genioplasti ile kombinasyonunun kompleks iskeletsel Sınıf II olgularda fonksiyonel ve estetik açıdan başarılı klinik sonuçlar sağlayabileceğini göstermektedir.

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DOSE-DEPENDENT VASCULAR TOLERABILITY OF HYDROCORTISONE IN THE IN OVO CHORIOALLANTOIC MEMBRANE MODEL: A FILTER-DISC-BASED STUDY

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Aim
The chick chorioallantoic membrane (CAM) model is a rapid, cost-effective, highly vascularized, and ethically advantageous *in ovo* platform for evaluating local vascular responses and preliminary biocompatibility. This study aimed to investigate the acute and 24-hour vascular tolerability of hydrocortisone at different concentrations using filter-disc-mediated local application and to determine a preliminary dose range for subsequent *in ovo* studies.

Material and Method
Fertilized chicken eggs were disinfected with 70% ethanol, candled, and incubated at 37 °C and 70% relative humidity with periodic turning. Approximately 3 mL of albumen was removed on embryonic day 3. On day 9, a shell window was opened, and viable eggs were randomly allocated to PBS control, 100 µM hydrocortisone, and 1000 µM hydrocortisone groups (n=7). Sterile filter-paper discs loaded with 50 µL of the corresponding solution were placed on vascularized CAM regions. CAMs were imaged using a stereomicroscope equipped with a digital camera immediately after application and at 24 hours. The images were descriptively evaluated for hemorrhage, vascular lysis, coagulation, vascular integrity, capillary visibility, avascular zone formation, and local morphological changes.

Results
Neither hydrocortisone concentration induced acute hemorrhage, vascular lysis, or coagulation. After 24 hours, the integrity of the main vessels and surrounding capillary networks was preserved, with no overt necrosis or clearly demarcated avascular zones. Mild localized changes were observed at some disc margins.

Conclusion
Filter-disc-mediated application of 100 and 1000 µM hydrocortisone was well tolerated by the CAM and caused no overt acute or delayed vascular damage. These concentrations may provide a suitable preliminary range for subsequent *in ovo* dose-optimization and pharmacological studies.
Keywords: Hydrocortisone, chorioallantoic membrane, *in ovo*, vascular tolerability.

Introduction
The Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM) was developed by Luepke and Kemper for the assessment of ocular irritation potential [1]. The method uses the highly vascularized chorioallantoic membrane (CAM) of fertilized chicken eggs to evaluate acute vascular responses to test substances and thereby estimate their irritation potential [2]. HET-CAM offers a rapid, relatively low-cost alternative that can reduce the need for conventional animal experimentation.
The assay is based on the evaluation of vascular reactions, including lysis, hemorrhage, and coagulation, following application of liquid or solid test substances to the CAM surface. Because these responses correlate with ocular irritation, HET-CAM has been widely used as an alternative or complementary approach to the Draize rabbit eye irritation test [3].
This study aimed to evaluate the acute and 24-hour vascular tolerability of hydrocortisone at different concentrations using filter-disc-mediated local application and to determine a preliminary dose range for subsequent *in ovo* studies.

Materials And Methods
Determination of Vascular Irritation Using the HET-CAM Assay
Egg Preparation and CAM Access: Fertilized chicken eggs (embryonic day 0, ED0) were obtained from a local poultry farm in Tavas, Denizli, Türkiye.

The eggs were inspected for cracks or visible damage, disinfected with a sterile cloth moistened with 70% ethanol, and candled to identify and mark the air sac. They were subsequently incubated at 37 °C and 70% relative humidity with automatic periodic rotation to support normal embryonic development. To facilitate chorioallantoic membrane (CAM) development and subsequent access, a small opening was created in each egg to allow the membrane to detach and descend. The eggs were then inverted, with the marked air sac positioned downward, and incubation was continued under the same conditions. On embryonic day 3 (ED3), approximately 3 mL of albumen was aseptically removed using a sterile syringe. The eggs were subsequently returned to the incubator and maintained at 37 °C and 70% relative humidity until treatment.

Experimental Groups, Application, Imaging, and Evaluation

On embryonic day 9 (ED9), viable eggs were randomly allocated to three experimental groups: PBS control, 100 µM hydrocortisone, and 1000 µM hydrocortisone (n=7 per group). Sterile filter-paper discs were loaded with 50 µL of the corresponding solution and carefully placed onto highly vascularized regions of the CAM.

Acute vascular responses, including hemorrhage, vascular lysis, and coagulation, were evaluated during the first 0–300 s following application. CAMs were imaged immediately after treatment and again at 24 h using a stereomicroscope equipped with a digital camera. The resulting images were descriptively assessed for hemorrhage, vascular lysis, coagulation, overall vascular integrity, capillary visibility, avascular zone formation, and local morphological changes surrounding the application site.

RESULTS AND DISCUSSION

No acute vascular irritation was observed in the PBS control or hydrocortisone-treated groups during the initial 0–300 s period. Neither 100 µM nor 1000 µM hydrocortisone induced hemorrhage, vascular lysis, or coagulation following filter-disc-mediated application. The PBS control group likewise showed no acute adverse vascular response.

Representative 0 h and 24 h images showed that the main vessels and surrounding capillary networks were largely preserved in all groups. In the PBS control group, no overt hemorrhage, necrotic appearance, or clearly demarcated avascular zone was observed at 24 h, although mild changes were occasionally noted at the disc margins, likely related to local mechanical contact **(Figure 1)**.

A similar vascular pattern was observed in the hydrocortisone-treated groups. In both the 100 µM and 1000 µM groups, vascular integrity was maintained at 24 h, with no clear destructive vascular response or extensive avascular area. Mild localized morphological changes were observed in some specimens but were not associated with marked vascular damage **(Figure 2 and Figure 3)**.

The absence of hemorrhage, vascular lysis, and coagulation in the acute phase, together with preserved vascular morphology at 24 h, indicates favorable local vascular tolerability of hydrocortisone at the tested concentrations. Accordingly, 100 and 1000 µM may represent suitable preliminary concentrations for further *in ovo* pharmacological studies.

The main limitations of the study were the descriptive nature of the image evaluation and minor variations in imaging angle, illumination, and magnification. In addition, the filter-paper disc itself may have contributed to subtle local changes at the application site.

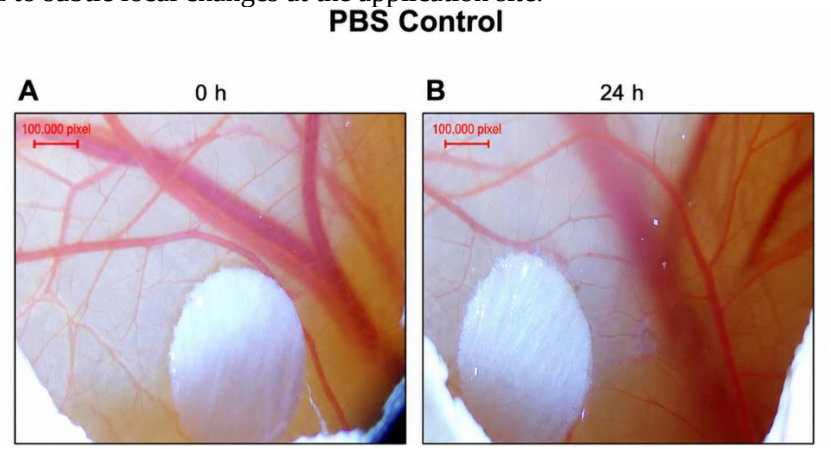


Figure 1. Representative CAM images of the PBS control group immediately after application (0 h) and at 24 h.

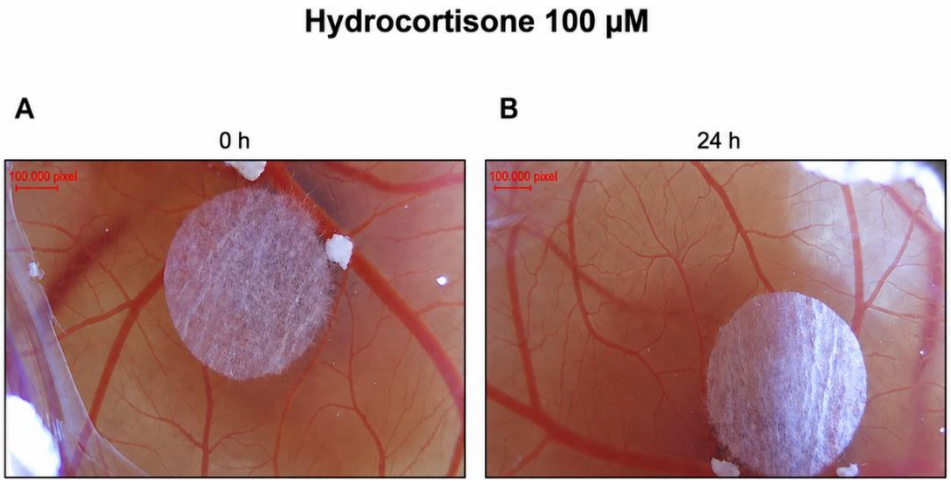


Figure 2. Representative CAM images of the 100 µM hydrocortisone group immediately after application (0 h) and at 24 h.

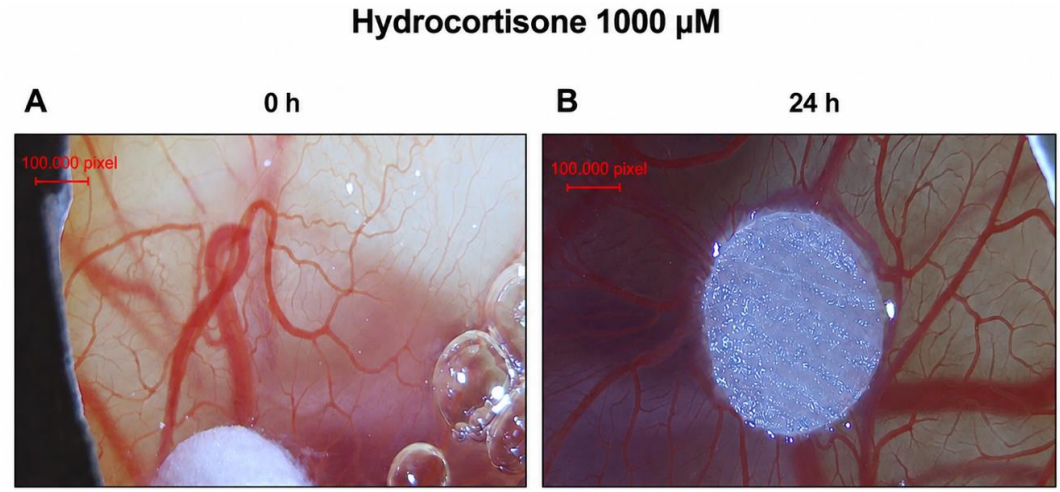


Figure 3. Representative CAM images of the 1000 µM hydrocortisone group immediately after application (0 h) and at 24 h.

Recent studies further support the applicability of the HET-CAM model for the assessment of ocular and local vascular tolerability. Mecheri et al. evaluated a broad range of topical cosmetic formulations using HET-CAM and emphasized the value of vascular endpoints such as hemorrhage, lysis, and coagulation for identifying irritation potential [4]. Similarly, Çoban et al. incorporated HET-CAM into the ocular safety assessment of a lacosamide-loaded in situ gel and reported concordant findings with complementary in vitro and in vivo evaluations [5]. In this context, the absence of acute vascular injury and the preservation of CAM architecture observed in the present study are consistent with the use of HET-CAM as a sensitive preliminary platform for evaluating local tolerability. However, because the present investigation focused primarily on morphological endpoints, future studies incorporating quantitative vascular analysis and additional concentrations would provide a more comprehensive characterization of hydrocortisone-related vascular effects.

Conclusion

The present study demonstrated that filter-disc-mediated application of hydrocortisone at 100 and 1000 µM was well tolerated in the HET-CAM model. Neither concentration induced acute hemorrhage, vascular lysis, or coagulation, and the overall vascular architecture remained preserved after 24 h. Although mild localized changes were observed around some application sites, no overt vascular damage or extensive avascular zone formation was detected. These findings suggest that both concentrations may represent suitable preliminary dose levels for subsequent *in ovo* pharmacological studies. Further investigations incorporating quantitative vascular analysis and additional dose levels would help to define the vascular effects of hydrocortisone more comprehensively.

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TRAVMAYA BAĞLI MAKSİLLER SANTRAL KESİCİ EKSİKLİĞİNİN ORTODONTİK YÖNETİMİ: OLGU SUNUMU

ORTHODONTIC MANAGEMENT OF A MISSING MAXILLARY CENTRAL INCISOR FOLLOWING TRAUMA: A CASE REPORT

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ÖZET

Amaç: Travmaya bağlı maksiller santral kesici diş kayıpları, büyüme ve gelişim dönemindeki hastalarda estetik, fonksiyonel ve psikososyal sorunlara yol açabilmektedir. Bu hastalarda implant tedavisi büyüme tamamlanıncaya kadar uygun olmadığından, ortodontik boşluk kapatılması önemli bir tedavi alternatifi olarak değerlendirilmektedir. Bu olgu sunumunun amacı, travmaya bağlı bilateral maksiller santral kesici diş kaybı bulunan büyüme ve gelişim dönemindeki bir hastada tüm üst ark mezializasyonu ile ortodontik boşluk kapatılması ve direkt kompozit build-up restorasyonları ile gerçekleştirilen multidisipliner tedavinin klinik ve radyografik sonuçlarını sunmaktır.

Materyal ve Yöntem

Travmaya bağlı 11 ve 21 numaralı dişlerini kaybeden hastada yapılan klinik muayenede bilateral maksiller santral kesici diş eksikliği, anterior bölgede estetik kayıp ve maksiller arkta boşluklar saptandı. Tedavi kapsamında sabit ortodontik tedavi ile tüm üst dental ark kontrollü olarak mezialize edildi, boşluklar tamamen kapatıldı ve lateral kesici dişler santral kesici pozisyonuna taşındı. Kaninlerin mezializasyonu ve ekstrüzyonu sonrasında selektif mine möllemesi ile lateral kesici morfolojisi kazandırıldı. Ardından estetik rehabilitasyon amacıyla direkt kompozit build-up restorasyonları uygulandı.

Bulgular

Tedavi sonunda anterior estetik belirgin olarak iyileşti, fonksiyonel overjet ve overbite elde edildi, dental ark bütünlüğü korundu ve implant gereksinimi ortadan kaldırıldı. Radyografik değerlendirmede kök paralelliğinin yeterli olduğu, periodontal dokuların korunduğu ve oklüzal ilişkinin stabil olduğu gözlendi.

Sonuç: Büyüme ve gelişim dönemindeki travmaya bağlı maksiller santral kesici diş kayıplarında tüm üst ark mezializasyonu ile ortodontik boşluk kapatılması ve direkt kompozit build-up restorasyonlarının birlikte uygulanması; estetik, fonksiyon ve periodontal sağlık açısından başarılı ve konservatif bir tedavi seçeneği olarak değerlendirilebilir.

Anahtar Kelimeler: Travmatik diş kaybı, tüm ark mezializasyonu, sabit ortodontik tedavi, multidisipliner tedavi.

ABSTRACT

Objective: Traumatic loss of the maxillary central incisors may result in significant esthetic, functional, and psychosocial problems, particularly in patients during the growth and developmental period. Since implant therapy is generally contraindicated until craniofacial growth is complete, orthodontic space closure is considered an important treatment alternative in these patients. The aim of this case report was to present the clinical and radiographic outcomes of a multidisciplinary treatment involving orthodontic space closure through mesialization of the entire maxillary dentition followed by direct composite build-up restorations in a growing patient with traumatic bilateral loss of the maxillary central incisors.

Materials and Methods
Clinical examination of a patient with traumatic loss of teeth 11 and 21 revealed bilateral absence of the maxillary central incisors, esthetic impairment in the anterior region, and residual spaces within the maxillary arch. Comprehensive fixed orthodontic treatment was performed to achieve controlled mesialization of the entire maxillary dentition, resulting in complete orthodontic space closure and repositioning of the lateral incisors into the central incisor positions. Following mesialization and extrusion of the canines, selective enamel recontouring was performed to establish lateral incisor morphology. Subsequently, direct composite build-up restorations were placed to achieve esthetic rehabilitation.

Results
At the completion of treatment, anterior esthetics were markedly improved, functional overjet and overbite were established, dental arch integrity was preserved, and the need for implant therapy was eliminated. Radiographic evaluation demonstrated satisfactory root parallelism, preservation of the periodontal tissues, and stable occlusal relationships.

Conclusion
Orthodontic space closure through mesialization of the entire maxillary dentition combined with direct composite build-up restorations may be considered a successful and conservative treatment approach for traumatic loss of the maxillary central incisors in growing patients, providing favorable esthetic, functional, and periodontal outcomes.
Keywords: Traumatic tooth loss; Full arch mesialization; Fixed orthodontic treatment; Multidisciplinary treatment.

GİRİŞ
Travmatik dental yaralanmalar, çocukluk ve adölesan dönemde en sık karşılaşılan ağız-diş sağlığı problemleri arasında yer almakta olup, özellikle maksiller anterior bölgede meydana gelen diş kayıpları fonksiyon, estetik, fonasyon ve psikososyal gelişim üzerinde önemli olumsuz etkiler oluşturabilmektedir. Maksiller santral kesici dişler, dental ark içerisindeki konumları nedeniyle travmaya en fazla maruz kalan dişler olup, travmalar sonucunda avülsiyon veya restorasyonu mümkün olmayan kron-kök kırıkları nedeniyle kaybedilebilmektedir.[1,2]
Büyüme ve gelişim döneminde meydana gelen anterior diş kayıplarının tedavisi, yalnızca eksik dişin yerine konulmasını değil, aynı zamanda alveoler kemiğin korunmasını, periodontal dokuların devamlılığını, estetik gülüşün yeniden oluşturulmasını ve fonksiyonel oklüzyonun sağlanmasını hedeflemektedir. Bu nedenle tedavi planlamasında hastanın kronolojik yaşı, büyüme potansiyeli, eksikliğin lokalizasyonu, alveoler kemik miktarı, oklüzal ilişkiler ve uzun dönem prognoz birlikte değerlendirilmelidir.[2,3]
Büyümesi devam eden hastalarda dental implant uygulamaları, implantın ankiloze olabilmesi ve çevre alveoler kemiğin büyümesine eşlik edememesi nedeniyle önerilmemektedir. Kraniyofasiyal büyüme tamamlanmadan yerleştirilen implantlar zaman içerisinde infraoklüzyon, estetik bozukluk, gingival seviyelerde uyumsuzluk ve alveoler gelişimde yetersizlik gibi komplikasyonlara yol açabilmektedir. Bu nedenle genç hastalarda implant tedavisi çoğunlukla büyüme tamamlanıncaya kadar ertelenmekte ve bu süreçte alternatif tedavi seçenekleri değerlendirilmektedir.[4,5]
Anterior diş eksikliklerinin tedavisinde hareketli veya sabit protetik restorasyonlar, adeziv köprüler, ototransplantasyon, implant destekli restorasyonlar ve ortodontik boşluk kapatma tedavileri uygulanabilmektedir. Son yıllarda biyolojik dokuların korunmasını esas alan minimal invaziv yaklaşımların önem kazanmasıyla birlikte ortodontik boşluk kapatma tedavisi, özellikle büyüme gelişim dönemindeki hastalarda başarılı bir tedavi alternatifi olarak kabul edilmektedir. Bu yaklaşım sayesinde alveoler kemik hacmi korunmakta, periodontal dokular desteklenmekte ve implant gereksinimi ortadan kaldırılabilmektedir.[6,7]
Ortodontik boşluk kapatma tedavisinde yalnızca eksik boşluğun kapatılması yeterli olmayıp, anterior estetiğin yeniden oluşturulabilmesi amacıyla diş morfolojisinin restoratif işlemlerle yeniden şekillendirilmesi gerekmektedir. Lateral kesici dişlerin santral kesici pozisyonuna taşınması ve kaninlerin lateral kesici morfolojisine dönüştürülmesi amacıyla uygulanan direkt kompozit build-up restorasyonları; minimal invaziv olmaları, diş dokusunu korumaları, ekonomik olmaları ve gerektiğinde

kolaylıkla revize edilebilmeleri nedeniyle sıklıkla tercih edilmektedir. Ortodonti ve restoratif diş tedavisinin birlikte planlandığı multidisipliner yaklaşımlar sayesinde doğal diş dokuları korunurken yüksek estetik ve fonksiyonel başarı elde edilebilmektedir.[5,6]

Bu olgu sunumunun amacı, travmaya bağlı bilateral maksiller santral kesici diş kaybı bulunan büyüme gelişim dönemindeki bir hastada, tüm maksiller arkın ortodontik mezializasyonu ile boşlukların tamamen kapatılması ve direkt kompozit build-up restorasyonları ile estetik rehabilitasyonun gerçekleştirildiği multidisipliner tedavi yaklaşımının klinik, radyografik ve estetik sonuçlarını güncel literatür eşliğinde sunmaktır.

Vaka Sunumu

Kronolojik yaşı 10 yıl 2 ay olan erkek hasta, çocukluk döneminde geçirdiği travma sonucunda maksiller santral kesici dişlerini kaybetmesi ve ön bölgede oluşan estetik bozukluk nedeniyle kliniğimize başvurmuştur. Alınan anamnezde travmanın 8 ay önce meydana geldiği, travma sonrasında 11-21 nolu dişlerin avülse olduğu ve kaybedildiği ve hastanın sistemik olarak sağlıklı olduğu öğrenilmiştir. Klinik değerlendirmede cephede simetrik görünüm, konveks profil, kompotent dudak ve anterior diş eksikliğine bağlı olarak gülüş estetiğinde olumsuz etkilenme olduğu gözlenmiştir. İntraoral muayenede anterior bölgede 7 mm genişliğinde dişsiz boşluk bulunduğu ve komşu lateral dişlerde avülsiyon bölgesinde devrilme/rotasyon izlendiği belirlenmiştir. Posterior bölgede Sınıf II kanin ve molar ilişki tespit edilmiştir. Maksiller ve mandibular ark formlarının korunduğu, periodontal dokuların sağlıklı olduğu ve ağız hijyeninin ortodontik tedaviye engel oluşturacak düzeyde olmadığı değerlendirilmiştir

Radyografik incelemede maksiller santral kesici dişlerin eksik olduğu, alveoler kemik yüksekliği ve genişliğinin korunduğu, komşu dişlerde kök rezorpsiyonu veya periapikal patoloji bulunmadığı belirlenmiştir. Lateral sefalometrik analizde hastanın iskeletsel sınıf 1 ilişkiye sahip olduğu (SNA: 79.9°, SNB: 76.3°, ANB: 3.6°), vertikal büyüme paterninin olduğu (SN-GoGn: 36.9°) ve üst ile alt keser eğimlerinin tedavi planlamasına uygun olduğu saptanmıştır. El-bilek radyografisinde büyüme ve gelişimin MP3= düzeyde devam ettiği değerlendirilmiştir.

Hastaya uygulanabilecek tedavi alternatifleri arasında hareketli parsiyel protez, adeziv köprü, büyüme tamamlandıktan sonra implant destekli restorasyon, ototransplantasyon ve ortodontik boşluk kapatılması ayrıntılı olarak anlatılmıştır. Hastanın büyüme gelişiminin devam etmesi, alveoler kemiğin korunmasının hedeflenmesi ve implant tedavisinin ilerleyen yaşlara ertelenmesi amacıyla tüm ark mezializasyon ile ortodontik boşluk kapatılması tercih edilmiştir. Tedavi planı hasta ve ebeveynine ayrıntılı olarak açıklanmış ve yazılı onam alınmıştır.

Sabit ortodontik tedavi 0.022” slot DAMON 3MX braketler (Ormco Company, San Diego, CA, ABD) kullanıldı. Seviyeleme ve hizalama aşaması sırasıyla 0.013”, 0.016”, 0.014x0.025”, 0.018x0.025” CuNiTi, 0.016x0.022” ve 0.018x0.025” SS teller kullanıldı. Maksiller dental arkın en-masse mezializasyonu amacıyla köşeli SS tellerde 3/16” 6 oz intermaksiller Sınıf III komponentli elastiklerle kuvvet uygulandı. Tedavi süresince ankraj kaybı ve herhangi bir biyolojik komplikasyon izlenmedi.

Ortodontik boşlukların tamamen kapatılmasının ardından lateral kesici dişler santral kesici pozisyonuna taşınmış, kanin dişler ise ekstrüzyon ve selektif mine möllemesi ile lateral kesici fonksiyonunu üstlenecek şekilde yeniden konumlandırıldı. İdeal estetik görünümün sağlanabilmesi amacıyla anterior keserler arasında boşluklar oluşturularak direkt kompozit build-up restorasyonları uygulanarak lateral kesici dişlere santral kesici, kanin dişlere ise lateral kesici morfolojisi kazandırıldı. Gingival konturlar bonding aşamasında braketlerin final oklüzyon konumuna yerleştirilmesi yöntemiyle düzenlenmiş ve estetik gülüş hattı optimize edilmiştir.

Toplam tedavi süresi 18 ay olarak tamamlanmıştır. Tedavi sonunda anterior boşlukların tamamen kapatıldığı, ark devamlılığının sağlandığı, estetik gülüş hattının yeniden oluşturulduğu ve fonksiyonel overjet ile overbite'ın elde edildiği gözlenmiştir. Tedavi sonrası sefalometrik analizde SNA değeri 79.46 SNB değeri 75.86 ANB değeri 3.6 Go-Gn to SN değeri 35.6 ölçülmüş, panoramik radyografide kök paralelliğinin yeterli olduğu, periodontal dokuların sağlığını koruduğu ve herhangi bir kök rezorpsiyonu gelişmediği belirlenmiştir. Tedavi süresince herhangi bir komplikasyon izlenmemiştir. Hastanın estetik beklentileri karşılanmış, fonksiyonel ve biyolojik açıdan başarılı sonuçlar elde edilmiştir.

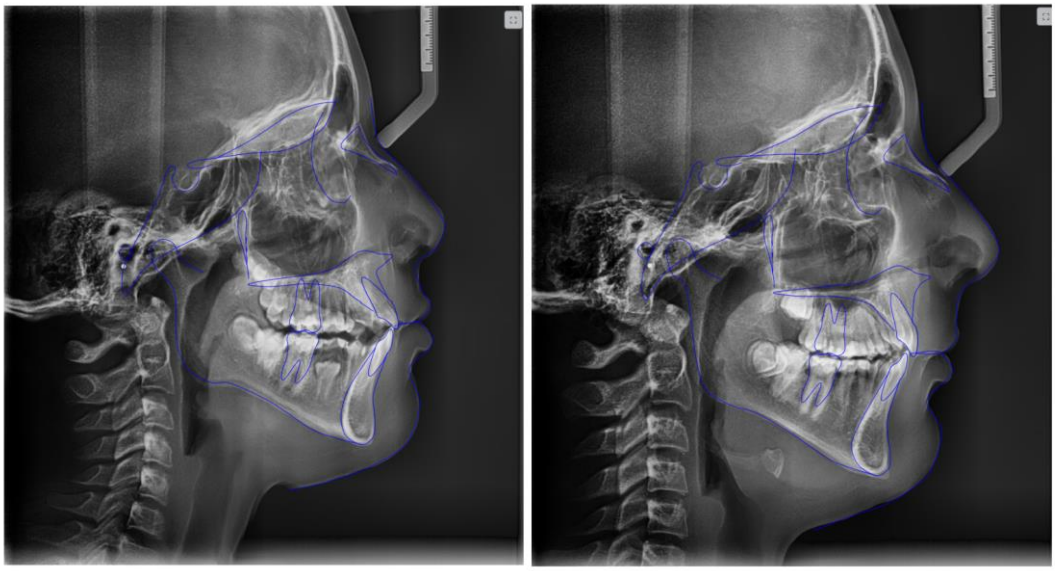
Klinik Görseller:
Resim 1. Tedavi öncesi intraoral ve ekstraoral klinik görüntüler.
Resim 2. Tedavi sonrası intraoral ve ekstraoral klinik görüntüler.
Resim 3. Tedavi öncesi ve sonrası lateral sefalometrik röntgenler.
Resim 4. Tedavi öncesi ve sonrası lateral panoramik röntgenler.



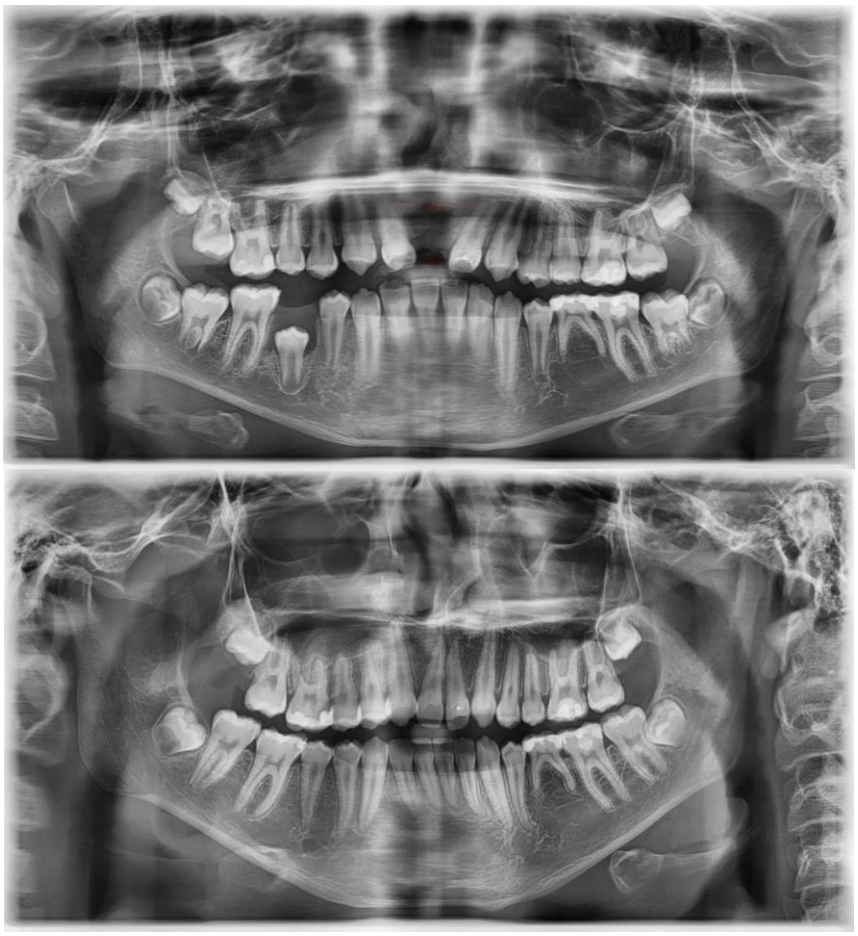
Resim 1. Tedavi öncesi intraoral ve ekstraoral klinik görüntüler.



Resim 2. Tedavi sonrası intraoral ve ekstraoral klinik görüntüler.



Resim 3. Tedavi öncesi ve sonrası lateral sefalometrik röntgenler.



Resim 4. Tedavi öncesi ve sonrası lateral panoramik röntgenler.

Tedavi Yaklaşımları

Travmaya bağlı maksiller santral kesici diş kayıpları, özellikle büyüme ve gelişim dönemindeki hastalarda estetik, fonksiyonel ve psikososyal açıdan önemli sorunlara neden olmaktadır. Bu olgularda tedavi planlaması; hastanın yaşı, büyüme potansiyeli, alveoler kemik miktarı, yumuşak doku profili, oklüzyon, mevcut diş dizilimi ve hastanın uzun dönem beklentileri göz önünde bulundurularak multidisipliner bir yaklaşımla yapılmalıdır.[2]

Maksiller santral diş eksikliklerinin rehabilitasyonunda implant destekli restorasyonlar, sabit protetik restorasyonlar, ototransplantasyon ve ortodontik boşluk kapatma başlıca tedavi seçenekleri arasında yer almaktadır.[3,7] Bununla birlikte büyüme gelişimin devam ettiği hastalarda implant uygulamaları, alveoler büyümenin sürmesi nedeniyle infraoklüzyon gelişimi ve estetik problemlere yol açabileceğinden kesin büyüme tamamlanıncaya kadar önerilmemektedir.[4]

Ortodontik boşluk kapatma yaklaşımı ise özellikle genç hastalarda biyolojik dokuların korunması, alveoler kemik hacminin devamlılığının sağlanması, cerrahi girişim gerektirmemesi ve uzun dönem stabilite açısından önemli avantajlar sunmaktadır.[6,7] Bu yöntemde lateral kesici dişlerin santral kesici pozisyonuna, kanin dişlerin ise lateral kesici pozisyonuna ortodontik olarak taşınmasını takiben estetik ve fonksiyonel rehabilitasyon kompozit rezin restorasyonlar veya porselen restorasyonlar ile tamamlanabilmektedir.[6]

Ortodontik boşluk kapatma tedavisinde başarılı sonuç elde edilebilmesi için kök paralelliğinin sağlanması, gingival konturların yeniden düzenlenmesi, kaninlerin tork ve rotasyonlarının kontrol edilmesi, oklüzal ilişkilerin optimize edilmesi ve anterior rehberliğin yeniden oluşturulması büyük önem taşımaktadır. Ayrıca restoratif işlemler sırasında diş morfolojisinin yeniden şekillendirilmesi ile estetik oranların korunması ve doğal bir gülüş estetiğinin elde edilmesi amaçlanmaktadır.[5,6]

Sunulan bu olguda, büyüme gelişimi devam eden ve travmaya bağlı bilateral maksiller santral kesici diş kaybı bulunan hastada implant tedavisinin ertelenmesi yerine ortodontik boşluk kapatma tedavisi tercih edilmiştir. Ortodontik diş hareketleri ile lateral kesici dişler santral kesici pozisyonuna, kanin dişler ise lateral kesici pozisyonuna taşınmış; tedavi sonunda kompozit rezin restorasyonlar ile diş morfolojisi yeniden şekillendirilerek fonksiyonel oklüzyon, periodontal sağlık ve tatmin edici estetik sonuçlar elde edilmiştir.[7]

Tartışma

Maksiller santral kesici dişler, estetik ve fonksiyon açısından dentisyonun en önemli elemanları arasında yer almakta olup, bu dişlerin travmaya bağlı kaybı özellikle büyüme ve gelişim dönemindeki bireylerde önemli klinik problemlere neden olmaktadır. Travma sonrası tedavi planlamasında hastanın yaşı, büyüme potansiyeli, alveoler kemik durumu, oklüzal ilişkileri ve uzun dönem estetik beklentileri birlikte değerlendirilmelidir. Büyümesi devam eden hastalarda uygulanacak tedavi yalnızca mevcut estetik sorunu gidermeyi değil, aynı zamanda alveoler kemiğin gelişimini koruyarak gelecekte oluşabilecek fonksiyonel ve estetik problemlerin önlenmesini de hedeflemelidir.[2,8]

Travmatik anterior diş kayıplarında implant destekli restorasyonlar erişkin hastalarda başarılı tedavi seçenekleri arasında kabul edilmesine rağmen, büyümesi devam eden bireylerde implantların alveoler büyümeye uyum sağlayamaması önemli bir dezavantaj oluşturmaktadır. Komşu dişlerin erüpsiyonunun ve alveoler proses gelişiminin devam etmesi sonucunda implant restorasyonları zamanla infraoklüzyonda kalabilmekte, gingival konturlarda uyumsuzluk gelişebilmekte ve estetik sonuçlar olumsuz etkilenebilmektedir. Bu nedenle güncel kılavuzlar, büyüme tamamlanıncaya kadar implant tedavisinin ertelenmesini ve mümkün olduğunda doğal dentisyonun korunmasına yönelik alternatif tedavi seçeneklerinin değerlendirilmesini önermektedir.[4,8]

Bu doğrultuda ortodontik boşluk kapatma, uygun endikasyon varlığında büyüme dönemindeki hastalar için biyolojik ve konservatif bir tedavi alternatifi olarak öne çıkmaktadır. Ortodontik diş hareketi sırasında periodontal ligament ve alveoler kemikte eş zamanlı remodelasyon meydana gelmesi, sert ve yumuşak dokuların dişlerle birlikte yeni pozisyonlarına adapte olmasına olanak sağlamakta; böylece alveoler kemik hacmi korunurken gelecekte gelişebilecek sert ve yumuşak doku defektlerinin oluşma riski azaltılmaktadır.[7,9]

Sunulan olguda da hastanın büyüme potansiyelinin devam etmesi ve bilateral maksiller santral kesici dişlerin kaybına bağlı geniş anterior boşlukların bulunması nedeniyle implant tedavisi yerine tüm maksiller arkın kontrollü mezializasyonu ile ortodontik boşluk kapatma tercih edilmiştir. Tedavi sonunda elde edilen kök paralelliği, sağlıklı periodontal dokular ve fonksiyonel oklüzal ilişkiler, uygulanan biyomekaniğin başarılı olduğunu göstermektedir.[5,9]

Ortodontik boşluk kapatma tedavisinin uzun dönem başarısı, yalnızca dişlerin eksik bölgeye taşınmasına değil, ortodontik ve restoratif tedavinin multidisipliner olarak planlanmasına da bağlıdır. Özellikle anterior bölgede komşu dişlerin substitüsyon amacıyla kullanıldığı olgularda dişlerin son pozisyonları, kök angulasyonları ve gingival konturlar restoratif rehabilitasyona uygun şekilde düzenlenmelidir.

Bu yaklaşım, minimal restoratif girişimlerle doğal dentisyona en yakın estetik sonucun elde edilmesine olanak sağlamaktadır.[5,6]

Sunulan olguda ortodontik tedavi sonrasında lateral kesici dişlere uygulanan direkt kompozit build-up restorasyonları ile santral kesici morfolojisi yeniden oluşturulmuş, kaninler ise lateral kesici formuna uygun şekilde yeniden şekillendirilmiştir. Direkt kompozit restorasyonlar; sağlıklı diş dokusunun korunmasına olanak sağlamaları, tek seansta uygulanabilmeleri, ekonomik olmaları ve gerektiğinde kolaylıkla tamir veya modifiye edilebilmeleri nedeniyle özellikle büyüme gelişimi devam eden bireylerde önemli avantajlar sunmaktadır. Bu nedenle adeziv restoratif yaklaşımlar, ortodontik boşluk kapatma tedavisini tamamlayan konservatif bir rehabilitasyon seçeneği olarak değerlendirilmektedir.[5,10]

Bu olguda tedavi sonunda sağlıklı periodontal dokuların korunması, kök paralelliğinin sağlanması ve estetik açıdan tatmin edici bir gülüş elde edilmesi, ortodontik ve restoratif tedavinin başarılı bir şekilde entegre edildiğini göstermektedir. Elde edilen sonuçlar, uygun hasta seçimi yapıldığında ortodontik boşluk kapatma yaklaşımının yalnızca estetik ve fonksiyonel beklentileri karşılamakla kalmayıp, doğal dişlerin ve periodontal dokuların korunmasına da katkı sağlayabileceğini desteklemektedir.[5,11]

Literatürde travmaya bağlı bilateral maksiller santral kesici diş kaybının tüm maksiller arkın mezializasyonu ve direkt kompozit restorasyonlarla rehabilite edildiği olgu bildirimleri bulunmaktadır. Bu yönüyle sunulan olgu, büyüme gelişimi devam eden hastalarda implant tedavisine biyolojik ve konservatif bir alternatif sunması bakımından dikkat çekmektedir. Bununla birlikte bu yaklaşımın uzun dönem stabilitesi, periodontal sağlığı ve hasta memnuniyeti üzerine yapılacak daha geniş örneklemli ve uzun süreli takip çalışmalarına ihtiyaç bulunmaktadır.[2,8]

Sonuç

Bu olguda, travmaya bağlı bilateral maksiller santral kesici diş kaybı bulunan büyüme ve gelişim dönemindeki bir hastada, tüm maksiller dentisyonun kontrollü mezializasyonu ile gerçekleştirilen ortodontik boşluk kapatma ve direkt kompozit restorasyonların kombinasyonu sonucunda başarılı estetik, fonksiyonel ve periodontal sonuçlar elde edilmiştir. Tedavi ile anterior dişsizlik boşlukları tamamen kapatılmış, doğal gülüş estetiği yeniden sağlanmış, fonksiyonel oklüzyon oluşturulmuş ve alveoler kemik ile periodontal dokular korunmuştur. Bu olgu, uygun hasta seçimi ve multidisipliner tedavi planlaması ile ortodontik boşluk kapatmanın, büyüme ve gelişim dönemindeki hastalarda implant tedavisine biyolojik ve konservatif bir alternatif oluşturabileceğini göstermektedir. Bununla birlikte, bu tedavi yaklaşımının uzun dönem stabilitesini ve periodontal başarısını değerlendirmek amacıyla daha geniş örneklemli ve uzun süreli klinik çalışmalara ihtiyaç bulunmaktadır.

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TÜRKİYE'DE ECZACI TARAFINDAN AŞI UYGULAMASI: MEVCUT DURUM ANALİZİ

PHARMACIST-ADMINISTERED VACCINATION IN TÜRKİYE: A LEGAL DOCUMENT ANALYSIS

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ÖZET

AMAÇ: Pek çok ülkede toplum eczacıları artık aşı uygulamasında aktif bir rol üstlenmektedir; ancak Türkiye'de bu uygulama yasal olarak tanımsız kalmaktadır. Bu çalışma, ilgili mevzuatı inceleyerek ve eczacıların aşılamaya ilişkin bilgi, tutum ve uygulamaları hakkındaki güncel ampirik bulguları sentezleyerek, Türkiye'de eczacı tarafından aşı uygulamasının mevcut yasal durumunu netleştirmeyi amaçlamaktadır.

MATERYAL VE YÖNTEM

Umumi Hıfzıssıhha Kanunu (No. 1593), Hemşirelik Kanunu (No. 6283), Tababet Kanunu (No. 1219) ve 2014 tarihli Eczacılar ve Eczaneler Hakkında Yönetmelik dahil olmak üzere birincil yasal metinler kullanılarak nitel bir doküman analizi yürütülmüştür. Bu kaynaklar, Türkiye'de eczacıların aşılamaya ilişkin bilgi, tutum ve uygulamalarını ele alan güncel hakemli çalışmalarla birlikte incelenmiştir.

BULGULAR

Mevzuat incelemesi, aşı uygulamasının eczacılara ne açıkça verildiğini ne de açıkça yasaklandığını göstermektedir; mevcut çerçeve bunun yerine eczacıların sorumluluklarını saklama, dağıtım ve farmakovijilans etrafında tanımlamaktadır. Güncel çalışmalar, eczacıların büyük çoğunluğunun aşı uygulaması için yasal yetkilendirmeyi desteklediğini, ancak birçoğunun aşıya özgü bilgi eksiklikleri ve anafilaksi gibi advers olayları yönetme konusunda sınırlı özgüven bildirdiğini ortaya koymaktadır. Eczacılık meslek örgütleri bu rolün yasal olarak tanınması çağrısında bulunmuş, ancak sağlık otoritelerinden resmî bir yanıt alınamamıştır.

SONUÇ

Türkiye'deki toplum eczacıları, yasal yetki olmaksızın teknik hazırlık konumundadır: aşı saklama ve danışmanlığa entegre olmakla birlikte, uygulamadan dışlanmış durumdadırlar. Eczacılar arasındaki mevcut bilgi ve eğitim eksiklikleriyle birleşen bu çözümlenmemiş yasal boşluk, yalnızca yasal değişikliğin, beraberinde bir eğitim altyapısı olmadan yetersiz kalacağını göstermektedir. Bu bulgular, eczacı tarafından aşı uygulamasına ilişkin gelecekteki karşılaştırmalı politika araştırmaları için belgelenmiş bir zemin sunmaktadır.

Anahtar Kelimeler: doküman analizi, eczacı aşı uygulaması, sağlık mevzuatı, toplum eczacılığı, Türkiye

ABSTRACT

PURPOSE

In many countries, community pharmacists now play an active role in vaccine administration, yet in Türkiye this practice remains legally undefined. This study aims to clarify the current legal status of pharmacist-administered vaccination in Türkiye by examining the relevant legislation and synthesising recent empirical findings on pharmacists' knowledge, attitudes, and practices regarding vaccination.

MATERIALS AND METHODS

A qualitative document analysis was conducted using primary legal texts, including the Public Hygiene Law (No. 1593), the Nursing Law (No. 6283), the Law on the Practice of Medicine (No. 1219), and the 2014 Regulation on Pharmacists and Pharmacies.

These sources were reviewed alongside recent peer-reviewed studies addressing pharmacists' vaccination-related knowledge, attitudes, and practices in Türkiye.

FINDINGS

The legislative review shows that vaccine administration is neither explicitly assigned to pharmacists nor explicitly prohibited; the current framework instead defines pharmacists' responsibilities around storage, dispensing, and pharmacovigilance. Recent studies indicate that most pharmacists support legal authorisation for vaccine administration, yet several also report gaps in vaccination-specific knowledge and limited confidence in managing adverse events such as anaphylaxis. Pharmacy professional associations have called for legal recognition of this role but have not received a formal response from health authorities.

CONCLUSION

Türkiye's community pharmacists occupy a position of technical readiness without legal authority: they are integrated into vaccine storage and counselling, yet excluded from administration. This unresolved legal gap, combined with existing knowledge and training gaps among pharmacists, suggests that legislative change alone would be insufficient without accompanying training infrastructure. These findings provide a documented basis for future comparative policy research on pharmacist-administered vaccination.

Keywords: community pharmacy, document analysis, health legislation, pharmacist-administered vaccination, Türkiye

GİRİŞ

Toplum eczacılarının sağlık hizmetlerindeki rolü, günümüzde ilaç temini ve danışmanlığın ötesine geçerek çeşitli halk sağlığı uygulamalarını da kapsayacak biçimde genişlemektedir. Bu uygulamalardan biri olan aşılama, son yıllarda uluslararası literatürde giderek daha fazla önem kazanan bir konu hâline gelmiştir. Otuz altı çalışmanın değerlendirildiği bir sistematik derleme ve meta-analizde, eczacıların eğitim, yönlendirme veya doğrudan aşı uygulama yoluyla aşılama sürecine katıldığı çalışmaların tamamında aşılama oranlarında artış bildirildiği görülmüştür.[1] Bununla birlikte, eczacıların aşılama hizmetlerindeki yetki ve sorumlulukları ülkeler arasında önemli farklılıklar göstermektedir. Bazı ülkelerde eczacılar geniş bir aşı yelpazesini doğrudan uygulayabilirken, bazı ülkelerde bu hizmet henüz politika geliştirme ve tartışma aşamasındadır.[2] Türkiye de ikinci grupta yer almaktadır. Toplum eczacıları aşıların temini, uygun koşullarda saklanması ve hastaların bilgilendirilmesi gibi süreçlerde aktif rol üstlenmekte, ancak eczane ortamında doğrudan aşı uygulama yetkisine sahip bulunmamaktadır. Bu çalışmada, Türkiye'de toplum eczacılarının aşı uygulamasına ilişkin mevcut yasal düzenlemelerin, konuya yönelik bilgi ve tutumlarının, ulusal aşılama sisteminin mevcut yapısının ve olası bir uygulama modeli öncesinde açıklığa kavuşturulması gereken politika alanlarının birlikte değerlendirilmesi amaçlanmıştır. Çalışma, birincil mevzuat kaynakları ile hakemli bilimsel yayınların incelenmesine dayalı bir doküman analizi olarak tasarlanmıştır. Herhangi bir birincil veri toplanmamış; mevcut mevzuat ve literatürdeki bulgular bir araya getirilerek bütüncül biçimde değerlendirilmiştir.

GELİŞME

Aşı Uygulamasına İlişkin Yasal Çerçeve

Türkiye'de toplum eczacılarının aşı uygulama yetkisini değerlendirebilmek için birbiriyle bağlantılı dört temel mevzuat düzenlemesinin birlikte ele alınması gerekmektedir. Bu düzenlemeler, mevcut sağlık mevzuatında aşılama hizmetine ilişkin görev ve yetkilerin sağlık meslekleri arasında nasıl tanımlandığını göstermektedir.

1593 sayılı Umumi Hıfzıssıhha Kanunu, Türkiye'de halk sağlığı hizmetlerinin temel yasal dayanaklarından biri olup aşılama faaliyetlerini devletin sorumluluğunda ele almaktadır.[3] Kanunun 95. maddesinde şu hüküm yer almaktadır:

"Sari hastalıklara karşı kullanılan her nevi serum ve aşılar Hükümet tarafından ihzar edilir. Hariçten getirilenlerin Sıhhat ve İçtimai Muavenet Vekaletince tayin olunan vasıf ve şartları haiz olmaları mecburidir. Dahilde beşeri serum ve aşı imali Sıhhat ve İçtimai Muavenet Vekaletinin müsaadesine ve murakabesine tabidir."

Bu hüküm, aşı ve serumların üretim ve denetiminin devlet kontrolü altında olduğunu ortaya koymaktadır. Kanunun 72. maddesinde salgın hastalıklarla mücadelede uygulanabilecek önlemler arasında "serum veya aşı tatbiki" sayılmakta, ancak bu işlemin hangi sağlık meslek mensubu tarafından gerçekleştirileceğine ilişkin açık bir düzenlemeye yer verilmemektedir. Eczacılar ise 61. madde kapsamında bildirim yükümlülüğü bulunan sağlık meslek mensupları arasında sayılmakta; 23. ve 24. maddelerde de il ve ilçe hıfzıssıhha meclislerinde görev almaktadır. Bununla birlikte, bu hükümlerin hiçbiri eczacılara doğrudan aşı uygulama yetkisi tanımamaktadır.

Hemşirelerin aşı uygulamasına ilişkin yetkisi tarihsel olarak 6283 sayılı Hemşirelik Kanunu'nun 1954 yılında yürürlüğe giren ilk hâlinin 4. maddesinin (B) bendinde açık biçimde düzenlenmiştir:[4]

"Hemşireler çiçek aşısını ve âcil hallerde icabeden pansumanları re'sen tatbik edebilecekleri gibi müdavi tabibin tavsiyesi üzerine sağlık kurumlarında veya dışarda hastalara deri altına, adale içine ve damar içine şırınga yapmaya yetkilidirler."

Bu hüküm yürürlükte olduğu dönemde hemşirelere aşı ve enjeksiyon uygulamasına ilişkin doğrudan bir yetki tanımaktaydı. Ancak söz konusu madde, 25/4/2007 tarihli ve 5634 sayılı Kanun'un 3. maddesiyle bütünüyle değiştirilmiş ve eski hüküm yürürlükten kalkmıştır.[5] Günümüzde yürürlükte olan 4. madde, hemşireleri acil durumlar dışında hekim tarafından yazılı olarak verilen tedavileri uygulamak; birey, aile ve toplumun hemşirelik bakım gereksinimlerini belirlemek, planlamak, uygulamak ve değerlendirmekle görevli ve yetkili sağlık personeli olarak tanımlamaktadır. Güncel kanun metninde aşı veya enjeksiyon gibi girişimler ayrıca sayılmamakta; ayrıntılı görev, yetki ve sorumlulukların Sağlık Bakanlığı tarafından çıkarılacak yönetmelikle düzenleneceği belirtilmektedir.

Bu düzenlemenin güncel uygulamadaki karşılığı Hemşirelik Yönetmeliği'nin Ek-3'ünde bulunan "Hemşirelik Girişimleri Listesi"nde görülmektedir. Söz konusu listede "aşı uygulama/bağışıklama", adı açıkça belirtilmiş bir hemşirelik girişimi olarak yer almaktadır.[6] İlgili girişimin yıldız işaretiyle gösterilmiş olması, ekip tarafından önceden ortak bakım planı veya protokolü oluşturulan durumlarda hemşirenin hekim istemini beklemeksizin girişimi gerçekleştirebilmesine olanak tanımaktadır. Dolayısıyla hemşirelerin aşı uygulamasına ilişkin yetkisi güncel düzenlemede de tanımlanmış olmakla birlikte, uygulamanın belirli mesleki ve kurumsal koşullar çerçevesinde ele alındığı görülmektedir.

Hekimlerin aşı uygulama yetkisi ise 1219 sayılı Tababet ve Şuabatı San'atlarının Tarzı İcrasına Dair Kanun'da aşılama özelinde ayrı bir hükümle düzenlenmemiştir.[7] Kanunun 8. maddesi hekimlere genel olarak hastalıkları tedavi etme hakkı tanımaktadır. Bu nedenle aşı uygulaması da hekimlerin genel tedavi yetkisi kapsamında değerlendirilmektedir. Aynı Kanunun 3. maddesinde yer alan cerrahi müdahalelere ilişkin sınırlamalar ise cerrahi işlemlere yönelik olup aşı uygulamasıyla doğrudan bağlantılı değildir.

Eczacıların görev ve yetkilerini ayrıntılı biçimde düzenleyen Eczacılar ve Eczaneler Hakkında Yönetmelik, 12 Nisan 2014 tarihli ve 28970 sayılı Resmî Gazete'de yayımlanmıştır. Yönetmeliğin 6. maddesinde eczacının görev ve yetkileri; ilaç hammaddelerinin temini, ilaçların hazırlanması ve hastaya sunulması, ilaç analizi, ilaçların etkililik ve güvenliliğinin izlenmesi, kalite güvencesi, ilaç kullanımına bağlı sorunlar konusunda hastaların bilgilendirilmesi, farmakovijilans ve çeşitli eczacılık faaliyetlerinin yürütülmesi gibi alanlarda tanımlanmaktadır.[8] Ancak bu görevler arasında aşı uygulaması yer almamaktadır. Buna karşılık Yönetmeliğin 40. maddesinde aşı ve serumların eczanelerde saklanmasına ilişkin koşullar açıkça düzenlenmiştir: "Bütün kimyevi ilaç hammaddeleri, hazır ilaçlar, aşı ve serumlar, Farmakopedeki özellikleri ve ambalaj üzerindeki muhafaza şartları göz önüne alınarak gerektiği gibi saklanır." Dolayısıyla mevcut mevzuat, eczanelerin aşıların temin ve saklama sürecindeki rolünü düzenlemekte; ancak eczacıya doğrudan aşı uygulama yetkisi vermemektedir.

Bu dört temel düzenleme birlikte ele alındığında, Türkiye'de eczacıların eczane ortamında aşı uygulamasına yönelik açık bir yetkilendirmenin bulunmadığı görülmektedir. Eczacının aşıların temini, saklanması ve hastaların bilgilendirilmesine ilişkin görevleri mevzuatta karşılık bulurken, doğrudan uygulayıcı rolü tanımlanmamıştır. Hemşireler açısından ise aşı uygulaması, güncel Hemşirelik Yönetmeliği'nde açıkça isimlendirilmiş bir hemşirelik girişimi olarak düzenlenmiştir.

Ulusal Aşılama Sistemi ve Eczacının Konumu

Türkiye'de aşılama hizmetlerinin temelini, yasal dayanağını 1593 sayılı Umumi Hıfzıssıhha Kanunu'ndan alan Genişletilmiş Bağışıklama Programı (GBP) oluşturmaktadır. Program kapsamında çocukların boğmaca, difteri, tetanoz, kızamık, kızamıkçık, kabakulak, tüberküloz, poliomyelit, hepatit B ve *Haemophilus influenzae* tip b gibi hastalıklara karşı ücretsiz aşılanması sağlanmaktadır. Türkiye, program kapsamında yürütülen çalışmalar sonucunda 2002 yılında çocuk felcini, 2009 yılında ise yenidoğan tetanozunu elimine etmiştir.[9]

Aşılama hizmetleri ağırlıklı olarak birinci basamak sağlık kuruluşları üzerinden sunulmaktadır. Nitekim İzmir'de yapılan bir araştırmada ebeveynlerin %99'unun çocuklarının aşılarını birinci basamak sağlık merkezlerinde yaptırdığı bildirilmiştir.[10]

Bu önemli kazanımlara rağmen, aşı tereddüdüne ilişkin geçmiş yıllardaki bazı göstergeler dikkat çekicidir. Türkiye'de aşılama oranı 2016 yılında %98 düzeyindeyken 2017 yılında %96'ya gerilemiştir. Aynı dönemde aşı reddine ilişkin beyanların sayısı da belirgin biçimde artmış; 2011 yılında 183 olan aşı ret formu sayısı 2016'da 12.000'e, 2017'de ise yaklaşık 23.000'e ulaşmıştır.[9] Bu bulgular, yüksek aşılama oranlarının korunmasının yanı sıra aşı tereddüdünün ele alınmasının da önemli bir halk sağlığı gereksinimi olduğunu göstermektedir. Toplum eczacıları, yaygın ve kolay erişilebilir sağlık profesyonelleri olmaları nedeniyle bu süreçte özellikle bilgilendirme ve danışmanlık açısından katkı sunabilecek meslek gruplarından biri olarak değerlendirilebilir.

Ulusal aşılama politikalarının güncel tartışma alanlarından biri de HPV aşısıdır. Afyonkarahisar'da 655 kadınla yürütülen kesitsel bir araştırmada HPV aşılanma oranının %7 olduğu bildirilmiştir.[11] Dünya Sağlık Örgütü'nün güncel verilerine göre HPV aşısı, 2025 yılı itibarıyla 162 ülkede ulusal bağışıklama programları veya hizmetleri kapsamında sunulmaktadır.[12] Türkiye'de ise Sağlık Bakanı Haziran 2025'te HPV aşısının öncelikle 13 yaş grubundan başlanarak 2025 yılı sonuna doğru ücretsiz sunulmasının planlandığını açıklamıştır.[13] Bununla birlikte, söz konusu açıklamanın yapıldığı dönemde program henüz uygulamaya geçirilmemiştir. Bu nedenle HPV aşısına ilişkin kapsam ve uygulama takvimi, güncel politika gelişmeleri doğrultusunda izlenmesi gereken bir konu olmaya devam etmektedir.

Toplum Eczacısının Aşılamadaki Mevcut Rolü: Ampirik Kanıtlar

Eczacıların doğrudan aşı uygulamasına ilişkin yasal bir yetkisi bulunmamakla birlikte, Türkiye'deki toplum eczaneleri aşılama sürecinin çeşitli aşamalarında hâlihazırda rol almaktadır. Ankara'da 15 toplum eczacısıyla gerçekleştirilen nitel bir araştırma, özellikle aşıların tedariki ve soğuk zincirin sürdürülmesi açısından mevcut uygulamalara ilişkin önemli bulgular sunmaktadır. Katılımcılar aşıların tedarikçilerden taşınabilir soğutucularla teslim alındığını, uygun koşullarda özel buzdolaplarında saklandığını ve sıcaklık ile nemin 7 gün 24 saat çalışan sistemlerle izlendiğini belirtmiştir. Aynı çalışmada eczanelerde influenza, tetanoz, hepatit, menenjit, HPV ve rotavirüs aşılarının bulundurulduğu bildirilmiştir. Bu sonuçlar, toplum eczanelerinin aşıların tedarik ve saklama sürecindeki mevcut rolünü ortaya koymaktadır.[14]

Toplum eczacılarının aşılama konusundaki tutum ve uygulamalarını değerlendiren kesitsel bir çalışmada 430 eczacıya ulaşılmış ve katılımcıların %88,6'sının hastalarına aşı önerdiği bildirilmiştir.[15] En sık önerilen aşı influenza aşısı olup bu oran %83,9'dur. Bununla birlikte aynı araştırma, eczacıların aşılamaya ilişkin bazı bilgi alanlarında eksikliklerinin bulunduğunu da göstermiştir. Katılımcıların %29,9'u gebelik döneminde aşılamaya ilişkin bilgi eksikliği bildirmiş; eczacıların yalnızca %31,5'inin bir önceki sezonda influenza aşısı yaptırdığı görülmüş ve gebeler ile çocuklar gibi bazı özel gruplara yönelik aşı önerilerinin daha düşük düzeyde kaldığı saptanmıştır. COVID-19 pandemisinin ilk dalgasında toplum eczacılarının rollerini değerlendiren bir değerlendirme yazısında eczacıların ilaç danışmanlığı, hasta eğitimi ve dezenfektan üretimi gibi çeşitli hizmetler sunduğunu ve aşılama kampanyalarında daha aktif rol almalarının değerlendirilebileceğini belirtmiştir.[16]

Eczacıların aşı uygulamasına yönelik tutumlarında da genel olarak olumlu bir eğilim görülmektedir. Aynı kesitsel çalışmada katılımcıların %90'ı eczanelerde aşı uygulamasının yasal hâle getirilmesi gerektiğini ifade etmiştir.[15] Katılımcılar, böyle bir hizmetin hastaların aşıya erişimini kolaylaştırabileceğini ve aşılama oranlarına olumlu katkı sağlayabileceğini düşünmektedir. Daha yakın tarihli ve 489 toplum eczacısını kapsayan bir çalışma ise olumlu tutumların yanında bazı önemli hazırlık gereksinimlerine de işaret etmektedir. Katılımcıların %87,1'i aşıların etkili olduğunu ve yine %87,1'i güvenli olduğunu belirtmiştir. Buna karşılık yalnızca %9'unun aşısız yetişkinleri belirlemeye yönelik bir mekanizmasının bulunduğu görülmüştür. Tetanoz aşılamasına ilişkin bilgi düzeyinde de eksiklikler saptanmış; hatırlatma dozunu bilenlerin oranı %59,3, primer serinin üç dozdan oluştuğunu doğru bilenlerin oranı ise %54,4 olarak bildirilmiştir. Katılımcıların %68,5'i de mevcut geri ödeme koşullarını yetersiz bulmuştur.[17]

Eczacıların eczane ortamında aşılama hizmetine yaklaşımını inceleyen nitel bulgular, meslek grubunun konuya ilişkin bazı çekinceler taşıdığını da göstermektedir. Yasal ve güvenlik kaygıları, personel eksikliği, eğitim yetersizliği ve özellikle anafilaksi gibi acil durumların yönetimi öne çıkan endişeler arasındadır. Çalışmadaki bir katılımcının, *"Bu konuda eğitim almıyoruz. Bu iş için uzmanlar var."* şeklindeki ifadesi eğitim konusundaki bu kaygıya örnek oluşturmaktadır.[14]

Benzer şekilde, 408 toplum eczacısıyla Planlanmış Davranış Teorisi temelinde yürütülen ve eczacıların eczacı güdümlü aşılama hizmeti sunma niyetlerini yapısal eşitlik modellemesiyle inceleyen araştırmada da temkinli bir yaklaşım gözlenmiştir. Katılımcıların hizmetin hasta yararına ilişkin değerlendirmeleri orta düzeyde iken, başlıca kaygılar eczane ortamında güvenlik sorunlarının yönetilmesi ve artabilecek iş yükü üzerinde yoğunlaşmıştır. Eczacıların altyapı yeterliliği ve olası advers olayları yönetme konusundaki özgüvenlerinin görece düşük olduğu, araştırmacılar tarafından bunun önemli ölçüde doğrudan deneyim eksikliğiyle ilişkili olabileceği belirtilmiştir. Buna karşılık, eczacıların bu yeni rolü bütünüyle reddetmediği ve konuya yönelik eğitim programlarına katılma isteğinin yüksek olduğu görülmüştür. Aynı araştırmada, Türkiye'de eczacı odalarının eczacıların aşılama hizmetlerine dahil edilmesine yönelik girişimlerde bulunduğu, ancak bu çağrıların somut bir politika değişikliğine dönüşmediği de bildirilmiştir.[18]

Mevcut Durumun Analizi: Engeller ve Gereksinimler

Mevcut bulgular birlikte değerlendirildiğinde, Türkiye'de toplum eczacılarının aşılama hizmetlerindeki konumunun birden fazla boyutta ele alınması gerektiği görülmektedir. Eczaneler hâlihazırda aşıların temini ve uygun koşullarda saklanmasına katkı sağlamakta ve çalışmalar eczacılar arasında eczanede aşı uygulamasına yönelik önemli düzeyde destek bulunduğunu göstermektedir. Bununla birlikte, bu desteğin standart bir uygulama modeline dönüşebilmesi için çeşitli yasal, mesleki ve sistem düzeyindeki gereksinimlerin karşılanması gerekmektedir.

İlk olarak, yetkilendirmeye ilişkin belirsizlik öne çıkmaktadır. Mevzuatta eczacıların aşı uygulamasını doğrudan yasaklayan açık bir hüküm bulunmamakla birlikte, eczacılara bu işlemi gerçekleştirme yetkisi veren açık bir düzenleme de mevcut değildir. Eczacıların mevcut görev alanları ağırlıklı olarak ilaç ve aşıların temini, saklanması, hastaya sunulması ve danışmanlık gibi hizmetler üzerinden tanımlanmakta; doğrudan aşı uygulama görevi mevzuatta yer almamaktadır.[17]

İkinci önemli alan eğitim ve bilgi düzeyidir. Tetanoz aşısına ilişkin bilgi eksiklikleri, aşısız yetişkinlerin belirlenmesine yönelik sistemlerin sınırlı olması ve çeşitli gruplarda aşılama gereksinimine yönelik farklılıklar, uygulama öncesinde aşıya özgü bilgi ve becerilerin güçlendirilmesine ihtiyaç olduğunu göstermektedir.[17] Eczacıların aşılama hizmetine katılım niyetini inceleyen çalışmada algılanan davranışsal kontrolün niyetle anlamlı ilişki göstermemesi de katılımcıların bu hizmete ilişkin doğrudan deneyimlerinin bulunmamasıyla açıklanmıştır.[18]

Bir diğer boyut, meslek mensuplarının hizmete ilişkin çekinceleridir. Eczacıların eczane ortamında aşı uygulamasına yönelik kaygılarının başında olası advers olayların yönetimi, mevcut iş yüküne eklenecek yeni sorumluluklar ve hizmetin sürdürülebilirliği gelmektedir.[18] Nitel bulgular da özellikle anafilaksi riskinin yönetimi ve klinik eğitim yetersizliğinin eczacıların bu hizmete daha temkinli yaklaşmasında etkili olduğunu göstermektedir.[14]

Son olarak, sistem düzeyindeki gereksinimler de dikkate alınmalıdır. Mevcut durumda eczacılar aşıların temini üzerinden geri ödeme almakta, ancak olası bir uygulama hizmetine ilişkin ayrı bir geri ödeme modeli bulunmamaktadır. Bunun yanında kayıt sistemlerinin entegrasyonu ve aşısız yetişkinlerin sistematik olarak belirlenmesi gibi alanlarda da eksiklikler bildirilmiştir.[17] Türkiye'de uzaktan eczacılık hizmetlerinin henüz açık bir yasal çerçeveye kavuşmamış olması gibi daha geniş düzenleyici konular da eczacılık hizmetlerinin kapsamının geliştirilmesine ilişkin tartışmaların bir parçasını oluşturmaktadır.[16]

Küresel Bağlamda Türkiye'nin Konumu

Uluslararası Eczacılık Federasyonu'nun (FIP) 2025 tarihli raporu, ülkeleri eczacı tarafından yürütülen aşılama hizmetlerinin mevcut durumuna göre farklı kategorilerde değerlendirmektedir. Bu sınıflandırmada Türkiye; Hırvatistan, Estonya, Macaristan, Hindistan, Malta, Sırbistan, Slovenya ve Uruguay ile birlikte eczacı tarafından aşı uygulamasının politika tartışması aşamasında bulunduğu, ancak henüz uygulamaya geçirilmediği ülkeler arasında yer almaktadır.[2] Raporda ayrıca Türkiye'de meslek örgütlerinin ilgili kamu otoriteleriyle temaslarda bulunduğu, hekim ve eczacıların görüşlerini değerlendirmeye yönelik araştırmalar gerçekleştirildiği ve eczacıları olası bir aşılama rolüne hazırlayabilecek eğitim materyallerinin geliştirildiği belirtilmektedir.[2]

Uluslararası uygulamalara bakıldığında eczacıların aşılama hizmetlerine katılım düzeyinin ülkeler arasında farklılaştığı görülmektedir. Amerika Birleşik Devletleri'nde 340.000'den fazla eczacının aşı uygulama konusunda sertifikalandırıldığı bildirilmiştir. İngiltere, Avustralya, Kanada ve Portekiz gibi ülkelerde eczaneler rutin aşılama hizmetlerinin sunulduğu sağlık noktaları arasında yer almaktadır.

Fransa, Norveç ve İsviçre'de eczacıların ulusal aşı programındaki daha geniş bir aşı grubunu uygulamasına izin verilirken; Belçika, Danimarka ve Almanya gibi bazı ülkelerde eczacıların yetkileri ağırlıklı olarak influenza ve COVID-19 aşılarıyla sınırlandırılmıştır.[17]

COVID-19 pandemisi, birçok ülkede eczane ağlarının aşılama hizmetlerine dahil edilmesini hızlandıran önemli bir gelişme olmuştur. Türkiye'de ise eczacılık meslek örgütlerinin eczacıların aşılama sürecine daha aktif biçimde dahil edilmesine yönelik çağrılarda bulunduğu, ancak söz konusu girişimlerin henüz somut bir uygulama modeline dönüşmediği bildirilmektedir.[18]

SONUÇ

Bu çalışmada değerlendirilen mevzuat ve ampirik bulgular, Türkiye'de toplum eczacılarının aşılama hizmetleri içindeki mevcut konumunu farklı yönleriyle ortaya koymaktadır. Eczacılar, aşıların temini ve uygun soğuk zincir koşullarında saklanması ile hastaların bilgilendirilmesi ve aşı danışmanlığı gibi hizmetlerle aşılama sürecinde hâlihazırda rol almaktadır. Araştırmalar ayrıca eczacılar arasında aşılamaya ilişkin genel olarak olumlu bir tutum bulunduğunu ve eczanede aşı uygulamasına yönelik desteğin yüksek olduğunu göstermektedir. Buna karşılık, eczacılar için doğrudan aşı uygulama yetkisi, standartlaştırılmış eğitim ve sertifikasyon süreçleri, ulusal kayıt sistemleriyle entegrasyon, acil durumlara müdahale altyapısı, geri ödeme modeli ve mesleki sorumluluk sınırları mevcut düzenlemelerde henüz açık biçimde tanımlanmamıştır.

Elde edilen bulgular, toplum eczacılarının bağışıklama hizmetlerine daha kapsamlı katkı sunabilecek bir potansiyele sahip olduğuna işaret etmektedir. Bununla birlikte, eczacı tarafından aşı uygulamasının güvenli ve uygulanabilir bir sağlık hizmeti modeli olarak değerlendirilebilmesi, yalnızca yasal yetkilendirmenin sağlanmasına bağlı değildir. Mevzuat düzenlemelerinin; eğitim ve sertifikasyon standartları, kayıt sistemleri, acil müdahale gereklilikleri, geri ödeme modeli ve mesleki sorumluluk çerçevesiyle birlikte ele alınması gerekmektedir. Bu bileşenlerin eş zamanlı ve bütüncül biçimde düzenlenmesi, mevcut mesleki desteğin güvenli ve sürdürülebilir bir uygulama modeline dönüşebilmesi açısından önem taşımaktadır. Çalışmada ortaya konulan mevcut durum, Türkiye'de eczacı tarafından aşı uygulamasına ilişkin ileride yürütülecek politika tartışmaları ve karşılaştırmalı araştırmalar için güncel bir başlangıç noktası sunmaktadır.

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ALTERNATIVE BIRTH METHODS: WATER BIRTH, PLANNED HOME BIRTH, VAGINAL BIRTH AFTER CESAREAN, AND EPIDURAL BIRTH

ALTERNATİF DOĞUM YÖNTEMLERİ: SUDA DOĞUM, PLANLI EVDE DOĞUM, SEZARYEN SONRASI VAJİNAL DOĞUM VE EPİDURAL DOĞUM

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ABSTRACT

Objective

Although the physiology of birth has remained unchanged for thousands of years, the ways in which birth is managed have evolved significantly. Alternative birth methods such as water birth, planned home birth, vaginal birth after cesarean (VBAC), and epidural birth have become increasingly popular with the common goals of careful monitoring, reducing unnecessary interventions, involving parents in decision-making, and supporting women's autonomy. This narrative review aims to examine the benefits, risks, eligibility criteria, and current evidence regarding these alternative birth methods.

Materials and Methods: This narrative review was conducted by synthesizing current national and international guidelines and evidence-based literature on water birth, planned home birth, vaginal birth after cesarean (VBAC), and epidural analgesia. Key sources included recommendations from ACOG and other professional organizations, along with recent clinical studies and systematic reviews related to maternal and neonatal outcomes of these alternative birth methods.

Results

Water immersion during the first stage of labor is associated with reduced pain perception, decreased need for pharmacological analgesia, shorter labor duration, and higher maternal satisfaction; however, evidence regarding the second stage remains limited, and ACOG recommends delivery out of water. Planned home birth, when conducted for low-risk women with appropriate preparation, can reduce rates of induction, episiotomy, and cesarean section while improving psychological outcomes. VBAC success rates generally range between 60% and 80%, with previous vaginal birth history being the strongest predictor, along with maternal height, estimated fetal weight, and cervical dilatation. Modern low-dose epidural analgesia provides effective pain relief with minimal impact on labor progress and operative delivery rates, and large-scale evidence suggests it may reduce severe maternal morbidity.

Conclusion

In conclusion, the safe implementation of alternative birth methods requires evidence-based protocols and woman-centered care. When appropriate eligibility criteria are applied and continuous monitoring is ensured, these methods can support maternal autonomy, reduce unnecessary interventions, and improve birth experiences without compromising safety.

Keywords: Water birth; Planned home birth; Vaginal birth after cesarean; Epidural analgesia

ÖZET

Amaç: Doğumun fizyolojisi değişmemiş olsa da yönetim şekilleri yıllar içinde çeşitlenmiştir. Suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum (SSVD/VBAC) ve epidural doğum gibi alternatif yöntemler, gereksiz müdahaleleri azaltma, ebeveynlerin karar alma süreçlerine katılımını artırma ve kadın merkezli bakım sunma amacıyla giderek daha fazla tercih edilmektedir. Bu derleme, söz konusu alternatif doğum yöntemlerinin yararları, riskleri, uygulama kriterleri ve güncel kanıtlar ışığında incelenmesini amaçlamaktadır.

Materyal ve Yöntem: Bu anlatısal derleme, suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum (SSVD) ve epidural analjezi konularındaki güncel ulusal ve uluslararası kılavuzlar ile kanıta dayalı literatürün sentezlenmesiyle gerçekleştirilmiştir.

Kaynaklar arasında ACOG önerileri, mesleki örgütlerin rehberleri ve bu alternatif doğum yöntemlerinin maternal ve neonatal sonuçlarına ilişkin klinik çalışmalar ile sistematik derlemeler yer almaktadır.
Bulgular: Suda doğum, özellikle doğumun birinci evresinde ağrı algısını azaltmakta, farmakolojik analjezi ihtiyacını düşürmekte ve doğum memnuniyetini artırmaktadır; ancak ikinci evrede su altında doğum konusunda kanıtlar sınırlıdır ve ACOG su dışında doğumu önermektedir. Planlı evde doğum, düşük riskli gebelerde indüksiyon, epizyotomi ve sezaryen oranlarını azaltırken, uygun hazırlıklarla gerçekleştirildiğinde güvenli bir seçenek olabilir. SSVD başarı oranı genel olarak %60-80 arasında değişmekte olup, önceki vajinal doğum öyküsü, maternal boy, fetal ağırlık ve servikal dilatasyon gibi faktörler başarıyı belirlemektedir. Epidural analjezi etkili ağrı kontrolü sağlarken, modern düşük doz tekniklerle doğum süresi ve operatif doğum riski üzerindeki olumsuz etkiler büyük ölçüde azalmıştır; ayrıca şiddetli maternal morbiditeyi azaltıcı etkisi bildirilmektedir.
Sonuç: Sonuç olarak, alternatif doğum yöntemlerinin güvenli uygulanması için kanıta dayalı protokoller ve kadın merkezli danışmanlık kritik öneme sahiptir. Uygun seçim kriterleri uygulandığında ve sürekli izlem sağlandığında, bu yöntemler maternal özerkliği destekleyebilir, gereksiz müdahaleleri azaltabilir ve doğum deneyimini iyileştirebilir.
Anahtar Kelimeler: Suda doğum; Planlı evde doğum; Sezaryen sonrası vajinal doğum; Epidural doğum

GİRİŞ

Doğum, insanlık tarihi boyunca var olan doğal bir süreç olmasına rağmen, modern tıbbın gelişmesiyle birlikte doğum yönetimi önemli ölçüde değişmiştir. Hastane temelli, müdahaleci yaklaşımların yaygınlaşmasıyla birlikte, birçok kadın daha az müdahaleli, kadın merkezli ve özerkliğini destekleyen alternatif doğum yöntemlerine yönelmiştir.[1] Suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum (SSVD) ve epidural analjezi eşliğinde doğum, bu alternatif yaklaşımların başlıcaları arasında yer almaktadır. Bu yöntemlerin ortak hedefleri; gereksiz tıbbi müdahaleleri azaltmak, ebeveynlerin karar alma süreçlerine aktif katılımını sağlamak, maternal memnuniyeti artırmak ve güvenli koşullarda fizyolojik doğumu desteklemektir.[2] Ancak her yöntemin kendine özgü yararları, riskleri ve uygulama kriterleri bulunmaktadır. Kanıta dayalı uygulamalar ve uygun aday seçimi, bu yöntemlerin güvenli şekilde sunulabilmesi için temel koşullardır. Bu anlatısal derlemenin amacı, suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum ve epidural doğum yöntemlerini güncel kılavuzlar ve bilimsel kanıtlar ışığında incelemek; yararları, riskleri, uygunluk kriterleri ve ebelik uygulamaları açısından değerlendirmektir.

GELİŞME

1. Suda Doğum

Suda doğum, doğum eyleminin birinci ve/veya ikinci evresinin ılık su dolu bir küvette gerçekleşmesini ifade eder. Birinci evrede suya daldırma (immersion), ağrı algısını azaltma, farmakolojik analjezi ihtiyacını düşürme, doğum süresini kısaltma ve maternal memnuniyeti artırma ile ilişkilendirilmiştir.[3],[4] ACOG, sağlıklı, komplike olmayan gebeliklerde (37 0/7 – 41 6/7 hafta) birinci evrede su immersiyonunu önerebileceğini belirtmektedir.[5]
İkinci evrede (bebeğin su içinde doğması) ise kanıtlar daha sınırlıdır. Sistematik derlemeler ve meta-analizler, düşük riskli gebelerde maternal enfeksiyon riskinin artmadığını, postpartum kanama riskinin azaldığını ve bazı neonatal sonuçların (düşük Apgar skoru, NICU yatışı) olumlu etkilendiğini bildirmektedir. Ancak kordon avülsiyonu riskinde hafif artış gözlenmiştir.[6] ACOG, ikinci evrede su içinde doğum için yeterli veri olmadığını vurgulayarak, doğumun karada gerçekleşmesini önermektedir.[5]
Uygun aday seçimi (düşük riskli gebelik, tekil, baş gelişi, term), hijyenik koşullar, deneyimli ekip ve acil durum protokollerinin hazır olması suda doğumun güvenliği için kritik öneme sahiptir. Ebeler, su immersiyonu sırasında sürekli izlem, pozisyon desteği ve anne-bebek bağlanmasının desteklenmesi konusunda önemli rol oynar.

2. Planlı Evde Doğum

Planlı evde doğum, düşük riskli gebelerin, deneyimli ebe veya doğum ekibi eşliğinde, önceden planlanmış şekilde ev ortamında doğum yapmasıdır. Literatürde planlı evde doğumun, hastane doğumuna kıyasla daha az müdahale (indüksiyon, epizyotomi, epidural, sezaryen) ile ilişkili olduğu gösterilmiştir.[7] Maternal memnuniyet ve psikolojik sonuçlar genellikle daha olumludur.

Ancak bazı meta-analizler, planlı evde doğumlarda neonatal mortalite riskinin hafif artış gösterebileceğini bildirmiştir. Bu nedenle, uygun aday seçimi (düşük risk, multiparite avantajı, acil transfer planı), deneyimli ekip, acil durum ekipmanı ve hastaneye hızlı transfer imkanı zorunludur.[8] ACOG, sezaryen sonrası vajinal doğum (TOLAC) adaylarının evde doğum için uygun olmadığını vurgulamaktadır.[9]

Türkiye'de planlı evde doğum uygulamaları sınırlı olup, yasal ve kurumsal altyapının güçlendirilmesi gerekmektedir. Ebeler, risk değerlendirmesi, bilgilendirilmiş onam, doğum planı hazırlığı ve postpartum izlem süreçlerinde merkezi rol üstlenir.

3. Sezaryen Sonrası Vajinal Doğum (SSVD / VBAC)

Sezaryen sonrası vajinal doğum (SSVD), önceki sezaryen doğumu olan kadınların sonraki gebeliklerinde vajinal doğum denemesidir (TOLAC – Trial of Labor After Cesarean). Başarı oranı genel olarak %60-80 arasında değişmekte olup, en güçlü öngörücü faktör önceki vajinal doğum öyküsüdür. Maternal boy, tahmini fetal ağırlık, servikal dilatasyon ve önceki kesi tipi de başarıyı etkileyen faktörler arasındadır.[10]

ACOG, tek düşük transvers kesi öyküsü olan çoğu kadının SSVD için aday olduğunu ve danışmanlık alması gerektiğini belirtmektedir. Kontrendikasyonlar arasında klasik veya T tipi kesi, önceki uterus rüptürü ve vajinal doğumu engelleyen diğer durumlar yer alır. Uterus rüptürü riski yaklaşık %0,5-1 civarındadır ve acil sezaryen imkanı olan merkezlerde uygulama önerilir.[11]

Epidural analjezi SSVD sırasında kullanılabilir. Evde SSVD ise yüksek risk nedeniyle önerilmemektedir. Ebeler, aday değerlendirmesi, risk-yarar bilgilendirmesi, doğum eylemi sırasında yakın izlem ve acil durum yönetiminde aktif rol alır.

4. Epidural Doğum (Epidural Analjezi)

Epidural analjezi, doğum sırasında en sık kullanılan farmakolojik ağrı kontrol yöntemidir. Modern düşük doz epidural teknikler, etkili ağrı giderimi sağlarken doğum süresi ve operatif doğum riski üzerindeki olumsuz etkileri büyük ölçüde azaltmıştır.[12] Epidural, sezaryen doğum riskini artırmamaktadır.

Yararları arasında yüksek maternal memnuniyet, ağrı kontrolü ve bazı çalışmalarda şiddetli maternal morbiditede azalma yer alır. Olası yan etkiler arasında hipotansiyon, motor blok, idrar retansiyonu ve nadiren ciddi nörolojik komplikasyonlar bulunur. Bebek üzerindeki etkiler genellikle geçicidir.[13]

Epidural uygulaması anestezi uzmanı tarafından gerçekleştirilmekle birlikte, ebeler doğum eylemi sırasında sürekli destek, pozisyon değişikliği, mesane yönetimi ve maternal-fetal izlem konularında kritik rol oynar. Kadın merkezli yaklaşımda epidural, "doğal doğumu bozan" bir müdahale olarak değil, bilinçli bir seçenek olarak sunulmalıdır.

5. Ebelik Açısından Değerlendirme ve Ortak İlkeler

Tüm alternatif doğum yöntemlerinde ortak olan temel ilkeler şunlardır:

- Kanıta dayalı uygunluk kriterlerinin uygulanması,
- Bilgilendirilmiş onam ve paylaşımlı karar verme,
- Sürekli risk değerlendirmesi ve acil durum hazırlığı,
- Kadın merkezli, saygılı ve destekleyici bakım,
- Multidisipliner ekip çalışması.

Ebeler, bu süreçlerin her aşamasında eğitici, danışman, savunucu ve bakım verici rollerini üstlenerek maternal özerkliği ve güvenli sonuçları destekler.

Suda doğum uygulamalarında ebelik bakımı, suyun sıcaklık kontrolü, annenin hidrasyonu, pozisyon değişikliklerinin desteklenmesi ve continuous support prensiplerinin uygulanmasını içerir. Ayrıca, doğum sonrası ilk emzirmenin su içinde veya hemen çıkış sonrası desteklenmesi maternal-infant bağlanmayı güçlendirir.

Planlı evde doğumda başarıyı etkileyen en önemli faktörler arasında multiparite, önceki vajinal doğum öyküsü, düşük risk profili ve acil transfer için hazırlıklı olunması yer alır. Ev ortamında doğum yapan kadınlar, hastane ortamına göre daha fazla hareket özgürlüğü, mahremiyet ve kontrol hissi bildirmektedir. Ancak perinatal mortalite riskindeki olası artış nedeniyle, seçim süreci dikkatli bilgilendirme ve risk-yarar analizini gerektirir.

SSVD sürecinde ebelik bakımı, doğum eyleminin yakın izlemi, uterus rüptürü belirtilerinin erken tanınması (ani ağrı, fetal kalp hızı değişiklikleri, kanama) ve acil sezaryene hazırlıklı olunmasını kapsar. Başarı oranını artırmak için, doğum eyleminin doğal seyrinin desteklenmesi, gereksiz indüksiyonlardan kaçınılması ve kadın merkezli destek önemlidir.

Epidural analjezi uygulanan kadınlarda ebelik bakımı, motor bloğun derecesine göre pozisyon değişikliği, mesane kateterizasyonu ihtiyacının değerlendirilmesi, kan basıncı izlemi ve ikinci evrede ıkınma desteğini içerir. Modern düşük doz epidural teknikler sayesinde kadınlar sıklıkla hareket edebilmekte ve aktif ıkınabilmektedir. Bu durum, operatif doğum riskinin azalmasına katkı sağlar.

Alternatif doğum yöntemlerinin güvenli şekilde yaygınlaştırılması için sağlık sistemlerinde altyapı, eğitim ve protokol geliştirme çalışmalarına ihtiyaç vardır. Ebelerin bu yöntemler konusunda yeterli bilgi ve beceriye sahip olması, sürekli mesleki gelişim programları ile desteklenmelidir. Ayrıca, kadınların bilinçli seçim yapabilmesi için antenetal dönemde kapsamlı bilgilendirme ve danışmanlık hizmetleri sunulmalıdır.

Sonuç olarak, suda doğum birinci evrede güçlü kanıtlarla desteklenirken ikinci evrede ihtiyatlı yaklaşım gerektirir; planlı evde doğum düşük riskli multiparlarda avantaj sağlarken neonatal riskleri dikkate almayı zorunlu kılar; SSVD uygun adaylarda yüksek başarı oranına sahiptir; epidural analjezi ise modern tekniklerle güvenli ve etkili bir seçenektir. Tüm bu yöntemlerde ortak nokta, kadın merkezli, kanıta dayalı ve güvenli bakım sunulmasıdır.

Literatürde alternatif doğum yöntemlerine ilişkin kanıt düzeyi yöntemler arasında farklılık göstermektedir. Suda doğumun birinci evresi için güçlü kanıtlar mevcutken, ikinci evre için daha fazla randomize kontrollü çalışmaya ihtiyaç vardır. Planlı evde doğum için seçim biası ve transfer oranları sonuçları etkileyebilmektedir. SSVD için prospektif kohort çalışmaları başarı oranlarını netleştirmiştir. Epidural analjezi için ise büyük ölçekli çalışmalar modern tekniklerin güvenliğini desteklemektedir.

Ebelik eğitiminde alternatif doğum yöntemlerine yer verilmesi, mezuniyet sonrası eğitim programlarının güçlendirilmesi ve klinik protokollerin standartlaştırılması, bu yöntemlerin güvenli şekilde sunulmasına katkı sağlayacaktır. Ayrıca, kadınların doğum tercihlerini etkileyen sosyokültürel faktörlerin anlaşılması ve danışmanlık süreçlerinde dikkate alınması önemlidir.

Gelecek araştırmalarda, Türkiye koşullarında alternatif doğum yöntemlerinin uygulanabilirliği, ebelik uygulamalarının etkinliği ve maternal-neonatal sonuçların değerlendirildiği çok merkezli çalışmaların yapılması önerilmektedir. Bu sayede ulusal kılavuzların geliştirilmesi ve kanıta dayalı uygulamaların yaygınlaştırılması mümkün olacaktır.

SONUÇ

Suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum ve epidural analjezi, uygun koşullarda uygulandığında maternal özerkliği destekleyen, gereksiz müdahaleleri azaltan ve doğum deneyimini olumlu etkileyen alternatif yöntemlerdir. Her yöntemin kendine özgü yarar ve risk profili bulunmaktadır; bu nedenle bireyselleştirilmiş risk değerlendirmesi ve kanıta dayalı protokoller zorunludur. Güvenli uygulama için; düşük riskli aday seçimi, deneyimli ekip, acil durum planları, sürekli izlem ve kadın merkezli danışmanlık temel unsurlardır. Ebeler, bu alternatif yöntemlerin güvenli ve saygılı şekilde sunulmasında kilit role sahiptir. Gelecekte, yerel koşullara uygun protokollerin geliştirilmesi ve ebelik uygulamalarına entegrasyonunun güçlendirilmesi önerilmektedir.

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THE IMPACT OF HEALTHY LIFESTYLE BEHAVIORS ON FERTILITY AND THE ROLE OF MIDWIVES IN SUPPORTING FERTILITY

SAĞLIKLI YAŞAM BİÇİMİ DAVRANIŞLARININ FERTİLİTE ÜZERİNDEKİ ETKİSİ VE FERTİLİTENİN DESTEKLENMESİNDE EBENİN ROLÜ

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ABSTRACT

Objective: Infertility is a global public health issue affecting approximately 10–15% of reproductive-aged couples and is defined by the World Health Organization (WHO, 2025) as a disease of the reproductive system. Alongside organic and pathological causes, modifiable lifestyle behaviors—including nutrition, body weight, physical activity, tobacco/alcohol/substance use, psychological stress, environmental toxins, endocrine-disrupting chemicals (EDCs), sleep disturbances, and electromagnetic exposure—play a critical role in infertility etiology. This narrative review aims to examine the biological and hormonal mechanisms through which healthy lifestyle behaviors influence fertility and to highlight the key roles of midwives as educators, counselors, and care providers in protecting reproductive health and supporting fertility.

Materials and Methods: A comprehensive literature search was conducted across PubMed, Web of Science, Scopus, ScienceDirect, CINAHL, and the YÖK Thesis Center databases using combinations of keywords including infertility, fertility, lifestyle factors (BMI, nutrition, exercise, toxic exposures), endocrine disruptors, and midwifery care. Current national and international clinical guidelines (WHO, 2025; ASRM, 2024; ESHRE) alongside evidence-based literature published between 2021 and 2026 were retrieved and synthesized in accordance with APA referencing standards.

Results: The synthesized literature demonstrates that obesity (BMI ≥ 30 kg/m²) and low body weight (BMI < 18.5 kg/m²) impair ovulation and oocyte quality in women while decreasing sperm concentration and motility in men. Adherence to a Mediterranean diet rich in antioxidants and omega-3 fatty acids positively correlates with improved semen parameters and higher IVF success rates. Moderate physical activity supports fertility; however, strenuous or elite exercise can negatively affect ovarian function and semen quality. Active and passive smoking, alcohol abuse, high caffeine intake (>300 mg/day), chronic stress, sleep deprivation, exposure to EDCs (phthalates, parabens, heavy metals in cosmetics), and elevated scrotal temperature are consistently associated with increased sperm DNA fragmentation, reduced ovarian reserve, and prolonged time-to-pregnancy.

Conclusion: Healthy lifestyle interventions represent cost-effective, high-impact strategies that significantly improve both natural conception rates and assisted reproductive technology outcomes. Midwives, operating on the frontline of primary healthcare and reproductive health services, are uniquely positioned to screen for lifestyle risk factors, deliver individualized counseling, facilitate stress and weight management, and foster sustainable health behavior changes. Integrating midwife-led holistic lifestyle coaching into preconception and infertility care pathways is strongly recommended.

Keywords: Infertility; Fertility; Lifestyle Behaviors; Endocrine Disruptors; Midwifery Care

ÖZET

Amaç: İnfertilite, üreme çağındaki çiftlerin yaklaşık %10-15'ini etkileyen küresel bir halk sağlığı sorunudur ve Dünya Sağlık Örgütü (WHO, 2025) tarafından üreme sisteminin bir hastalığı olarak tanımlanmaktadır. Organik ve patolojik nedenlerin yanı sıra, beslenme, vücut ağırlığı, fiziksel aktivite, tütün/alkol/madde kullanımı, psikolojik stres, çevresel toksinler, endokrin bozucu kimyasallar (EDC'ler), uyku bozuklukları ve elektromanyetik maruziyet gibi değiştirilebilir yaşam biçimi davranışları infertilite etiyolojisinde kritik rol oynamaktadır. Bu derlemenin amacı, sağlıklı yaşam biçimi davranışlarının fertiliteyi etkilediği biyolojik ve hormonal mekanizmaları incelemek ve ebelerin üreme sağlığını koruma ile fertilitenin desteklenmesindeki eğitici, danışman ve bakım verici rollerini vurgulamaktır.

Materyal ve Yöntem: Bu anlatısal derleme için PubMed, Web of Science, Scopus, ScienceDirect, CINAHL ve YÖK Tez Merkezi veritabanlarında infertilite, fertilite, yaşam biçimi faktörleri (BKİ, beslenme, egzersiz, toksik maruziyetler), endokrin bozucular ve ebelik bakımı anahtar kelimeleri kullanılarak kapsamlı bir literatür taraması yapılmıştır. 2021-2026 yılları arasında yayımlanan kanıta dayalı literatür ile güncel ulusal ve uluslararası klinik kılavuzlar (WHO, 2025; ASRM, 2024; ESHRE) AMA referans standartlarına uygun şekilde taranmış ve sentezlenmiştir.
Bulgular: Sentezlenen literatür, obezite (BKİ ≥ 30 kg/m²) ve düşük vücut ağırlığının (BKİ < 18,5 kg/m²) kadınlarda ovulasyon ve oosit kalitesini bozduğunu, erkeklerde ise sperm konsantrasyonu ve motilitesini azalttığını göstermektedir. Antioksidan ve omega-3 yağ asitlerinden zengin Akdeniz diyetine uyum, semen parametrelerinde iyileşme ve daha yüksek IVF başarı oranları ile pozitif ilişkilidir. Orta düzeyde fiziksel aktivite fertiliteyi desteklerken, aşırı/elit düzeyde egzersiz over fonksiyonunu ve semen kalitesini olumsuz etkileyebilmektedir. Aktif ve pasif sigara kullanımı, alkol kötüye kullanımı, yüksek kafein alımı (>300 mg/gün), kronik stres, uyku yoksunluğu, EDC'lere (kozmetiklerdeki fitalatlar, parabenler, ağır metaller) maruziyet ve artmış skrotal sıcaklık; artmış sperm DNA fragmantasyonu, azalmış over rezervi ve uzamış gebe kalma süresi ile tutarlı şekilde ilişkilendirilmiştir.
Sonuç: Sağlıklı yaşam biçimi müdahaleleri, hem doğal konsepsiyon oranlarını hem de yardımcı üreme teknikleri sonuçlarını önemli ölçüde iyileştiren maliyet-etkin ve yüksek etkili stratejilerdir. Birinci basamak sağlık hizmetleri ve üreme sağlığı hizmetlerinin ön saflarında yer alan ebeler, yaşam biçimi risk faktörlerini tarama, bireyselleştirilmiş danışmanlık sunma, stres ve kilo yönetimini kolaylaştırma ve sürdürülebilir sağlık davranışı değişikliklerini teşvik etme konusunda benzersiz bir konuma sahiptir. Ebe liderliğindeki bütüncül yaşam tarzı koçluğunun prekonsepsiyonel ve infertilite bakım yollarına entegre edilmesi güçlü şekilde önerilmektedir.
Anahtar Kelimeler: İnfertilite; Fertilite; Yaşam Biçimi Davranışları; Endokrin Bozucular; Ebelik Bakımı

GİRİŞ

İnfertilite, Dünya Sağlık Örgütü tarafından üreme sisteminin bir hastalığı olarak tanımlanmakta olup, dünya genelinde üreme çağındaki bireylerin yaklaşık altıda birini etkilemektedir.[1] Bu durum yalnızca bireysel ve ailevi düzeyde psikososyal yük oluşturmakla kalmayıp, aynı zamanda önemli bir halk sağlığı sorunu olarak kabul edilmektedir. Organik nedenler (tubal faktör, erkek faktörü, ovulatuar disfonksiyon, endometriozis vb.) yanında, modifiye edilebilir yaşam biçimi faktörlerinin infertilite etiyolojisindeki rolü son yıllarda giderek daha fazla dikkat çekmektedir.[2,3]
Beslenme alışkanlıkları, vücut kitle indeksi (BKİ), fiziksel aktivite düzeyi, tütün ve alkol kullanımı, psikolojik stres, uyku kalitesi, çevresel toksinler ve endokrin bozucu kimyasallara (EDC) maruziyet gibi faktörler, hem kadın hem de erkek üreme sağlığını doğrudan veya dolaylı yoldan etkilemektedir. Bu faktörlerin büyük kısmı değiştirilebilir niteliktedir ve prekonsepsiyonel dönemde yapılan müdahalelerle hem doğal gebelik şansı hem de yardımcı üreme teknikleri (YÜT) başarı oranları artırılabilmektedir.[4,5]
Ebelik mesleği, birinci basamak sağlık hizmetleri ve üreme sağlığı hizmetlerinin ön saflarında yer alması nedeniyle, yaşam biçimi risk faktörlerinin erken dönemde taranması, bireyselleştirilmiş danışmanlık verilmesi ve davranış değişikliğinin desteklenmesi açısından kritik bir konumdadır. WHO'nun 2025 tarihli infertilite kılavuzu da düşük maliyetli yaşam biçimi danışmanlığının infertilite tedavi süreçlerine entegrasyonunu önermektedir.[1]
Bu anlatısal derlemenin amacı, sağlıklı yaşam biçimi davranışlarının fertilite üzerindeki biyolojik ve hormonal etkilerini güncel kanıtlar ışığında incelemek ve ebelerin fertilitenin desteklenmesindeki rollerini ortaya koymaktır.

GELİŞME

1. Vücut Ağırlığı ve Beden Kitle İndeksinin Fertilite Üzerindeki Etkisi

Hem fazla kilo (obezite) hem de düşük vücut ağırlığı, kadın ve erkek üreme fonksiyonlarını olumsuz etkilemektedir. Kadınlarda BKİ ≥30 kg/m² olduğunda, insülin direnci, hiperandrojenemi ve kronik düşük dereceli inflamasyon yoluyla ovulatuar disfonksiyon, oosit kalitesinde bozulma ve endometrial reseptivitede azalma görülmektedir.[6] Obezite, anovulatuar infertilite riskini yaklaşık üç kat artırmakta ve IVF sikluslarında daha düşük gebelik ve canlı doğum oranlarıyla ilişkilendirilmektedir.[7,8]
Düşük vücut ağırlığı (BKİ <18,5 kg/m²) ise hipotalamik-hipofizer-ovaryan aksın baskılanmasına, gonadotropin salınımının bozulmasına ve amenoreye yol açabilmektedir. Erkeklerde obezite, artmış

aromatizasyon yoluyla östrojen düzeylerini yükseltirken, testosteron ve seks hormon bağlayıcı globulin (SHBG) düzeylerini düşürmekte; sperm konsantrasyonu, motilite ve morfolojide bozulmaya neden olmaktadır.[9],[10] Prekonsepsiyonel dönemde %5-10 oranında kilo kaybı bile ovulasyonun yeniden başlamasına ve doğal gebelik şansının artmasına katkı sağlamaktadır.[11]

2. Beslenme ve Diyet Örüntüleri

Akdeniz tipi diyet (yüksek miktarda sebze, meyve, tam tahıl, baklagil, kuruyemiş, zeytinyağı ve balık; sınırlı kırmızı et ve işlenmiş gıda) fertilite açısından en tutarlı olumlu sonuçları gösteren diyet örüntüsüdür. Antioksidanlar, omega-3 yağ asitleri ve bitkisel proteinler oksidatif stresi azaltarak oosit ve sperm kalitesini desteklemektedir.[12],[13] Gözlemsel çalışmalar ve meta-analizler, yüksek Akdeniz diyeti uyumunun klinik gebelik ve canlı doğum oranlarını artırdığını, özellikle YÜT uygulanan kadınlarda embriyo kalitesini iyileştirdiğini bildirmektedir.[14],[15] Tersine, Batı tipi diyet (yüksek işlenmiş gıda, şeker, doymuş yağ ve kırmızı et) ovulatuar infertilite riskini artırmaktadır. Folat, D vitamini, çinko, selenyum ve koenzim Q10 gibi mikrobesinlerin yetersiz alımı da üreme sağlığını olumsuz etkileyebilmektedir. Prekonsepsiyonel dönemde folik asit suplementasyonu nöral tüp defektlerini önlemenin yanı sıra, genel üreme sağlığını da desteklemektedir.[16]

3. Fiziksel Aktivite

Orta düzeyde düzenli fiziksel aktivite (haftada en az 150 dakika orta yoğunlukta aktivite), hem kadın hem erkek fertilitesini olumlu etkilemektedir. İnsülin duyarlılığını artırarak, vücut kompozisyonunu iyileştirerek ve stres düzeyini azaltarak üreme fonksiyonlarını destekler.[17] Ancak aşırı veya elit düzeyde egzersiz (özellikle dayanıklılık sporları), kadınlarda hipotalamik amenore, luteal faz yetmezliği ve azalmış over rezervi; erkeklerde ise testosteron düşüklüğü ve semen parametrelerinde bozulma ile ilişkilendirilmiştir.[18] Dengeli ve sürdürülebilir bir aktivite programı önerilmektedir.

4. Tütün, Alkol ve Kafein Kullanımı

Sigara içmek (aktif ve pasif), kadınlarda over rezervinin azalması, oosit kalitesinin bozulması, ektopik gebelik ve erken menopoz riskinin artması; erkeklerde ise sperm DNA fragmantasyonu, azalmış motilite ve konsantrasyon ile ilişkilidir.[19],[20] Sigara içen kadınlarda IVF başarı oranları belirgin şekilde düşmektedir. Alkol tüketimi, özellikle ağır kullanım, sperm morfolojisini olumsuz etkilemekte ve kadınlarda hormonal dengeyi bozabilmektedir. Kafein alımının günde 300 mg'ın üzerinde olması, gebelik süresini uzatabilmektedir.[21] Prekonsepsiyonel dönemde tütün bırakma danışmanlığı ve alkol sınırlaması kritik öneme sahiptir.

5. Psikolojik Stres, Uyku ve Diğer Faktörler

Kronik psikolojik stres, hipotalamik-hipofizer-adrenal aksın aktivasyonu yoluyla gonadotropin salınımını baskılayarak ovulasyonu ve sperm üretimini olumsuz etkileyebilmektedir. Uyku bozuklukları ve yetersiz uyku süresi de hormonal ritimleri bozarak fertiliteyi azaltmaktadır.[22] Elektromanyetik alan maruziyeti ve artmış skrotal sıcaklık (laptop kullanımı, dar giysiler) erkek fertilitesini olumsuz etkileyebilmektedir.

6. Endokrin Bozucu Kimyasallar (EDC'ler)

Fitalatlar, parabenler, bisfenol A (BPA), ağır metaller ve pestisitler gibi EDC'ler, hormon reseptörlerine bağlanarak veya hormon sentezini bozarak üreme sistemini etkilemektedir. Kozmetik ürünler, plastik ambalajlar, temizlik malzemeleri ve tarım ürünleri yoluyla maruziyet söz konusu olabilmektedir. EDC maruziyeti, kadınlarda over rezervinin azalması, endometriyozis ve PCOS riskinin artması; erkeklerde ise sperm kalitesinde bozulma ile ilişkilendirilmiştir.[23],[24] Prekonsepsiyonel dönemde EDC maruziyetinin azaltılmasına yönelik danışmanlık (plastik kullanımını sınırlama, doğal kozmetik tercih etme vb.) önerilmektedir.

7. Fertilitenin Desteklenmesinde Ebenin Rolü

Ebeler, kadın sağlığı ve üreme sağlığı hizmetlerinin birinci basamağında yer almaları nedeniyle, prekonsepsiyonel danışmanlık ve yaşam biçimi müdahaleleri için ideal konumdadır. WHO ve ASRM kılavuzları, prekonsepsiyonel bakımın rutin jinekolojik ve ebelik hizmetlerine entegre edilmesini önermektedir.[1],[25] Ebelerin rolleri şunları kapsamaktadır:

• Yaşam biçimi risk faktörlerinin (BKİ, beslenme, sigara, alkol, stres, uyku, EDC maruziyeti) sistematik taranması,
• Bireyselleştirilmiş, kanıta dayalı danışmanlık ve motivasyonel görüşme teknikleriyle davranış değişikliğinin desteklenmesi,
• Kilo yönetimi, beslenme düzenlemesi ve fiziksel aktivite planlamasında rehberlik,
• Stres yönetimi ve ruh sağlığı desteği için uygun yönlendirme,
• Yardımcı üreme teknikleri sürecinde çiftlere bütüncül destek sağlanması,
• Toplum temelli eğitim programları ve sağlık okuryazarlığının artırılması.

Ebe liderliğindeki prekonsepsiyonel yaşam tarzı koçluğu programları, hem doğal gebelik oranlarını hem de YÜT başarılarını artırma potansiyeline sahiptir. Ayrıca, bu yaklaşımlar maliyet-etkin olup, sağlık sistemleri üzerindeki yükü azaltmaya katkı sağlamaktadır.[26],[27]

SONUÇ

Sağlıklı yaşam biçimi davranışları, fertiliteyi etkileyen değiştirilebilir risk faktörlerinin başında yer almaktadır. Optimal vücut ağırlığının korunması, Akdeniz tipi beslenme örüntüsünün benimsenmesi, orta düzeyde fiziksel aktivite, tütün ve aşırı alkolden uzak durma, stres yönetimi, yeterli uyku ve EDC maruziyetinin azaltılması; hem doğal konsepsiyon şansını hem de yardımcı üreme tekniklerinin başarısını anlamlı ölçüde artırmaktadır. Ebeler, birinci basamak ve üreme sağlığı hizmetlerindeki konumları sayesinde, bu müdahalelerin etkili bir şekilde uygulanmasında kilit rol oynamaktadır. Prekonsepsiyonel bakım ve infertilite yönetim süreçlerine ebe liderliğindeki bütüncül yaşam tarzı danışmanlığının entegre edilmesi, kanıta dayalı, maliyet-etkin ve sürdürülebilir bir yaklaşım olarak önerilmektedir. Gelecekte, ebelik uygulamalarına özgü yaşam biçimi müdahale modellerinin etkinliğini değerlendiren randomize kontrollü çalışmaların artırılması, bu alandaki kanıt düzeyini güçlendirecektir.

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THE APPLICATION OF NANOPARTICLES AS A THERAPEUTIC AGENT

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Abstract
Nanoparticles (NPs), ranging from 1–100 nm, have become transformative therapeutic agents due to their customizable physicochemical traits, ability to traverse biological barriers, and multifunctionality. Applications include targeted drug delivery, controlled release, theranostics, gene therapy, and immunomodulation. This review highlights recent advancements during 2023–2025, focusing on nanoparticle classes such as polymeric, lipid-based, metallic, and hybrid systems. It presents mechanisms of action and applications across cancer, neurodegenerative and cardiovascular disorders, and organ-targeted therapies. While offering significant advantages—improved specificity, reduced toxicity, and enhanced bioavailability—nanoparticle-based treatments face challenges in safety, scalability, and clinical translation. Future directions involve personalized smart nanoparticles, scalable manufacturing techniques, and theranostic platforms, promising to revolutionize therapeutic landscapes.
Keywords: Nanoparticles, Therapeutic agents, Nanomedicine, Drug delivery, Theranostics, Smart nanoparticles

Introduction

Nanoparticles are critical to modern nanomedicine, providing novel strategies for therapeutics owing to their high surface area, tunable surface chemistry, and ability to cross physiological barriers. Recent clinical translation has accelerated with innovations in lipid and polymeric carriers. The advent of smart delivery systems, advanced manufacturing, and new therapeutic targets underscores the evolving role of nanoparticles in medicine (Rehan et al., 2024).

Types of Nanoparticles in Therapeutics

Polymeric Nanoparticles

Advanced polymer-based delivery systems remain at the forefront of targeted therapy. A comprehensive Chemical Reviews article (2024) details recent progress in polymeric nanoparticle design, functionalization, and therapeutic deployment.

Solid Lipid and Hybrid Nanoparticles

Solid lipid nanoparticles (SLNs) have shown promising results in cervical cancer therapy, highlighting improved therapeutic efficacy and clinical prospects (Tiwary et al., 2025). Hybrid liposome-based systems are also on the rise, integrating diagnostic and therapeutic functionalities—theranostics—for precise cancer treatment (Azimizonuzi et al., 2025).

Nanocarrier Classification Frameworks

A systematic categorization of nanocarriers published in early 2025 offers insights into design principles, aiding rational development of medical nanoparticles (Gressler et al., 2025).

Emerging Nanomaterials & Quantum Dots

Quantum dots (QDs) maintain relevance for imaging and drug delivery, though toxicity remains a challenge. A May 2025 review outlines recent advances and mitigation strategies. Thermally activated magnetic fiber platforms for remote-controlled release are in development, offering smart, externally regulated delivery systems (Ziegler et al., 2024).

Mechanisms of Action

Nanoparticles can act as therapeutic agents by **carrying or releasing active molecules at specific tissues or cells**. Their mechanism generally involves:

- **Targeting:** Nanoparticles can be engineered with specific surface properties or ligands that promote accumulation at diseased tissues or recognition of target cells, thereby improving therapeutic delivery and reducing off-target effects (Nguyen et al., 2024).

- **Cellular uptake:** After reaching target cells, nanoparticles are internalized mainly through endocytosis, including clathrin-mediated endocytosis, caveolar pathways, and macropinocytosis (Neupane et al., 2025).
- **Intracellular trafficking:** Following uptake, nanoparticles may be transported through intracellular compartments and, when appropriately designed, overcome endosomal barriers to deliver their therapeutic cargo to the cytoplasm or specific organelles (Liu et al., 2024).
- **Controlled release:** The therapeutic payload can be released in response to conditions such as **pH, enzymes, redox conditions, or temperature**, allowing drug release at the desired site (Liu et al., 2024).
- **Therapeutic action:** Once released, the active molecule reaches its biological target and produces the intended therapeutic effect, while nanoparticle-mediated targeting and controlled release can improve efficacy and reduce unwanted effects (Bresinsky & Goepferich, 2025).

Targeting → cellular uptake → intracellular trafficking → controlled release → therapeutic action.

Applications Across Diseases

Cancer Therapy

SLNs in treating cervical cancer (Tiwary et al., 2025)

Theranostic liposome hybrids offer simultaneous therapy and diagnostics (Azimizonuzi et al., 2025)

Smart vaccine delivery for enhanced antitumor immunity (Qiu & Wu, 2025)

Neurological Disorders

Breakthroughs in crossing the blood-brain barrier using polymeric nanocarriers by OSU show promise for treating cachexia and neuroinflammation (OSU, 2025).

Cardiovascular Therapeutics

Emerging nanotechnologies can target arterial plaques, reduce inflammation, and assist in early diagnosis—marking a significant leap in heart disease treatment (2025).

Colon-Targeted Chemotherapy

Nanogels derived from natural resin achieved high-efficiency, site-specific delivery of 5-FU, improving colorectal cancer therapy (Andhra Pradesh study, 2025).

Advantages

Precision and specificity through functionalized targeting.

Multimodal platforms allow combination therapy plus diagnostics.

Barrier penetration, such as across the BBB or gastrointestinal tract.

Controlled release, including remotely triggered systems.

Limitations

Toxicity concerns, especially with QDs and non-biodegradable materials.

Production scalability remains a hurdle — though innovative processes like Sequential NanoPrecipitation (SNaP) are promising.

Regulatory complexity due to multifunctionality and new materials.

Need for extensive in vivo validation before clinical translation.

Future Perspectives

Smart, stimuli-responsive systems (magnetic, thermal, pH).

Scalable manufacturing techniques like SNaP.

Personalized nanomedicine, integrating diagnostics and therapy in one unit.

Cross-disciplinary integration for workflow—from design to bedside.

Conclusion

Recent years (2023–2025) have seen remarkable progress in nanoparticle therapeutics—from advanced polymeric and lipid platforms to theranostic hybrids and breakthrough barrier-penetrating systems. While challenges in toxicity, manufacturing, and regulation remain, the emerging landscape of smart, multifunctional nanoparticles stands poised to reshape therapeutic strategies. Ongoing interdisciplinary efforts are essential to transform these innovations into safe, impactful clinical solutions.

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GREEN HYBRID NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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Abstract
Green hybrid nanoparticles have emerged as a promising class of nanomaterials that combine the advantages of multiple components synthesized via environmentally friendly methods. Unlike conventional chemical and physical techniques, green synthesis utilizes plant extracts, microorganisms, and biopolymers, offering safer, cost-effective, and sustainable approaches. Hybrid nanoparticles, such as metal–metal oxide, metal–polymer, and multi-metal composites, exhibit enhanced physicochemical properties, including high stability, biocompatibility, and multifunctionality. These unique features make them particularly valuable in biomedical fields, ranging from antimicrobial and anticancer therapies to wound healing, bioimaging, biosensing, and drug delivery. Their mechanisms of action typically involve reactive oxygen species (ROS) generation, membrane disruption, DNA and protein interactions, and synergistic effects arising from the hybrid composition. Despite their promise, challenges such as cytotoxicity, large-scale synthesis, reproducibility, and regulatory approval hinder clinical translation. This review highlights recent advances in the green synthesis, characterization, and biomedical applications of hybrid nanoparticles, with a focus on their therapeutic potential and future prospects in precision medicine.
Keywords: Green, Hybrid, Nanoparticles, Biomedical Application, Reactive Oxygen Species.

1. Introduction

Nanotechnology has revolutionized biomedical sciences by enabling the design of materials at the nanoscale with unique physicochemical and biological properties. Among these, nanoparticles (NPs) have attracted significant interest due to their high surface-to-volume ratio, tunable functionality, and ability to interact with biological systems at the molecular level (Bhatia, 2016). Traditionally, nanoparticles are synthesized using chemical or physical routes, which often involve toxic reagents, harsh conditions, and high energy consumption, raising concerns about environmental sustainability and biocompatibility (Ahmed et al., 2019).

In response to these limitations, green synthesis approaches have gained traction as eco-friendly alternatives. These methods employ biological agents such as plant phytochemicals, bacteria, fungi, algae, and biopolymers to mediate the synthesis of nanoparticles under mild conditions (Iravani, 2020). The biomolecules act as natural reducing, capping, and stabilizing agents, resulting in nanoparticles with improved stability and reduced toxicity compared to those produced by conventional techniques.

A recent trend in nanomedicine is the development of hybrid nanoparticles, which are engineered by combining two or more materials—such as metals, metal oxides, or polymers—to generate synergistic properties (Huang et al., 2021). These hybrids exhibit multifunctionality, including enhanced antimicrobial activity, improved drug-loading capacity, controlled release profiles, and superior imaging contrast. For example, silver–zinc oxide (Ag-ZnO) hybrids demonstrate potent antibacterial activity, while gold–iron oxide (Au-Fe_2O_3) nanoparticles are widely used in targeted cancer therapy and magnetic resonance imaging (MRI) (Rajendran et al., 2022).

Biomedical applications of green hybrid nanoparticles are diverse and rapidly expanding. They are being investigated for use as antimicrobial agents against multidrug-resistant (MDR) pathogens, as anticancer therapeutics through targeted drug delivery, and as wound healing agents due to their ability to accelerate tissue regeneration. Furthermore, they hold promise in bioimaging, biosensing, and nanotheranostics, offering integrated platforms for diagnosis and treatment (Chowdhury et al., 2023).

However, despite their immense potential, challenges remain regarding their clinical application. Issues such as cytotoxicity, biodistribution, immune responses, scalability of green synthesis, and regulatory frameworks must be addressed before widespread clinical translation can be achieved.

This paper provides a comprehensive review of green hybrid nanoparticles, focusing on their synthesis, characterization, biomedical applications, mechanisms of action, toxicity concerns, and future perspectives.

2. Green Synthesis of Hybrid Nanoparticles

2.1 Plant-Mediated Synthesis

Plants represent one of the most widely used resources for nanoparticle synthesis. Their phytochemicals—flavonoids, alkaloids, terpenoids, polyphenols, and proteins—serve as reducing, capping, and stabilizing agents (Ahmed et al., 2019). For instance, Psidium guajava leaf extract has been reported to facilitate the green synthesis of silver–iron oxide–zinc oxide (Ag-Fe_2O_3-ZnO) hybrid nanoparticles with strong antibacterial activity (Ogunyemi et al., 2022). Similarly, Azadirachta indica (neem) extract has been used to synthesize silver–gold (Ag-Au) hybrids with improved antioxidant and anticancer properties (Makarov et al., 2014).

Plant-mediated synthesis is advantageous due to the abundance of bioactive compounds, rapid reaction rates, and ease of scalability. However, variability in phytochemical composition caused by seasonal, geographic, and physiological factors may lead to inconsistency in nanoparticle quality.

2.2 Microbial-Mediated Synthesis

Bacteria, fungi, and algae can produce hybrid nanoparticles through their intrinsic metabolic activities. These microorganisms secrete enzymes and biomolecules that reduce metal ions and stabilize nanoparticles (Iravani, 2020). For example, Fusarium oxysporum has been utilized in the biosynthesis of Ag-Au hybrid nanoparticles, while cyanobacteria-mediated approaches have been employed for Fe_2O_3-ZnO hybrids (Salvadori et al., 2017).

Microbial-mediated synthesis offers high specificity and reproducibility, but challenges such as culture maintenance, risk of pathogenic contamination, and slower synthesis rates compared to plant extracts limit its application.

2.3 Biopolymer-Assisted Synthesis

Biopolymers such as chitosan, alginate, starch, and cellulose not only act as reducing agents but also serve as stabilizers and carriers for hybrid nanoparticles. Chitosan-stabilized Ag-ZnO nanoparticles, for example, exhibit enhanced antimicrobial activity and biocompatibility compared to their single-component counterparts (Anand et al., 2021).

The use of biopolymers facilitates controlled size, shape, and surface modification, which are crucial for biomedical applications. Additionally, biopolymers improve solubility, prolong circulation time, and enhance the drug delivery potential of hybrid nanoparticles

3. Characterization of Green Hybrid Nanoparticles

Characterization is crucial to confirm nanoparticle formation, understand their structural and functional properties, and ensure reproducibility.

UV–Vis Spectroscopy: Used to monitor the surface plasmon resonance (SPR) peaks of metallic nanoparticles, confirming synthesis.

Fourier Transform Infrared Spectroscopy (FTIR): Identifies functional groups involved in reduction and capping by plant extracts or biopolymers.

X-ray Diffraction (XRD): Confirms crystalline structure, phase purity, and particle size.

Transmission Electron Microscopy (TEM) & Scanning Electron Microscopy (SEM): Provide morphology, particle size, and hybrid architecture.

Dynamic Light Scattering (DLS) & Zeta Potential: Determine hydrodynamic size, polydispersity, and colloidal stability.

Thermogravimetric Analysis (TGA): Evaluates thermal stability and organic–inorganic composition.

Proper characterization ensures the reproducibility, stability, and predictability of nanoparticle properties in biomedical systems (Rajendran et al., 2022).

4. Biomedical Applications of Green Hybrid Nanoparticles

4.1 Antimicrobial Activity

Hybrid nanoparticles exhibit enhanced antimicrobial effects compared to single nanoparticles due to synergistic mechanisms. Ag-ZnO hybrids show strong bactericidal activity against Escherichia coli and Staphylococcus aureus, driven by ROS generation, ion release, and membrane disruption (Siddiqi et al.,

2018). Similarly, Ag-Fe_2O_3 hybrids have demonstrated effectiveness against multidrug-resistant (MDR) pathogens.

4.2 Anticancer Applications

Gold–iron oxide (Au-Fe_3O_4) hybrid nanoparticles are widely studied for cancer therapy, combining photothermal therapy (Au) with magnetic targeting and MRI (Fe_3O_4). Plant-mediated Ag-Au hybrids have shown cytotoxicity against breast and lung cancer cell lines, mediated by apoptosis induction and ROS generation (Chowdhury et al., 2023).

4.3 Wound Healing

Ag-ZnO and Ag-CuO hybrid nanoparticles incorporated into hydrogels accelerate wound healing by reducing infection, stimulating collagen deposition, and promoting angiogenesis (Anand et al., 2021). Their green synthesis further enhances safety and clinical applicability.

4.4 Bioimaging and Biosensing

Au-Fe_3O_4 nanoparticles are applied in multimodal imaging (MRI, CT, and photoacoustic imaging), while ZnO-graphene oxide hybrids are explored for biosensors detecting glucose and cancer biomarkers (Rajendran et al., 2022).

4.5 Drug Delivery

Hybrid nanoparticles offer tunable surfaces for drug loading, controlled release, and targeted delivery. Biopolymer-functionalized Ag-ZnO nanoparticles enhance bioavailability while reducing systemic toxicity in drug delivery applications (Huang et al., 2021).

5. Mechanisms of Action of Green Hybrid Nanoparticles

The biomedical activities of hybrid nanoparticles are mediated by multiple synergistic mechanisms:

Reactive Oxygen Species (ROS) Generation: Induces oxidative stress leading to bacterial or cancer cell apoptosis.

Membrane Disruption: Direct interaction with microbial or cancer cell membranes compromises integrity.

DNA and Protein Interactions: Metal ions bind with DNA and proteins, disrupting replication and enzyme activity.

Synergistic Hybrid Effects: Combining two or more nanoparticles enhances stability, bioavailability, and therapeutic outcomes.

For example, Ag-ZnO hybrids exhibit stronger antimicrobial activity than individual Ag or ZnO nanoparticles due to simultaneous ion release and ROS-mediated stress (Siddiqi et al., 2018).

6. Toxicity, Challenges, and Future Perspectives

Despite their promise, several challenges limit the clinical translation of green hybrid nanoparticles:

Cytotoxicity and Biocompatibility: Although green synthesis reduces toxicity, nanoparticle accumulation in organs such as the liver, kidney, and spleen raises safety concerns.

Reproducibility: Variability in biological sources (plant phytochemicals, microbial strains) may affect nanoparticle properties.

Scalability: Large-scale production with consistent quality remains challenging.

Regulatory Approval: Lack of standardized protocols for evaluation, toxicity testing, and approval delays clinical applications.

Future perspectives emphasize integrating artificial intelligence (AI) and machine learning for predictive modeling of nanoparticle properties, optimizing green synthesis for scalability, and developing multifunctional hybrid systems for theranostics (Chowdhury et al., 2023).

7. Conclusion

Green hybrid nanoparticles represent a convergence of sustainability and biomedical innovation. Their eco-friendly synthesis, multifunctional properties, and enhanced biomedical efficacy highlight their potential as next-generation therapeutics. Applications ranging from antimicrobial and anticancer therapies to wound healing, imaging, and drug delivery make them highly promising.

However, challenges such as cytotoxicity, reproducibility, large-scale synthesis, and regulatory approval must be addressed to facilitate clinical translation. Future research should focus on standardized synthesis protocols, long-term toxicity studies, and advanced hybrid designs tailored for precision medicine.

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THE EFFECT OF BORAGE OIL ON INFLAMMATION IN 2,4-DINITROCHLOROBENZENE-INDUCED ATOPIC DERMATITIS-LIKE SKIN LESIONS IN BALB/C MICE

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Objective
Atopic dermatitis (AD) is a chronic inflammatory skin disease with complex pathogenesis involving genetic, immunological, and environmental factors. As our understanding of AD pathophysiology continues to improve, novel therapeutic strategies have been explored. This study aimed to investigate the therapeutic effects of topical borage oil, a natural source rich in γ-linolenic acid (GLA), in an experimental DNCB-induced atopic dermatitis model by evaluating the levels of inflammatory cytokines and histopathological changes.

Materials and Methods
Thirty-five female BALB/c mice (8–12 weeks old, 25–30 g) were randomly allocated into six groups (n = 7): Control, DNCB, acetone–olive oil, borage oil and corticosteroid,. AD-like skin lesions were induced using 2,4-dinitrochlorobenzene (DNCB). The control group received no treatment, other than dorsal shaving. One day after dorsal epilation (approximately 4 cm^2), 150 µL of 1% DNCB dissolved in an acetone- oil mixture (3:1, v/v) was applied to the dorsal skin once daily for nine consecutive days. Beginning five days after epilation, 150 µL of 0.2% DNCB in the same solvent was applied three times weekly for three weeks to maintain AD-like lesions. Following the establishment of dermatitis, borage oil was applied topically for 16 days. At the end of the experiment, serum IgE, histamine, IL-4, IL-25, and IL-33 levels were measured using commercially available mouse-specific ELISA kits. Histopathological evaluation of the skin tissue was also performed.
Results: Serum IgE concentrations were significantly higher in the DNCB, acetone–olive oil, and borage oil groups than in the control group ($p < 0.05$), but no significant differences were observed among the remaining groups ($p > 0.05$). Serum IL-4 and histamine levels were not significantly different between the experimental and control groups ($p > 0.05$). Although serum IL-25 and IL-33 concentrations tended to increase in the experimental groups, statistical significance was observed only in the borage oil-treated group ($p < 0.05$). Histopathological examination revealed that topical borage oil reduced epidermal hyperkeratosis and improved skin morphology compared to untreated DNCB-induced lesions.

Conclusion
Topical borage oil application did not significantly alter most systemic inflammatory cytokine levels in the DNCB-induced AD model. Nevertheless, histopathological findings indicated that borage oil alleviated epidermal hyperkeratosis and improved skin architecture, suggesting a protective effect on local skin tissue despite the absence of marked systemic immunological changes in the study. These findings indicate that borage oil may be a promising complementary topical treatment for improving skin lesions associated with atopic dermatitis, although further studies are needed to clarify its underlying mechanisms.
Keywords: Atopic dermatitis, borage oil, DNCB, IgE, IL-4, IL-25, IL-33

Introductıon
Atopic dermatitis (AD) is a chronic, inflammatory, and recurrent skin condition whose prevalence has been steadily increasing in recent years. Although it is more common in childhood, it can affect people of all ages. It has been reported that its global prevalence can reach up to 20% in some populations (Weidinger and Novak, 2016).

The disease not only causes skin lesions but also leads to significant consequences, such as itching, sleep disturbances, and a marked decrease in quality of life. The pathogenesis of AD is quite complex and develops as a result of interactions between genetic predisposition, impairments in skin barrier function, immune system dysregulation, and environmental factors (Boguniewicz and Leung, 2011).

Impaired skin barrier integrity is considered one of the key components of AD pathogenesis. In particular, mutations in the filaggrin gene are one of the best-defined genetic causes of impaired epidermal barrier function (Palmer et al., 2006). However, in a significant proportion of moderate-to-severe AD cases, reduced filaggrin expression can also develop independently of genetic mutations. In particular, it has been reported that increased expression of cytokines associated with type 2 inflammation, such as interleukin (IL)-4 and IL-13, contributes to the disruption of epidermal barrier integrity by suppressing filaggrin production in keratinocytes (Peters and Peters, 2019). This impairment in barrier function facilitates the penetration of allergens, irritants, and microorganisms into the skin, leading to further intensification of the local inflammatory response.

The predominance of T helper 2 (Th2) cell responses plays a significant role in the immunopathogenesis of AD. While Th2 cells produce various cytokines, primarily IL-4, IL-5, and IL-13, Th1 cells primarily secrete IL-2 and interferon-γ (IFN-γ). In particular, IL-4 and IL-13 contribute to the development of a typical atopic response in AD by promoting immunoglobulin E (IgE) class switching and IgE production in B cells (Dawid, 2013; Zari and Zari, 2015). Elevated serum IgE levels have been reported in approximately 75–80% of patients with AD (Yeşilova et al., 2010). Elevated IgE levels are one of the key indicators of the immune response to allergens and play a central role in the immunopathogenesis of the disease.

A key step in the development of IgE-mediated immune responses is the stimulation of B cells by IL-4 and other cytokines released from Th2 cells in response to allergens. IgE binds to cells expressing high-affinity IgE receptors, predominantly mast cells and basophils. mast cells and basophils. The interaction of the allergen with IgE on the cell surface results in the release of histamine, leukotrienes, chemokines, and various proinflammatory mediators from mast and other effector cells. These mediators amplify the inflammatory response, contributing to the emergence and exacerbation of clinical manifestations of AD, such as itching, erythema, and lesion formation. Therefore, serum total IgE levels are one of the biomarkers frequently used in the assessment of the immunological characteristics of AD (Kitamura et al., 2018).

In AD, not only lymphocytes but also numerous inflammatory cells, such as macrophages, eosinophils, and mast cells, play a role in the initiation and maintenance of the inflammatory response. In particular, it has been reported that macrophages are present in high numbers in both acute and chronic AD lesions and contribute to the chronic inflammatory process of the disease. In addition to antigen presentation and phagocytosis, macrophages play a role in sustaining the inflammatory response by producing proinflammatory cytokines and growth factors (Kwak et al., 2019). In experimental AD models, chitinase-3-like-1 protein has been shown to influence Th2 inflammation, M2 macrophage activation, and skin barrier function (Kasraie and Werfel, 2013). These findings indicate that AD pathogenesis results from the interaction of immunological and epidermal mechanisms.

It has been suggested that, in addition to immunological mechanisms, changes in essential fatty acid (EFA) metabolism may also play a role in the pathophysiology of AD. Particular attention has been focused on changes in the levels of γ-linolenic acid (GLA), an important intermediate product of omega-6 (ω-6) fatty acid metabolism (Horrobin, 2000; Wright, 1991). While EFAs play a key role in maintaining the structural integrity and fluidity of cell membranes, they can also influence the functions of membrane-bound receptors and enzymes. In addition, ω-6 fatty acids, as precursors of biologically active lipid mediators such as prostaglandins and leukotrienes, contribute to the regulation of inflammatory and immunological responses (Ziboh et al., 2000).

Disturbances in essential fatty acid (EFA) metabolism have been reported to adversely affect epidermal structure and function, leading to dry, erythematous, scaly, and inflammatory skin lesions. It has been demonstrated that skin changes developing in animal models with experimentally induced EFA deficiency can be partially or completely reversed by the administration of ω-6 fatty acids, and these findings highlight the importance of EFA metabolism in skin homeostasis (Horrobin, 1992). However, whether disturbances in EFA metabolism are the primary cause of AD remains debatable. Current data suggest that EFA metabolism may contribute to the pathophysiology of AD through both epidermal barrier function and regulation of immune response.

In this context, plant oils rich in GLA are attracting attention as potential therapeutic agents for the adjunctive treatment of AD. In particular, borage (Borago officinalis L.) oil has garnered attention owing to its high GLA content. According to Foster et al. (2010), the gamma-linolenic acid (GLA) content in borage oil is approximately two to three times greater than that found in evening primrose oil. Given the potential effects of GLA on epidermal lipid metabolism and the formation of inflammatory mediators, borage oil is thought to be beneficial in supporting the impaired skin barrier and modulating the inflammatory response in AD.

However, current findings regarding the effects of borage oil on AD are limited, and there is a need to elucidate in greater detail its effects on inflammation, IgE response, and histopathological changes, particularly in experimental AD models. Therefore, the aim of the present study was to evaluate the effects of topical borage oil application on the inflammatory response and histopathological changes in experimentally induced AD-like skin lesions.

Materıals And Methods

Experimental Atopic Dermatitis The study used 35 female BALB/c mice, 8–12 weeks old, and weighing 25–30 g. The animals were housed in hygienic Makrolen cages in climate-controlled rooms under a 12-hour light/12-hour dark cycle. After the mice's backs were shaved, the shaved area was sensitized with DNCB to induce AD-like skin lesions. The control group received no treatment other than shaving. One day after dorsal epilation (approximately 4 cm^2), a 150 ml mixture of 1% DNCB in acetone:olive oil (3:1 volume/volume) was applied to the dorsal skin for 9 days. Five days after dorsal epilation, a 0.2% DNCB solution in a 3:1 (volume/volume) acetone:olive oil mixture (150 mL) was applied to the dorsal skin three times a week for 3 weeks (Kim et al., 2014). After a 9-day sensitization period, the mice were randomly divided into six groups (n = 7 per group). The treatments were administered to the groups as follows:

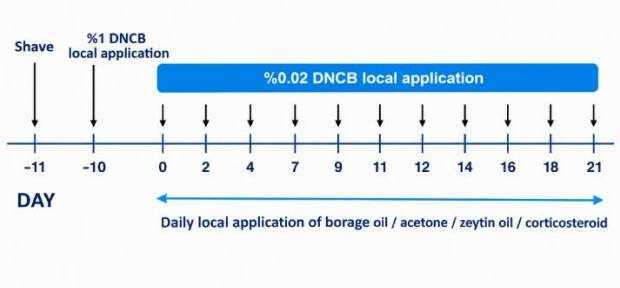
(1) Control group: No treatment was administered, and only the dorsal region was shaved.

(2) Acetone-olive oil group: In the negative control group, only the acetone:olive oil mixture (3:1 v/v)—used as a solvent to dissolve DNCB—was applied at the same time as DNCB.

(3) Atopic dermatitis (AD) group: A 1% DNCB solution dissolved in acetone-olive oil (3:1 volume/volume) was applied at a dose of 150 ml for 10 days following dorsal epilation. After day 10, application of 0.02% DNCB was continued three times a week for 16 days (Kim et al., 2014).

(4) Corticosteroid group (Corticosteroid+AD): A commercial corticosteroid cream containing 0.05% w/w clobetasol 17-propionate as the active ingredient was applied topically to the lesion sites of mice with experimentally induced AD every day for 16 days following the completion of the 1% DNCB application, in parallel with borage oil application.

(5) Borage oil group: 2–3 mL of borage oil (Biopurus) was applied topically to the lesion sites of mice with experimentally induced AD every day for 16 days following the completion of the 1% DNCB application.



At the end of the experiment, the mice were euthanized via cervical dislocation under anesthesia (ketamine + xylazine). Blood samples were collected from the heart using a syringe (2 cc); after serum was separated, the samples were stored at -80°C until analysis. Skin samples were collected from the mice, fixed in 3.7% formalin, stained with hematoxylin/eosin solution, and evaluated histopathologically under a light microscope. Histopathological examinations were outsourced to a specialized laboratory. In serum samples, mouse-specific ELISA kits were used to measure IgE (BT-LAB/E0449Mo), histamine (BT-LAB/E0248Mo), IL-4 (BT-LAB/E0051Mo), IL-25 (BT-LAB/E1656Mo), and IL-33 (BT-LAB/E1182Mo) were performed colorimetrically using mouse-specific ELISA kits, as specified in the kits' package inserts.

Statistical Analysis

SPSS 21 (Statistical Package for the Social Sciences 21, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data obtained in this study. The Shapiro-Wilk test was used to assess whether the data followed a normal distribution. Groups showing a normal distribution were compared using the ANOVA test; post hoc corrections were performed using the Tukey test, and $p < 0.05$ was considered statistically significant.

Results

Histopathological Results

Figures 1–5 illustrate the microscopic changes in the epidermis after treatment with borage oil and corticosteroids in groups with experimentally induced atopic dermatitis. No histopathological changes were detected in the control group (Figure 1). In the AD group, hyperkeratosis and fibrosis in the dermal papillae were observed (Figure 2). In the acetone-olive oil group, hyperkeratosis, vacuolar degeneration in the epithelium, and infiltration of mast cells and eosinophils in the dermis were detected (Figure 3). In the borage group, fibrosis and lymphocyte infiltration were observed in the papillary dermis (Figure 4). In the corticosteroid group, ulceration and necrosis were observed in the epidermis, and a fungal infection (Figure 5) was noted.

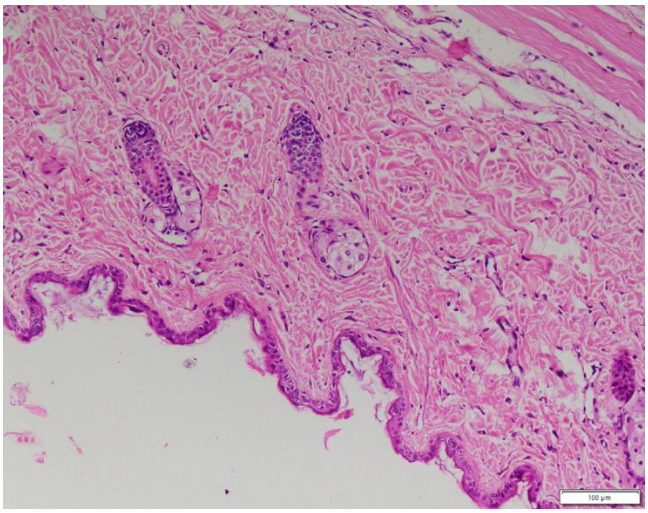


Figure 1. Histopathological examination of the control group's skin (Hematoxylin & Eosin, ×100)

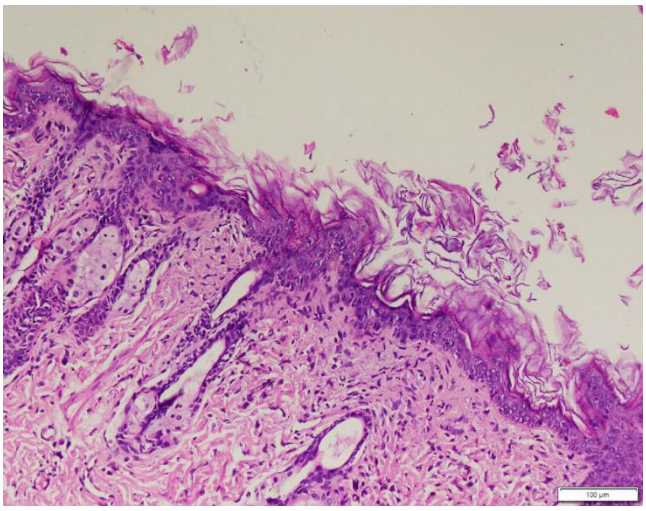


Figure 2. Histopathological examination of skin from a patient with atopic dermatitis. (Hyperkeratosis, fibrosis of the dermal papillae) (Hematoxylin & Eosin, ×100)

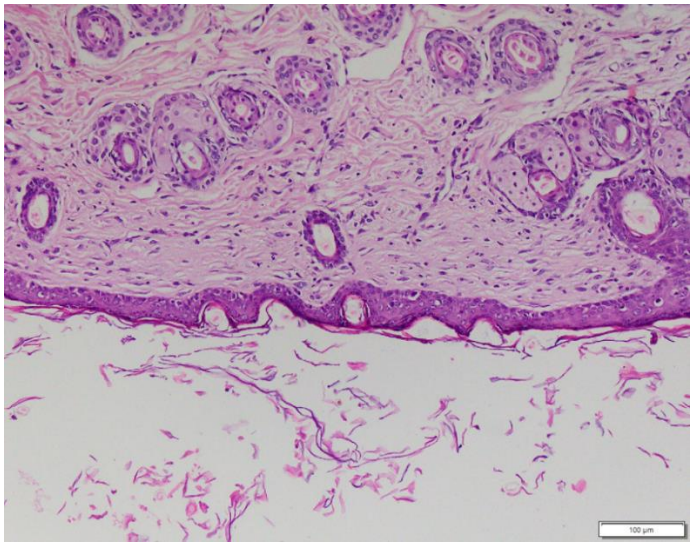


Figure 3. Histopathological examination of the skin in the acetone-olive oil group. (Hyperkeratosis, vacuolar degeneration of the epithelium, and infiltration of mast cells and eosinophils in the dermis) (Hematoxylin & Eosin, ×100)

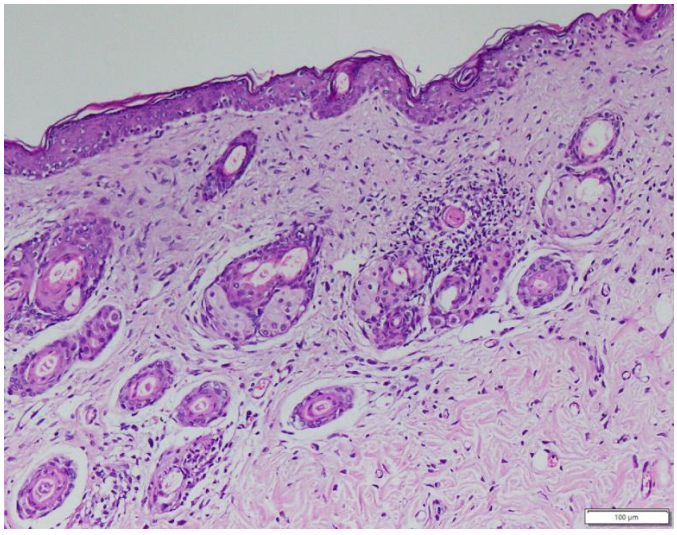


Figure 4. Histopathological examination of the borage oil group. (Fibrosis and lymphocytes in the papillary dermis) (Hematoxylin & Eosin, ×100)

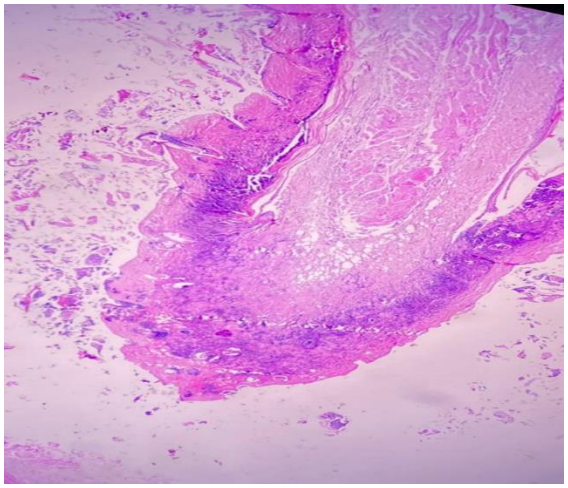


Figure 5. Histopathological examination of the skin in the corticosteroid group. (Ulceration, fungal infection, and necrosis in the epidermis) (Hematoxylin & Eosin, ×100)

IgE and Cytokine Results

The serum IgE, IL-4, IL-25, IL-33, and histamine levels in the experimental groups are presented in Table 1. Serum IgE levels in mice from the Experimental AD and Acetone-Olive Oil groups were found to be statistically significantly higher than those in the control group ($p<0.05$), whereas no significant difference was observed in the other groups ($p>0.05$). No significant changes in serum IL-4 and histamine levels were observed in the experimental groups compared to the control group ($p > 0.05$). Increased serum IL-25 and IL-33 levels were observed in the treatment groups compared to the control group; however, only the difference in the γ-linolenic acid group was statistically significant ($p < 0.05$).

Table 1. Cytokine levels in the groups (x ± Sx) (n = 7)

ng/L	Control	Atopic dermatitis	Acetone-Olive Oil	Borage oil	Corticosteroid
IgE	2,12±0,4[a]	5,07±0,9[b]	5,28±1i23[b]	3,99±1,3[ab]	3,3±0,8[a]
IL4	97,3±8,9	94,4±11,9	105±16,9	105,9±26	108±19,1
IL25	1,6±0,3	2,34±0,74	2,68±0,79	2,47±0,58	2,56±0,58
IL33	62,3±21,7[a]	113,3±36,4byt[ab]	202,5±117[b]	195,1±59,6[b]	145,8±55,1[ab]
Histamine	16,87±2,18	18,8±3,6	16,86±8,7	14,6±4	13,4±5,8

Different letters indicate statistical significance (p>0,05)

Dıscussıon

Atopic dermatitis (AD) is a complex and chronic inflammatory skin disease that develops as a result of the interaction between genetic predisposition, impairments in skin barrier function, immunological dysregulation, and environmental factors. Disruption of the skin barrier leads to increased transepidermal water loss and facilitates the penetration of irritants, allergens, and microorganisms through the epidermis; the resulting inflammatory response contributes to the chronicity of the disease. Moreover, the heightened colonization of Staphylococcus aureus in skin afflicted by atopic dermatitis may contribute to the intensification of the inflammatory process (Leung et al., 2003). Therefore, the primary goal treatment of AD is to support the skin barrier and control the inflammatory response.

Currently, various treatment options are used for AD, including moisturizers, topical corticosteroids, topical calcineurin inhibitors, and antihistamines. In severe or uncontrolled cases, systemic immunomodulators and biological agents may be incorporated into the treatment (Kim, 2021; Han et al., 2018). Although topical corticosteroids are effective anti-inflammatory agents, they can cause local side effects, such as skin atrophy, discoloration, purpura, telangiectasia, and striae, particularly with long-term and high-potency use (Del Rosso and Friedlander, 2005; Eichenfield et al., 2014). Therefore, it is important to investigate alternative or complementary treatment options that offer similar efficacy but carry a lower risk of side effects.

In experimental AD models, various agents such as ovalbumin, 2,4-dinitrochlorobenzene (DNCB), and trinitrochlorobenzene (TMA) are used (Gu et al., 2018; An et al., 2018; Sur et al., 2016). DNCB application is one of the experimental models commonly used to induce AD-like skin lesions in mice (Yang et al., 2021). In this study, AD-like clinical findings, such as erythema, edema, pruritus, excoriation, and wound formation, were observed in mice following DNCB and acetone-olive oil applications. Furthermore, the increase in serum IgE levels in the AD group compared to the control group supports the successful establishment of the experimental model. This finding is consistent with previous studies reporting increased IgE levels in AD models induced by DNCB (Lee et al., 2020).

The increase in serum IgE levels is one of the characteristic immunological features of AD. In the pathogenesis of AD, the predominance of a Th2-type immune response—and the resulting increase in cytokines such as IL-4 and IL-13—contributes to the stimulation of IgE production by B cells. The release of inflammatory mediators triggered by elevated IgE through mast cells and other effector cells is considered a key mechanism in the development of clinical and histopathological findings of AD. Therefore, serum IgE levels are frequently used to assess the immunological activity of the disease in experimental AD models (Angeli et al., 2004; Kitamura et al., 2018).

One of the notable findings of this study was that topical borage oil application resulted in a significant decrease in serum IgE levels. The fact that IgE levels in the borage oil-treated group approached those of the control group suggests that borage oil may suppress the IgE response associated with AD.

Similarly, a significant decrease in serum IgE levels was observed in the group treated with corticosteroids. While this result supports the expected anti-inflammatory effect of the conventional treatment agent used in the study on the experimental model, it also indicates that borage oil may exert an effect similar to that of corticosteroids in terms of IgE response.

This effect of borage oil may be related to its high content of γ-linolenic acid (GLA). GLA is an important intermediate in omega-6 fatty acid metabolism and may play a role in regulating the structural properties of cell membranes and inflammatory responses. It has previously been suggested that borage oil may exhibit anti-inflammatory properties due to its high GLA content (Foster et al., 2010; Ibrahim and Alshammaa, 2023). However, the fact that no significant changes in serum cytokines were detected in the present study precludes a definitive conclusion that the effect of borage oil on IgE occurs directly through systemic cytokine suppression.

In this study, no statistically significant difference was found between the groups in terms of serum histamine, IL-4, and IL-25 levels. IL-33 levels were higher in all experimental groups compared to the control group; however, a statistically significant difference was observed only in the groups treated with borage oil and γ-linolenic acid. These findings suggest that the serum cytokines evaluated in the experimental AD model may not fully reflect local skin inflammation. Particularly given that the inflammatory response in AD occurs largely within the skin tissue, the limited changes in serum levels do not rule out the local effect of borage oil.

It is known that cytokines such as IL-4, IL-25, and IL-33 play important roles in the pathogenesis of AD. While IL-4 is one of the key regulators of the Th2 response and IgE production, IL-25 and IL-33 also play a role in the initiation and maintenance of the type 2 inflammatory response (Leung and Bieber, 2003; Novak and Bieber, 2003; Fort et al., 2001; Cayrol and Girard, 2014). However, the serum levels of these cytokines may not always correlate with the disease activity at the local tissue level. Therefore, the fact that no significant change in serum cytokine levels was observed following borage oil application in our study should not be interpreted as indicating that borage oil has no effect on inflammation. On the contrary, the significant decrease in serum IgE levels and the improvement in histopathological findings suggest that the effect may occur primarily through local skin mechanisms.

The histopathological findings of this study support this view. The epidermal and dermal changes observed in the AD group are consistent with the inflammatory and structural changes expected in the experimental AD model induced by DNCB. Previous studies have reported histopathological changes such as epidermal thickening, hyperkeratosis, dermal fibrosis, and inflammatory cell infiltration in models induced by DNCB or other AD-inducing agents (Jung et al., 2017; Yang et al., 2021). However, in this study, the significant reduction or prevention of dermal hyperkeratosis in the group treated with topical borage oil suggests that borage oil may have a positive effect on preserving skin structure.

This positive effect of borage oil on histopathological findings may be related to the potential effects of GLA and other biologically active components in the oil on epidermal lipid metabolism and skin barrier function. It has previously been reported that EFAs play an important role in the structural integrity of the epidermal barrier, and that changes in omega-6 fatty acid metabolism may affect skin inflammation and barrier function. Therefore, it is possible that borage oil reduces the histopathological severity of AD-like lesions not only by suppressing the inflammatory response but also by supporting the structural integrity of the epidermal barrier.

However, the results of previous studies on the therapeutic potential of borage oil in AD are inconsistent. Foster et al. (2010) reviewed the results of 12 clinical trials evaluating the oral or topical use of borage oil and noted that five studies reported significant results, five reported insignificant results, and two reported mixed results. Overall, it was concluded that oral borage oil does not have a strong and consistent clinical effect on AD, but may provide limited benefit in some mild cases. These differences may stem from factors such as the route of administration, dose, duration of treatment, GLA content of the oil used, patient age and clinical characteristics, and severity of AD. Therefore, the positive findings obtained in the present study suggest that borage oil is not a definitive treatment option for AD but rather a complementary treatment candidate worth investigating, particularly for topical use.

An important finding of our study is that, although borage oil had positive effects on serum IgE levels and skin histopathology, it did not cause any significant changes in serum histamine, IL-4, and IL-25 levels. This result suggests that the effect of borage oil may be related to mechanisms such as support of the local skin barrier, regulation of lipid metabolism, and modulation of the local inflammatory response, rather than classical systemic immunosuppression.

However, to confirm this hypothesis, direct assessment of cytokine levels, inflammatory cell infiltration, and barrier proteins in skin tissue is required.

The study has some limitations. First, the evaluation of inflammatory markers based on serum levels prevents a full characterization of the local immunological response in skin tissue. Furthermore, the mechanistic effects of GLA and other biologically active components—which are thought to play a role in the efficacy of borage oil—have not been directly evaluated. Extending the treatment duration and comparing different doses could also elucidate the dose-response relationship of borage oil. Therefore, in future studies, evaluating cytokines such as IL-4, IL-13, IL-25, IL-33, and IFN-γ, as well as epidermal barrier proteins such as filaggrin, loricrin, and involucrin in skin tissue, will contribute to a more detailed explanation of the mechanism of action of borage oil.

Conclusıon

In this study, the effects of topical borage oil on serum IgE levels, inflammatory markers, and histopathological changes in skin tissue were evaluated in a DNCB-induced experimental model of atopic dermatitis (AD). Successful induction of the AD-like model was supported by the observed clinical findings and increased serum IgE levels. Topical application of borage oil significantly reduced serum IgE levels, bringing them closer to those observed in the control group.

In contrast, topical borage oil did not result in significant changes in serum histamine, IL-4, or IL-25 levels. Significant differences in serum IL-33 levels were observed among the treatment groups, particularly in the borage oil and γ-linolenic acid groups. Taken together, these findings suggest that the effects of topical borage oil may be mediated predominantly through local mechanisms in the skin and improvement of skin barrier integrity rather than through broad systemic suppression of inflammatory cytokines.

Histopathological evaluation further demonstrated that topical borage oil was associated with reduced dermal hyperkeratosis. This finding suggests a potential protective effect of borage oil on skin integrity and epidermal barrier function. The concurrent reduction in serum IgE levels and attenuation of histopathological alterations indicate that topical borage oil may exert beneficial effects on both immunological responses and skin structure in this experimental AD model.

In conclusion, the present findings suggest that topical borage oil may represent a potential complementary therapeutic approach for AD. However, these experimental findings are insufficient to establish the clinical efficacy of borage oil in patients with AD. Further studies using different doses and longer treatment periods are warranted to clarify its mechanisms of action. In particular, assessment of cytokine profiles in skin tissue, inflammatory cell infiltration, and epidermal barrier proteins such as filaggrin, loricrin, and involucrin may provide further insight into the local effects of borage oil and its potential therapeutic role in AD.

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DIRECT LARYNGOSCOPY-ASSISTED I-GEL PLACEMENT FOR FLEXIBLE BRONCHOSCOPIC CRYOTHERAPY IN SEVERE POST-INTUBATION TRACHEAL STENOSIS: A CASE REPORT

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ABSTRACT

Objective

This case report describes direct laryngoscopy-assisted i-gel placement and perioperative anesthetic management after two unsuccessful blind i-gel insertion attempts in a patient with severe post-intubation tracheal stenosis and prior hypoxic cardiac arrest following failed intubation.

Materials and Methods

A 59-year-old man (78 kg, 174 cm) with ASA physical status IV was scheduled for flexible bronchoscopic cryotherapy and dilation. He had biphasic stridor at rest, air hunger, and could speak only in short phrases. Preoperative room-air SpO_2 was 89%, heart rate was 104 beats/min, and respiratory rate was 20 breaths/min. Computed tomography showed severe proximal tracheal stenosis 35 mm below the vocal cords, with an anteroposterior luminal diameter of 4.43 mm. After five minutes of preoxygenation, SpO_2 increased to 100%. Following propofol-fentanyl induction, mask ventilation was confirmed before rocuronium administration. Two blind insertion attempts with a size 5 i-gel resulted in marked air leakage and inadequate ventilation. Direct laryngoscopy with a size 3 Macintosh blade was then used to elevate the laryngeal structures and guide the i-gel into the hypopharynx.

Results

Adequate tidal volume, bilateral chest expansion, and a consistent capnography waveform were achieved on the first laryngoscopy-assisted attempt, and flexible bronchoscopy confirmed the i-gel position. The bronchoscope was then advanced through the i-gel, and cryotherapy, dilation, and biopsy were performed. Minimum SpO_2 was 91% and maximum $EtCO_2$ was 41 mmHg. The procedure was completed without a major airway-related complication. After 48 hours of intensive care monitoring, the patient was transferred to the ward with marked improvement in stridor and resolution of air hunger.

Conclusion

In severe proximal tracheal stenosis, a supraglottic airway device can provide ventilation and a working channel for bronchoscopy without traversing the stenotic segment. When standard blind i-gel insertion fails, direct laryngoscopy-guided placement may offer a practical rescue option and avoid repeated blind attempts.

Keywords: Tracheal stenosis; i-gel; supraglottic airway; direct laryngoscopy; flexible bronchoscopy; cryotherapy; difficult airway

INTRODUCTION

Post-intubation tracheal stenosis is a delayed and potentially life-threatening complication of prolonged or traumatic endotracheal intubation. When the stenosis is severe and close to the vocal cords, major concerns include inability to pass an endotracheal tube through the narrowed segment, mucosal trauma, bleeding, perforation, and complete airway obstruction after induction. Supraglottic airway devices may be useful during interventional bronchoscopy because they can provide ventilation without traversing the stenotic segment and offer a wide working channel for flexible bronchoscopy.[1-4]

The i-gel has a noninflatable, anatomically shaped cuff that permits rapid insertion and provides access for flexible bronchoscopy.

Blind insertion may nevertheless result in malposition or air leakage if the distal tip abuts the laryngeal inlet, the epiglottis folds, or the device does not advance adequately along the hypopharyngeal curve. Laryngoscopy-assisted placement has been reported to improve first-attempt success and oropharyngeal seal pressure.[5] This report describes direct laryngoscopy-assisted i-gel placement and anesthetic management during flexible bronchoscopic cryotherapy in a high-risk patient with severe post-intubation tracheal stenosis and a history of hypoxic cardiac arrest after failed intubation.

MAIN TEXT

Case presentation

A 59-year-old man (174 cm, 78 kg; body mass index, 25.8 kg/m²) was evaluated for flexible bronchoscopic cryotherapy and dilation for post-intubation tracheal stenosis. His medical history included coronary artery disease, previous inferior myocardial infarction, coronary stent implantation, atrial fibrillation, recurrent ventricular tachycardia/ventricular fibrillation, and an implantable cardioverter-defibrillator (ICD). Echocardiography showed a left ventricular ejection fraction of 40%, global hypokinesia, moderate mitral regurgitation, mild aortic and tricuspid regurgitation, and biatrial dilatation.

During a previous hospitalization, failed intubation attempts had resulted in severe hypoxemia followed by cardiac arrest. Return of spontaneous circulation was achieved after approximately 35 minutes of cardiopulmonary resuscitation. The patient was reported to have required mechanical ventilation for approximately seven days and subsequently developed progressive dyspnea and biphasic stridor after discharge. At preoperative assessment, he was using accessory respiratory muscles, could speak only in short phrases with pauses, and continued to have stridor in the supine position. Blood pressure was 143/85 mmHg, heart rate was 104 beats/min, respiratory rate was 20 breaths/min, and room-air SpO_2 was 89%. Airway examination showed Mallampati class II, adequate mouth opening, and normal neck mobility.

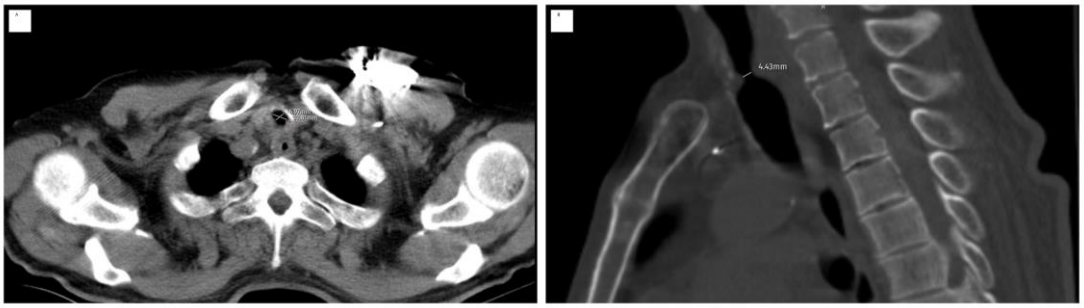


Figure 1. (A) Axial thoracic computed tomography image showing severe proximal tracheal narrowing and approximate measurements of the stenotic lumen. (B) Sagittal reconstruction showing the stenotic segment approximately 35 mm distal to the vocal cords and reduction of the anteroposterior luminal diameter to 4.43 mm.

Preoperative thoracic computed tomography demonstrated severe proximal tracheal stenosis approximately 35 mm distal to the vocal cords (Figure 1). At a normal tracheal segment, the anteroposterior and transverse diameters measured 22 and 21 mm, respectively, whereas the anteroposterior luminal diameter at the stenosis was 4.43 mm, corresponding to an approximately 80% reduction in anteroposterior diameter. Otolaryngologic endoscopy showed symmetric vocal cord motion, an adequate glottic opening, and narrowing below the vocal cords.

The patient was classified as ASA physical status IV. The ICD tachyarrhythmia therapies were disabled by the cardiology team before the procedure, and an external defibrillator with pads was kept immediately available. A videolaryngoscope, small-bore endotracheal tubes, a rigid bronchoscope, an emergency tracheostomy set, and surgical airway equipment were prepared in the operating room. The thoracic surgery team and two experienced anesthesiologists were present throughout the procedure. Two 20-gauge peripheral intravenous catheters were placed. Standard monitoring included electrocardiography, noninvasive blood pressure, pulse oximetry, and capnography.

Because of marked air hunger and reliance on accessory respiratory muscle activity, a sedation technique that preserved spontaneous ventilation was considered unlikely to provide adequate respiratory

conditions. Passage of an endotracheal tube through the stenotic segment also carried a risk of failure and could have interfered with the bronchoscopic working field. The primary airway plan was therefore controlled ventilation through a size 5 i-gel, with flexible bronchoscopy performed through the device. The patient was preoxygenated with 100% oxygen by face mask for five minutes. Despite an initial spontaneous tidal volume of approximately 210 mL, SpO_2 increased to 100%.

Anesthesia was induced with slowly administered intravenous propofol 110 mg and fentanyl 100 µg. After loss of consciousness, effective face-mask ventilation was confirmed before rocuronium 50 mg was administered. A size 5 i-gel was inserted using the standard blind technique; however, marked air leakage, low tidal volume, and ineffective ventilation were observed. Jaw thrust and head-neck extension did not correct the problem, and a second blind insertion attempt was also unsuccessful.

To avoid further blind attempts, direct laryngoscopy was performed with a size 3 Macintosh blade. A Cormack-Lehane grade III view was obtained. The blade was positioned in the vallecula and the tongue base and laryngeal structures were elevated. The distal tip of the i-gel appeared to be impinging on the laryngeal inlet and failing to advance sufficiently into the hypopharynx. Laryngeal elevation widened the hypopharyngeal passage, allowing the distal tip of the i-gel to be directed in a controlled manner toward the upper esophageal inlet. On the first laryngoscopy-assisted attempt, the device was observed to advance into an appropriate position. Bilateral chest expansion, adequate tidal volume, and a consistent capnography waveform were obtained. Flexible bronchoscopy confirmed the i-gel position and the laryngeal inlet. No oropharyngeal trauma or bleeding occurred.

Anesthesia was maintained with propofol 8 mg/kg/h and remifentanil 2.5 µg/kg/h infusions. Ventilation was continued manually with the reservoir bag using 100% oxygen and a high fresh gas flow. The flexible bronchoscope was advanced through the i-gel beyond the vocal cords. Cryotherapy and flexible bronchoscopic dilation were applied to the subglottic/proximal tracheal stenosis; protruding tissue was treated with additional cryotherapy, and a forceps biopsy was obtained. Rigid bronchoscopic dilation was not performed. The bronchoscopic procedure lasted approximately 35 minutes.

During the procedure, the minimum SpO_2 was 91% and the maximum $EtCO_2$ was 41 mmHg. Continuous numerical $EtCO_2$ measurement was intermittently limited by circuit leak while the bronchoscope was advanced through the i-gel, although capnographic trend monitoring was maintained. No severe hypoxemia or desaturation requiring an additional rescue intervention occurred. The lowest blood pressure was 75/50 mmHg; a total of 10 mg ephedrine was administered in two equal doses. Intravenous crystalloid administration was limited to avoid excessive volume loading in the setting of left ventricular systolic dysfunction. No intraoperative arrhythmia or i-gel displacement occurred.

At the end of the procedure, neuromuscular blockade was reversed with sugammadex 2 mg/kg. The i-gel was removed after adequate spontaneous ventilation and protective airway reflexes had returned. Apart from minimal stridor, there was no laryngospasm, bronchospasm, severe hypoxemia, or hemodynamic complication during the early postoperative period. A postprocedural chest radiograph showed no pneumothorax or other early procedure-related thoracic complication (Figure 2). The ICD was re-interrogated by cardiology after the procedure and its tachyarrhythmia therapies were re-enabled. The patient was monitored in the intensive care unit for 48 hours and was transferred to the ward in stable condition after marked improvement in stridor and resolution of air hunger. Written informed consent was obtained for publication of the case and the clinical and radiologic images.



Figure 2. Postprocedural anteroposterior chest radiograph. The ICD is visible in the left pectoral region; no pneumothorax or other evident early thoracic complication related to the procedure is seen.

Discussion

This case illustrates that direct laryngoscopy can facilitate i-gel placement after failed blind insertion and establish adequate ventilation in a patient with severe proximal tracheal stenosis, previous hypoxic cardiac arrest after failed intubation, and substantial cardiac comorbidity. In patients with tracheal stenosis, loss of muscle tone during induction, changes in negative intrathoracic pressure, and transition to controlled ventilation may increase dynamic obstruction at the stenotic segment. A primary airway plan and clearly defined rescue strategies should therefore be established with the procedural team before induction.

Supraglottic airway devices do not bypass the stenotic segment. They may, however, avoid passage of an endotracheal tube through the stenosis, limit direct trauma to the narrowed segment, and provide unobstructed bronchoscopic access to the subglottic airway while ventilation is maintained. Successful use of the i-gel and other laryngeal mask devices has been reported in tracheal surgery and interventional bronchoscopy.[2-4,6] In a recent randomized trial of advanced bronchoscopy, laryngeal mask airway and high-flow nasal oxygen reduced hypoxemia and the need for intervention compared with standard nasal cannula oxygen.[1]

In this patient, air leakage and inadequate ventilation during two blind insertions of the size 5 i-gel may have resulted from the distal tip impinging on the laryngeal inlet or failing to follow the hypopharyngeal curve. Because additional blind attempts could have increased the risk of pharyngeal trauma, bleeding, edema, and hypoxemia, direct laryngoscopy was chosen instead of a third blind attempt. Laryngeal elevation widened the hypopharyngeal passage and allowed the distal tip to be advanced along the anatomic axis toward the upper esophageal inlet. In the randomized study by Miyazaki et al, laryngoscopy-assisted i-gel insertion improved first-attempt success, increased seal pressure, and reduced insertion difficulty.[5] Previous reports of difficult laryngeal mask placement likewise emphasize avoiding repeated blind attempts and considering underlying anatomic causes after repeated failure.[7]

Sedation with preservation of spontaneous ventilation may be appropriate in selected patients with severe tracheal stenosis.[2] In the present patient, however, room-air SpO_2 was 89%, air hunger was marked, accessory respiratory muscles were being used, and speech was limited to short phrases. These findings raised concern that sedation-related depression of respiratory drive would not be well tolerated. Controlled general anesthesia was therefore selected, and neuromuscular blockade was administered only after effective mask ventilation had been confirmed. Given the history of hypoxic cardiac arrest, this sequence was an important component of the airway plan.

Cardiac comorbidity added further complexity to anesthetic management. The patient had an ejection fraction of 40%, complex coronary artery disease, atrial fibrillation, a history of ventricular arrhythmias, and an ICD. Disabling the ICD tachyarrhythmia therapies before the procedure, maintaining immediate access to external defibrillation, and re-enabling device therapies afterward were important precautions. When hypotension occurred, small doses of ephedrine were used while large-volume fluid administration was avoided to limit volume loading in the setting of systolic dysfunction.

The limitations of this case include the absence of detailed airway records from the previous outside-hospital intubation, tracheal cuff-pressure data, exact records of the duration of mechanical ventilation, and the histopathologic result. The diameter of the cryotherapy probe, the number of applications, and the duration of each application were also not recorded. Nevertheless, the radiologic measurements of the stenosis, the intraoperative airway maneuver, and the clinical course were documented in detail.

Conclusion

Airway management in patients with severe proximal tracheal stenosis and a history of hypoxic cardiac arrest following failed intubation requires a multidisciplinary, stepwise rescue plan before induction. When blind i-gel placement results in air leakage and inadequate ventilation, direct laryngoscopy-assisted anatomic guidance may be a practical rescue option rather than repeated blind attempts. This approach may allow ventilation to be maintained without traversing the stenotic segment and permit flexible bronchoscopic treatment to be completed.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and the anonymized clinical and radiologic images.

Conflict of interest
The authors declare no conflicts of interest.

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YABAN HAYATI REHABİLİTASYONUNA KABUL EDİLEN BAYAĞI ŞAHİN (BUTEO BUTEO) VE ARI ŞAHİNLERİNDE (PERNİS APİVORUS) KLİNİK, AKUT FAZ PROTEİNLERİ VE BİYOKİMYASAL BULGULARIN ÖN DEĞERLENDİRİLMESİ

PRELIMINARY EVALUATION OF CLINICAL, ACUTE-PHASE PROTEIN, AND BIOCHEMICAL FINDINGS IN COMMON BUZZARDS (BUTEO BUTEO) AND EUROPEAN HONEY BUZZARDS (Pernis Apivorus) ADMITTED TO WILDLIFE REHABILITATION

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ÖZET

Amaç: Bayağı şahin (*Buteo buteo*) ve arı şahini (*Pernis apivorus*), farklı ekolojik ve beslenme özelliklerine sahip iki yırtıcı kuş türüdür. Arı şahininin *Hymenoptera* ağırlıklı özelleşmiş beslenme ekolojisi, biyokimyasal bulguların yorumlanmasında dikkate alınmalıdır. Bayağı şahine ilişkin sınırlı veri bulunmakla birlikte, özellikle arı şahininde akut faz proteinleri ve kapsamlı biyokimyasal profil verileri oldukça kısıtlıdır. Bu çalışmanın amacı, Erzurum Doğa Koruma ve Milli Parklar (DKMP) Müdürlüğüne getirilen bu iki türe ait bireylerin kabul nedenlerini, klinik durumlarını, serum amiloid A (SAA) ve haptoglobin (Hp) düzeyleri ile biyokimyasal parametrelerini tanımlayıcı olarak ön değerlendirmeye tabi tutmaktır.

Materyal ve Yöntem

Çalışma materyali; ağır kanat travması ve açık yaralanması bulunan üç erişkin bayağı şahin ile beslenme yetersizliği, kanat kırığı veya ileri bitkinlik ve şiddetli kaşeksi bulgularıyla kabul edilen üç arı şahininden (iki erişkin, bir yavru) oluşmaktadır. İlk fiziksel muayene sonrası alınan serum örneklerinde akut faz proteinlerinden SAA, Hp ile hepatik, renal, enerji, lipid ve demir metabolizmasına yönelik biyokimyasal parametreler (AST, ALT, GGT, ALP, TP, albümin, glukoz, üre, TG, TK, HDL-C, Fe, DDBK) ölçülmüştür. Örneklem küçüklüğü nedeniyle istatistiksel karşılaştırma yapılmamış, bulgular tanımlayıcı olarak değerlendirilmiştir.

Bulgular

Bayağı şahinlerin tamamında yüksek üre, travma ve olası sıvı kaybı nedeniyle prerenal mekanizmalarla; düşük Fe ise inflamasyona bağlı demir sekestrasyonuyla ilişkilendirilmiştir. Şiddetli kaşeksiyle kabul edilen arı şahininde saptanan yüksek üre ve düşük TK, ileri malnütrisyon, sıvı kaybı ve uzamış katabolizmayla ilişkilendirilmiştir. SAA ve Hp testlerinin bu türler için analitik validasyonunun bulunmaması bir sınırlılıktır; bu nedenle sonuçlar bireysel düzeyde değerlendirilmiştir.

Sonuç

Bu tanımlayıcı olgu serisi, laboratuvar bulgularının klinik durumla birlikte yorumlanması gerektiğini göstermektedir. Küçük örneklem, tek zamanlı örnekleme ve tür-spesifik referans aralığı eksikliği nedeniyle bulgular genellenemez; mevcut veriler, gelecekteki geniş ölçekli tür-spesifik çalışmalar için ön veri niteliğindedir.

Anahtar Kelimeler: Arı şahini, bayağı şahin, akut faz proteinleri, klinik biyokimya, yaban hayatı rehabilitasyonu.

ABSTRACT

Objective: The common buzzard (*Buteo buteo*) and European honey buzzard (*Pernis apivorus*) are raptor species with distinct ecological and dietary characteristics. The Hymenoptera-dominated feeding ecology of the honey buzzard should be considered when interpreting its biochemical findings. Although limited biochemical data exist for the common buzzard, acute-phase protein and comprehensive biochemical profile data remain scarce, particularly for the honey buzzard.

This study aimed to descriptively evaluate the reasons for admission, clinical status, serum amyloid A (SAA) and haptoglobin (Hp) concentrations, and biochemical parameters in individuals of these two species admitted to the Erzurum Directorate of Nature Conservation and National Parks (DKMP).

Materials and Methods
The material comprised three adult common buzzards with severe wing trauma and open wounds, and three honey buzzards (two adults, one juvenile) admitted with malnutrition, wing fracture, or severe cachexia. Serum samples taken after initial examination were analyzed for SAA, Hp, and biochemical parameters reflecting hepatic, renal, energy, lipid, and iron metabolism (AST, ALT, GGT, ALP, TP, albumin, glucose, urea, TG, TC, HDL-C, Fe, UIBC). Owing to the small sample size, no statistical comparisons were performed; findings were evaluated descriptively.

Results
In all common buzzards, elevated urea was attributed to prerenal mechanisms related to trauma and fluid loss, while low Fe was associated with inflammation-related iron sequestration. In the cachectic honey buzzard, elevated urea and markedly low TC were associated with advanced malnutrition, fluid loss, and prolonged catabolism. Lack of species-specific analytical validation for the SAA and Hp assays is a limitation; results were therefore evaluated individually.

Conclusion
This descriptive case series demonstrates the importance of interpreting laboratory findings alongside clinical status. Owing to the small sample, single-time-point sampling, and limited species-specific reference intervals, findings cannot be generalized; the data provide preliminary information for future, larger-scale, species-specific clinicopathological studies.
Keywords: European honey buzzard, common buzzard, acute-phase proteins, clinical biochemistry, wildlife rehabilitation.

1. GİRİŞ
Yaban hayatı rehabilitasyon merkezlerine kabul edilen yırtıcı kuşların klinik durumlarının objektif bir biçimde değerlendirilmesi, tedavi başarılarının artırılması ve doğaya yeniden kazandırılabilmesi açısından büyük önem taşımaktadır. Bayağı şahin (*Buteo buteo*) ve arı şahini (*Pernis apivorus*), ekosistemlerde önemli roller üstlenen ancak birbirinden farklı ekolojik ve biyolojik özelliklere sahip iki yırtıcı kuş türüdür. Özellikle arı şahininin büyük ölçüde Hymenoptera üyeleri ve larvalarını içeren özelleşmiş beslenme ekolojisi, bu türün biyokimyasal bulgularının değerlendirilmesinde dikkate alınması gereken önemli bir biyolojik özellik oluşturmaktadır.[1] Bayağı şahine ilişkin bazı hematolojik ve biyokimyasal veriler bulunmakla birlikte[2,3], özellikle arı şahininin akut faz proteinleri ve kapsamlı klinik biyokimyasal profiline ilişkin veriler sınırlıdır.
Erzurum Doğa Koruma ve Milli Parklar (DKMP) Müdürlüğüne kabul edilen yaban hayvanlarında ortopedik travmalar, yumuşak doku yaralanmaları ve sistemik hastalıkların rehabilitasyona kabul nedenleri arasında önemli yer tuttuğu uzun dönemli vaka analizlerinde de bildirilmiştir.[4] Ancak yırtıcı kuşlarda hastalık belirtilerini gizleme eğilimi (maskeleme fenomeni) nedeniyle, yalnızca fiziksel muayeneye dayalı klinik değerlendirmeler hastanın gerçek fizyolojik tablosunu yansıtmada sıklıkla yetersiz kalmaktadır. Bu nedenle organizmadaki inflamasyonun, doku hasarının ve organ fonksiyonlarının değerlendirilmesinde akut faz proteinleri (AFP) ve klinik biyokimya panellerinin kullanımı giderek önem kazanmaktadır[5,6]. Bu çalışmanın amacı; rehabilitasyon amacıyla merkeze getirilen sınırlı sayıdaki bayağı şahin ve arı şahini bireylerinin rehabilitasyona kabul nedenlerini, klinik durumlarını, akut faz proteinleri olan serum amiloid A (SAA) ve haptoglobin (Hp) düzeylerini ve çeşitli biyokimyasal parametrelerini, istatistiksel genellemelere gidilmeksizin bireysel ve tanımlayıcı bir yaklaşımla ön değerlendirmeye tabi tutmaktır.

2. GELİŞME
2.1. Materyal ve Yöntem
2.1.1. Etik İzinler, Hayvan Materyali ve Klinik Değerlendirme
Bu çalışma, Kafkas Üniversitesi Hayvan Deneyleri Yerel Etik Kurulunun 05.06.2024 tarih ve 2024/120 sayılı kararı ile T.C. Tarım ve Orman Bakanlığı Doğa Koruma ve Milli Parklar (DKMP) Genel Müdürlüğünün 08.08.2024 tarih ve E-21264211-288.04-15356280 sayılı araştırma izni doğrultusunda

gerçekleştirilmiştir. Çalışma materyalini, Erzurum DKMP Müdürlüğüne çeşitli travma ve bitkinlik şikâyetleriyle kabul edilen toplam altı yaban yırtıcı kuşu oluşturmuştur. Vakalar; ağır kanat travması ve açık yaralanması bulunan üç erişkin bayağı şahin (*Buteo buteo*) ile beslenme yetersizliği, kanat kırığı veya ileri derecede bitkinlik ve şiddetli kaşeksi bulgularıyla kabul edilen üç arı şahininden (iki erişkin ve bir yavru; *Pernis apivorus*) oluşmaktadır. İlk fiziksel muayeneleri gerçekleştirilen bireyler, sıvı veya medikal tedavi prosedürlerine başlanmadan önce örneklemeye alınmıştır.

2.1.2. Kan Örneklemesi ve Laboratuvar Analizleri

Fiziksel kısıtlama altındaki kuşların *Vena basilica*'sından alınan kan örnekleri, uygun antikoagülansız serum tüplerine alınmış, yaklaşık 1500 ×g'de 10 dakika santrifüj edilerek serumları ayrılmış ve analizlere kadar -20 °C'de saklanmıştır. Biyokimyasal parametreler ticari kitler (Biolabo, Fransa) kullanılarak Epoch mikroplaka spektrofotometresi (BioTek Instruments, ABD) ile analiz edilmiştir. SAA ve Hp düzeyleri ise sırasıyla Phase Multispecies SAA Kit ve Phase Haptoglobin Kit (Tridelta Development Ltd., İrlanda) kullanılarak üretici talimatları doğrultusunda ölçülmüştür.

Eş zamanlı olarak hepatik, renal, enerji, lipid ve demir metabolizmasını yansıtan biyokimyasal paneller kapsamında; aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), gamma-glutamil transferaz (GGT), alkalen fosfataz (ALP), total protein (TP), albümin, glukoz, üre, trigliserid (TG), total kolesterol (TK), yüksek yoğunluklu lipoprotein-kolesterol (HDL-C), serum demiri (Fe) ve doymamış demir bağlama kapasitesi (DDBK) analiz edilmiştir.

2.1.3. Veri Değerlendirme Yaklaşımı

Her iki tür için örneklem büyüklüğünün kısıtlı (n=3) olması nedeniyle gruplar veya türler arası istatistiksel bir hipotez testi (karşılaştırma) yapılmamıştır. Elde edilen laboratuvar bulguları, bireysel klinik durumlar ve türe özgü biyolojik/ekolojik farklılıklar temelinde tanımlayıcı olarak değerlendirilmiştir.

2.2. Bulgular

Bayağı şahin (n=3) ve arı şahini (n=3) vakalarından elde edilen bireysel klinik durum, akut faz proteinleri ve biyokimyasal verilere ait bulgular Tablo 1'de sunulmuştur. Bayağı şahin vakalarının tamamında üre düzeylerinin 149,5–161,7 mg/dL arasında değiştiği, serum Fe düzeylerinin ise 29,1–54,3 µg/dL aralığında olduğu belirlenmiştir. Bu gruptaki SAA seviyeleri 0,45 ile 2,17 mg/L aralığında bireysel değişkenlik gösterirken, Hp düzeylerinin 3,75 ile 4,91 mg/mL aralığında dağıldığı saptanmıştır. Arı şahinlerinde TK düzeylerinin 9,50 ile 200,99 mg/dL arasında olduğu ve özellikle şiddetli kaşeksi tablosundaki bir bireyde 9,50 mg/dL olarak saptandığı belirlenmiştir. Arı şahinlerinde SAA düzeyleri 0,79–1,78 mg/L, Hp düzeyleri ise 2,19–4,14 mg/mL arasında ölçülmüştür.

Tablo 1. Yaban hayatı rehabilitasyonuna kabul edilen bayağı şahin (*Buteo buteo*) ve arı şahini (*Pernis apivorus*) bireylerine ait demografik, temel klinik ve seçilmiş laboratuvar bulguların yorumlanması.

Tür	Yaş	Kabul Nedeni	Klinik Durum	SAA (mg/L)	Hp (mg/mL)	Üre (mg/dL)	Fe (µg/dL)	TK (mg/dL)	Başlıca Klinik Yorum
Bayağı Şahin-1	Erişkin	Kanat Yarası	Ağır Ortopedik Travma	2,17	4,91	158,26	54,30	198,42	Ağır doku hasarı ve yüksek üre düzeyi
Bayağı Şahin-2	Erişkin	Kanatta Kırık	Ortopedik Travma	0,45	3,75	149,57	29,14	200,40	Yüksek üre ve düşük Fe düzeyi
Bayağı Şahin-3	Erişkin	Kanatta Kırık	Ortopedik Travma	1,48	4,52	161,74	49,01	200,59	Yüksek üre düzeyi
Arı Şahini-1	Yavru	Beslenme Eksikliği	Sistemik (Bitkinlik)	0,79	2,19	93,91	29,14	198,42	Bitkinlik ve beslenme yetersizliği
Arı Şahini-2	Erişkin	Kanatta Kırık	Ortopedik Travma	1,48	2,97	166,96	62,25	200,99	Ortopedik travma ve doku hasarı
Arı Şahini-3	Erişkin	İleri Derece Bitkinlik	Sistemik (Şiddetli Kaşeksi)	1,78	4,14	243,48	30,46	9,50	Şiddetli kaşeksi ve olası dehidrasyon

Her türde örneklem sayısının sınırlı olması (n=3) nedeniyle veriler istatistiksel karşılaştırmaya tabi tutulmamış, bireysel klinik durumlar ve laboratuvar bulguları tanımlayıcı olarak sunulmuştur. SAA: Serum amiloid A; Hp: Haptoglobin; Fe: Serum demiri; TK: Total kolesterol.

2.3. Tartışma

Bu çalışmada, iki farklı yırtıcı kuş türüne ait altı bireyden elde edilen klinik, akut faz proteinleri ve biyokimyasal bulgular bireysel olgu serisi temelinde tanımlayıcı olarak değerlendirilmiştir. Bayağı şahinlerde hematolojik ve biyokimyasal referans aralıklarının belirlenmesine yönelik sınırlı sayıda tür-spesifik çalışma bulunmaktadır.[3] Mevcut çalışmada her üç bayağı şahinde 149,57–161,74 mg/dL aralığında saptanan üre değerlerinin, ağır travmatik tablo ve kliniğe ulaştırılana kadar gelişmiş olabilecek sıvı kaybıyla birlikte değerlendirildiğinde prerenal mekanizmalarla ilişkili olabileceği düşünülmüştür.[7,8] Kuşlar ürikotelik canlılar olmalarına rağmen, ürik asit atılımının büyük ölçüde aktif tübüler sekresyonla gerçekleşmesi nedeniyle dehidrasyonun erken evrelerinde kanda anlamlı bir yükseliş gözlenmeyebilir. Buna karşılık atılımı glomerüler filtrasyona bağlı olan üre, idrar akışının yavaşladığı akut sıvı kaybı durumlarında kana geri emilerek prerenal azoteminin çok daha hassas bir erken belirteci olarak çalışmaktadır.[7,8] Bununla birlikte, üre değerlerinin tek başına renal veya prerenal bozukluk tanısı koydurmadığı ve klinik bulgularla birlikte değerlendirilmesi gerektiği göz önünde bulundurulmalıdır. Aynı bireylerde 29,14–54,30 µg/dL arasında değişen serum Fe düzeylerinin ise travma ve doku hasarına eşlik eden inflamatuvar süreçlerde görülebilen demir sekestrasyonu mekanizmasıyla ilişkili olabileceği değerlendirilmiştir.[9]

Arı şahinleri içerisinde şiddetli kaşeksi (belirgin pektoral kas atrofisi ve keskinleşmiş karina) tablosuyla kabul edilen arı şahini-3 bireyinde saptanan 243,48 mg/dL üre düzeyi; klinik olarak gözlenen ileri derecede bitkinlik, beslenme yetersizliği ve olası sıvı kaybıyla birlikte değerlendirildiğinde, dehidrasyonla ilişkili olabileceği şeklinde yorumlanmıştır. Aynı bireyde saptanan ekstrem düşük TK değeri (9,50 mg/dL) ise, belirgin pektoral kas atrofisi ve şiddetli kaşeksi bulgularıyla birlikte değerlendirildiğinde, ileri malnütrisyon ve uzamış katabolik süreçle ilişkili olabilecek bir biyokimyasal bulgu olarak değerlendirilmiştir. Bununla birlikte, örneklem büyüklüğünün sınırlı olması ve arı şahini için karşılaştırmaya olanak sağlayacak kapsamlı tür-spesifik referans aralıklarının bulunmaması nedeniyle bu ilişkilerin nedensel olarak değerlendirilmesi mümkün değildir. Ayrıca olguların farklı mevsimlerde ve iki farklı yılda rehabilitasyona kabul edilmiş olması nedeniyle, biyokimyasal parametreler üzerindeki olası mevsimsel ve çevresel değişkenlik dışlanamamıştır.

Her iki türde SAA ve Hp düzeylerinin bireyler arasında değişkenlik göstermesi; akut travmatik hasarın niteliği, inflamatuvar yanıtın evresi ve bireysel metabolik durumdaki farklılıklarla ilişkili olabilir. Kuşlarda memelilerdeki klasik Hp yerine genomik olarak homolog bir protein olan PIT54 eksprese edilse de; bu çalışmada antikor çapraz reaksiyonuna (cross-reactivity) duyarlı immünolojik kitler yerine, doğrudan hemoglobin bağlama kapasitesini (fonksiyonel peroksidaz aktivitesini) ölçen kolorimetrik bir kitin kullanılması, kuşlardaki haptoglobin benzeri aktivitenin fonksiyonel düzeyde değerlendirilmesine olanak sağlamıştır. Bununla birlikte, yaban hayatı hekimliğinde travmanın başlangıç zamanının bilinmemesi ve tek zamanlı örnekleme yapılması, SAA düzeylerinin yorumlanmasını güçleştirmektedir. Ayrıca bu türler için tür-spesifik referans aralıklarının ve kullanılan testlere ilişkin analitik validasyon verilerinin bulunmaması nedeniyle, ölçülen SAA düzeylerinin akut faz yanıtının hangi evresini yansıttığı kesin olarak belirlenememektedir. Literatürde SAA'nın yabani kuşlarda inflamatuvar durumların ve subklinik hastalıkların değerlendirilmesinde tamamlayıcı bir biyobelirteç olarak kullanılabileceği bildirilmiştir.[10] SAA ve Hp dâhil akut faz proteinlerinin ise enfeksiyon, inflamasyon ve travmaya verilen sistemik yanıtın değerlendirilmesinde tamamlayıcı klinik bilgi sağlayabileceği belirtilmektedir.[5,6]

3. Sonuç

Sonuç olarak, literatürde özellikle akut faz proteinleri ve kapsamlı klinik biyokimyasal profiller açısından sınırlı veri bulunan bu iki türdeki altı bireye ait ayrıntılı olgu serisi, farklı klinik tabloların ve türe özgü biyolojik özelliklerin laboratuvar bulguları üzerindeki olası etkilerinin anlaşılması açısından değer taşımaktadır. İstatistiksel genelleme amacı taşımayan bu tanımlayıcı ön değerlendirme, yaban hayatı hekimliğinde laboratuvar bulgularının fiziksel muayene ve bireysel klinik durumla birlikte yorumlanmasının önemini ortaya koymakta; özellikle dehidrasyon, malnütrisyon ve travmatik hasar gibi klinik tabloların yönetiminde bireyselleştirilmiş destekleyici yaklaşımların planlanmasına katkı sağlayabilecek ön veriler sunmaktadır.

Elde edilen bulguların, gelecekte daha geniş örneklemlerle gerçekleştirilecek tür-spesifik klinikopatolojik çalışmalar için temel oluşturabileceği düşünülmektedir.

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YIRTICI KUŞLARDA MASKELEME FENOMENİ VE GÖZLEM ÖNCELİKLİ KLİNİK YAKLAŞIM (GÖKY)

MASKING PHENOMENON IN RAPTORS AND INTRODUCING THE OBSERVATION-FIRST CLINICAL APPROACH (OFCA)

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ÖZET

Amaç: Yırtıcı kuşlar, hayatta kalma içgüdüleriyle zayıflıklarını ve hastalık belirtilerini gizleme konusunda önemli bir evrimsel eğilime sahiptir. Bu çalışmada, erken fiziksel muayenenin getireceği yakalama miyopatisi ve stresi önlemek adına, hayvan refahını merkeze alan sistematik bir "Gözlem Öncelikli Klinik Yaklaşım (GÖKY)" tanıtılmaktadır.

Materyal ve Yöntem
Bu çalışma, anlatısal bir literatür derlemesi (narrative review) ile uzun yıllara dayanan yaban hayatı veteriner hekimliği saha deneyimlerinin sentezlendiği bir perspektif değerlendirmesidir. Literatür verileri; Web of Science, PubMed ve Google Scholar veri tabanlarında spesifik anahtar kelimelerle taranarak hastalık gizleme davranışının evrimsel temelleri açısından incelenmiş; saha deneyimleri ise ilk kabul, triyaj, gözlem ve tedavi planlaması süreçleri bağlamında bu verilerle harmanlanmıştır.

Bulgular
Literatür ve saha gözlemleri, yırtıcı kuşların tehdit algısı altında klinik bulguları maskelediğini ve hasta kuş bakışı'nın ancak ileri dekompanzasyon evrelerinde ortaya çıktığını göstermektedir. Geleneksel fiziksel muayeneler tek başına uygulandığında klinisyeni yanılgıya düşürebilmektedir. Önerilen bu yaklaşım sayesinde, hastanın kliniğe ilk kabulünden itibaren stresörlerin minimize edilmesi, uzaktan davranış gözleminin yapılması ve ancak bunun ardından hedefe yönelik kısa fiziksel muayeneye geçilmesi sağlanmaktadır.

Sonuç
İlk klinik kararları doğrudan etkileyen bu maskeleme davranışı önemli bir hasta yönetimi sorunudur. GÖKY, yırtıcı kuşların ilk değerlendirmesinde maskelenmiş patolojilerin kaçırılma riskini azaltmak ve hastanın enerji rezervlerini korumak için düşük stresli, pratik ve gözlem odaklı bir yaklaşım sunmaktadır.
Anahtar Kelimeler: Yırtıcı kuşlar, maskeleme fenomeni, GÖKY, yaban hayatı rehabilitasyonu, davranışsal değerlendirme.

ABSTRACT

Objective: Raptors have a significant evolutionary tendency to conceal signs of weakness and disease as a survival strategy. In this study, a systematic "Observation-First Clinical Approach (OFCA)", which centers on animal welfare, is introduced to prevent capture myopathy and stress caused by early physical examination.

Materials and methods
This study is a perspective evaluation synthesizing a narrative literature review with long-term wildlife veterinary field experiences. Literature data were searched in databases such as Web of Science, PubMed, and Google Scholar to review the evolutionary foundations of masking behavior; field experiences were integrated with these data in the context of initial admission, triage, observation, and treatment planning processes.

Results
Literature and field observations show that raptors mask clinical signs under perceived threat, and the "sick bird look" only appears in advanced decompensation stages. Immediate conventional physical examinations alone can mislead the clinician. Through the OFCA, stressors are minimized from the

patient's initial admission to the clinic, remote behavioral observation is conducted, and only then is a targeted brief physical examination performed.

Conclusion
The masking behavior is a patient management issue that directly affects clinical decisions. OFCA provides a low-stress, practical, and observation-focused clinical approach to reduce the risk of missing masked pathologies and to preserve the patient's energy reserves during the initial assessment of raptors.
Keywords: Raptors, masking phenomenon, OFCA, wildlife rehabilitation, behavioral assessment.

1. Giriş

Yırtıcı kuşlar, yaban hayatı ekosistemlerinde besin zincirinin en üst basamağında yer alan apeks predatörler olarak biyolojik çeşitliliğin korunmasında ve ekosistem dengesinin sürdürülmesinde kritik roller üstlenmektedir.[1,2] Ancak günümüzde artan antropojenik tehditler, habitat kayıpları, ateşli silah yaralanmaları ve araç çarpmaları gibi nedenlerle sıklıkla yaban hayatı rehabilitasyon merkezlerine yaralı veya hasta olarak kabul edilmektedirler.[3,4]

Bu kuşların kliniğe ilk kabullerindeki değerlendirme ve triyaj süreçleri, veteriner hekimler için büyük zorluklar barındırır. Hayatta kalma içgüdüleriyle hareket eden yırtıcı kuşlar, doğada zayıf görünmemek, doğal avcıların veya rakiplerinin dikkatini çekmemek amacıyla hastalık veya yaralanma belirtilerini artık kompanse edemeyecekleri ileri safhalara kadar gizleme konusunda evrimsel eğilim gösterirler.[5] Kanatlı tıbbı literatüründe sıklıkla korunma refleksi (preservation reflex) olarak bilinen bu genel hayatta kalma davranışının klinik değerlendirmede tanısal yanıltıcılığı ifade etmek amacıyla**,** bu çalışmada "maskeleme fenomeni" (masking phenomenon) kavramı operasyonel olarak kullanılmaktadır.[6,7] Bu fenomen nedeniyle, kliniğe kabul edilen ve dışarıdan bakıldığında tamamen stabil, tetikte ve sağlıklı görünen bir kuşun hücresel homeostazi aslında ciddi bir yıkım sürecinde olabilmektedir. Bu yanıltıcı tablo, yalnızca doğrudan temasa ve erken fiziksel muayeneye dayalı klinik değerlendirmelerin, hastanın gerçek fizyolojik durumunu yansıtmada ve doğru prognoz tayininde sıklıkla yetersiz kalmasına da yol açmaktadır.[8,9]

Literatürde yırtıcı kuşların hastalık belirtilerini gizleme adaptasyonu davranışsal ve fizyopatolojik yönleriyle tanımlanmış olmasına rağmen, bu teorik bilginin rehabilitasyon merkezlerindeki ilk müdahale sürecine nasıl aktarılacağına dair hedefe yönelik bir klinik yaklaşım eksikliği bulunmaktadır. Mevcut literatür taramamız doğrultusunda, gözlem önceliğini temel alan standartlaştırılmış bir yaklaşımın daha önce tanımlanmadığı görülmüştür. Bu gereksinimden yola çıkarak, geleneksel muayene yöntemlerinin yaratabileceği yakalama miyopatisi (capture myopathy) ve iatrojenik stres risklerini ortadan kaldırmayı hedefleyen "Gözlem Öncelikli Klinik Yaklaşım (GÖKY)" (uluslararası literatürdeki karşılığıyla *Observation-First Clinical Approach - OFCA*) bu çalışmada tanıtılmaktadır. Bu çalışmanın amacı, yaban hayatı rehabilitasyon merkezlerine kabul edilen yırtıcı kuşlarda maskeleme fenomeninin triyaj süreçleri üzerindeki yanıltıcı etkilerini güncel literatür ışığında incelemek ve uzun yıllara dayanan saha deneyimleriyle desteklenmiş, stresi en aza indiren GÖKY'yi yaban hayatı hekimliği literatürüne kazandırmaktır.

2. Gelişme

2.1. Materyal ve Yöntem

Bu çalışma, yaban hayatı veteriner hekimliği literatürünün anlatısal bir derlemesi (narrative review) ile yazarın yaban hayatı rehabilitasyon merkezlerinde uzun yıllar boyunca yürüttüğü klinik saha uygulamalarından elde edilen gözlemlerin sentezlendiği bir perspektif (görüş) makalesidir. Çalışmanın literatür altyapısını oluşturmak amacıyla Web of Science, PubMed ve Google Scholar veri tabanlarında kapsamlı bir tarama gerçekleştirilmiştir. Tarama stratejisinde İngilizce ve Türkçe olarak "raptors (yırtıcı kuşlar)", "birds of prey (avcı kuşlar)", "masking phenomenon (maskeleme fenomeni)", "preservation reflex (korunma refleksi)", "wildlife rehabilitation (yaban hayatı rehabilitasyonu)", "clinical assessment (klinik değerlendirme)" ve "capture myopathy (yakalama miyopatisi)" anahtar kelimeleri kullanılmıştır. Literatür taramasında temel veteriner hekimlik ders kitaplarının[6-9] yanı sıra, konuyla ilgili son 30 yıla ait güncel araştırma makaleleri, derlemeler ve vaka sunumları değerlendirmeye dâhil edilmiştir.

Elde edilen literatür verileri, hastalık gizleme refleksinin evrimsel kökenleri ve fiziksel muayenenin sınırları açısından incelenmiştir. Saha deneyimleri ise hastanın kliniğe ilk kabulü, stres yönetimi, uzaktan davranış gözlemi, triyaj, fiziksel muayene ve tedavi planlaması süreçleri bağlamında ele alınmış

ve taranan literatür verileriyle harmanlanarak 3 ana faz ve bunlara bağlı 8 ardışık adımdan oluşan "Gözlem Öncelikli Klinik Yaklaşım (GÖKY)" kurgulanmıştır.

2.2. Bulgular

Literatür bulguları

Literatür incelemeleri, yırtıcı kuşlarda hastalık belirtisi olarak kabul edilen "hasta kuş bakışı"nın (kabartılmış tüyler, yarı kapalı gözler, tüneğe tutunamama ve şiddetli letarji), organizmanın genellikle maskeleme yapamayacak kadar güçten düştüğü ve fizyolojik enerji rezervlerinin tamamen tükendiği ileri dekompanzasyon evrelerinde ortaya çıkabildiğini göstermektedir.[6,7] Klinik ortama kabulde tehdit algısıyla dışarıya karşı stabil, dik, tetikte ve agresif görünen birçok bireyin aslında o an yüksek katekolamin (adrenalin) deşarjı ile ayakta kaldığı ve bu durumun şiddetli akut stres yanıtının bir parçası olduğu bildirilmektedir.[7,10] Yaban hayatı literatüründeki kapsamlı çalışmalar, kanatlı hastaların hastalık ileri safhalara ulaşana kadar belirgin klinik belirtiler göstermediklerini ve hastaya doğrudan müdahale içeren geleneksel fiziksel muayeneye dayanan yaklaşımların, bu evrimsel savunma refleksi nedeniyle tanıda yetersiz kalabileceğini vurgulamaktadır.[5,7,9]

Klinik saha gözlemleri

Uzun yıllar boyunca yürütülen yaban hayatı rehabilitasyon uygulamalarında, yaralı veya bakıma muhtaç olarak teslim edilen yaban hayvanlarının büyük bölümünde ilk kabul sırasında belirgin bir stres ve panik yanıtı gözlenmiştir. Bu süreçte birçok bireyin insan faktörünü doğrudan bir "predatör" olarak algıladığı ve çevreye karşı yüksek derecede tetikte görünmeye devam ettiği, buna karşın altta yatan (örneğin ortopedik veya sistemik) patolojik durumlarını davranışsal olarak maskelediği izlenmiştir. Ayrıca yoğun tehdit algısı altında sürdürülen bu "savaş veya kaç" davranışının, hayvanın onarım için kullanması gereken sınırlı enerji rezervlerinin hızla tüketilmesine katkıda bulunduğu gözlenmiştir. Ağır yaralı bireylerde ayrıntılı fiziksel klinik muayenenin stres faktörleri izole edilmeden erken dönemde gerçekleştirilmesinin; şiddetli laktik asidoz, geri dönüşümsüz yakalama miyopatisi (capture myopathy) krizleri ve akut kardiyovasküler kollapslara yol açabildiği tecrübe edilmiş olup, bu gözlemler yabani kuşlardaki spesifik ekzersiyonel miyopati (exertional myopathy) bildirimleriyle de bütünüyle örtüşmektedir.[10-13]

Gözlem Öncelikli Klinik Yaklaşım (GÖKY) Algoritması

Maskeleme fenomeninin klinik tanıda yaratabileceği yanılgıları ve hayvanın maruz kaldığı stres faktörlerini minimize etmek amacıyla, klinik saha deneyimlerine dayanan sistematik bir GÖKY algoritması geliştirilmiştir. Önerilen bu model; ilk kabul ve stabilizasyon, gözlem ve hedefe yönelik değerlendirme ile rehabilitasyon ve salım öncesi değerlendirme olmak üzere birbirini takip eden 3 ana faz ve bunlara bağlı 8 ardışık adımdan oluşmaktadır. Sürecin akış diyagramı Şekil 1'de özetlenmiş olup, fazların ve adımların klinik detayları aşağıda sunulmuştur:

FAZ I: İlk Kabul ve Stabilizasyon (Initial Admission and Stabilization)

Bu fazın temel amacı, kliniğe ulaşan hastanın akut stres seviyesini düşürmek, hayati risk taşıyan durumları saniyeler içinde taramak ve hipotermi/şok tablosunu kontrollü bir şekilde regüle etmektir.

1. **İlk kabul (minimal temas):** Hastanın kliniğe ulaştığı ilk temas anıdır. Kuşu getiren kişiden detaylı anamnez (bulunma şekli, süresi, ortamı) alınırken kuşun bulunduğu taşıma kutusunda loş ve sessiz bir alana alınması sağlanır. Kutunun kapağı hemen açılmaz, ortamdaki gereksiz gürültü ve personel sayısı en aza indirilir.[6,7,9]
2. **Hayati risk (triyaj) değerlendirmesi:** Bu aşamada hasta sadece görsel olarak saniyeler içerisinde taranır. Amaç detaylı muayene değil, hastanın anında müdahale edilmezse öleceği durumların (aktif fışkıran kanamalar, açık solunum/dispne, nöbet geçirme) tespit edilmesidir. Hayati tehlike yoksa doğrudan 3. adıma geçilir.[6,7,9]
3. **Kontrollü termal ilk barındırma ve hipovolemi yönetimi:** Yırtıcı kuşların kliniğe genellikle travma sonrası hipotermik ve şok tablosunda ulaşırlar. Bu aşamada hastayı sadece sessiz bir odaya almak yeterli değildir. Endotermik olan kuşun vücut ısısını yavaşça regüle etmek amacıyla inkübatör veya kontrollü ısıtma pedleri yardımıyla türe, vücut ağırlığına, hipotermi derecesine ve şok tablosuna göre bireyselleştirilmiş, kontrollü bir termal destek (genel klinik kılavuzlar doğrultusunda sıklıkla 25–30 °C) sağlanır.[6,7,9] Vücut ısısı düşük bir kuşun metabolizması yavaşlayacağı için gastrointestinal veya farmakolojik tedavilere yanıt vermeyeceği, hatta enerji kaybına bağlı olarak hipoglisemik şoktan ölebileceği göz önünde bulundurulmalıdır.[6,7] Bireyin klinik durumuna ve

fizyolojik stabilizasyon hızına bağlı olarak genellikle en az 30–60 dakika uyum ve sakinleşme payı verilir.

FAZ II: Gözlem ve Hedefe Yönelik Klinik Değerlendirme (Observation and Targeted Clinical Assessment)

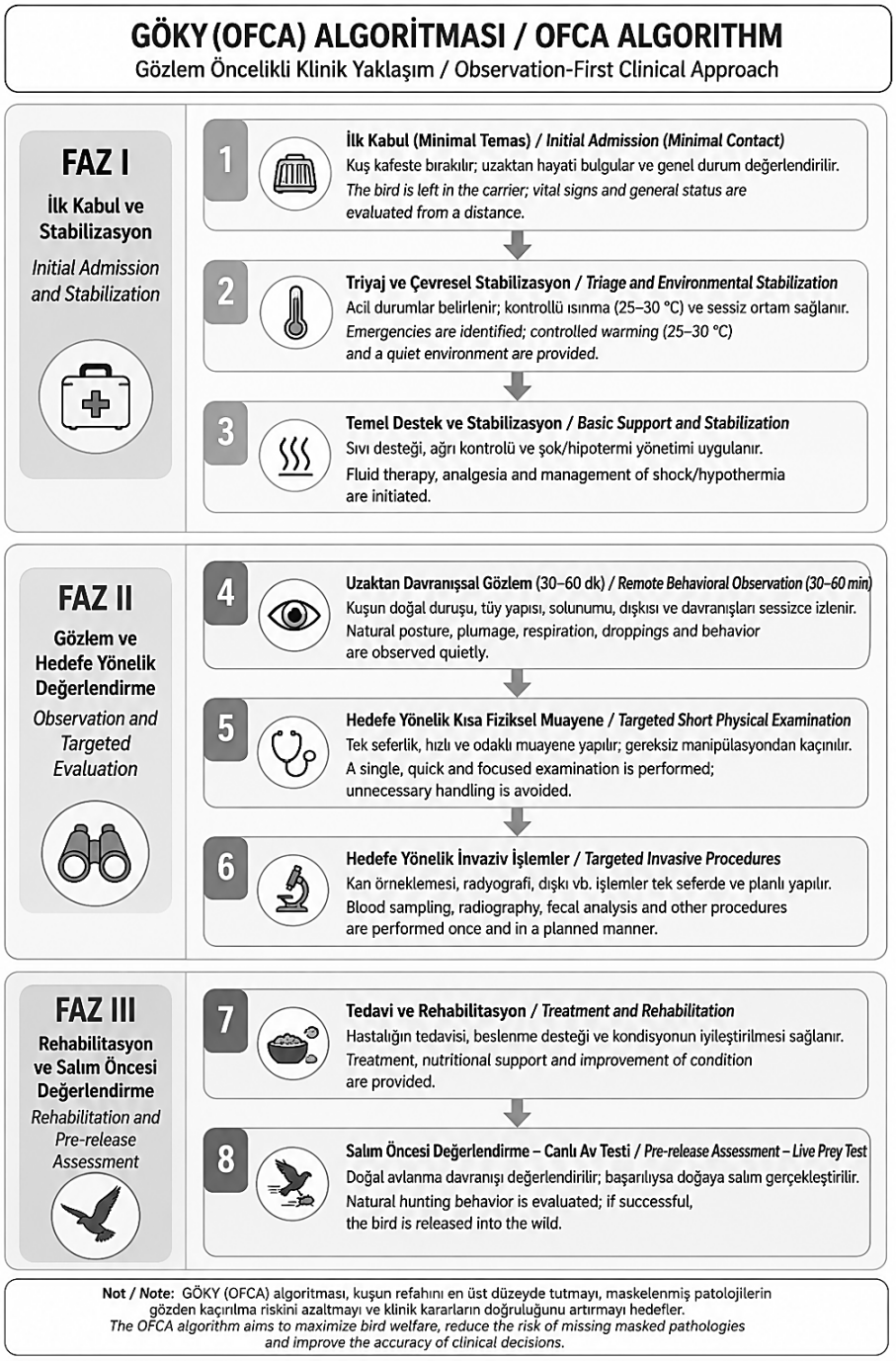
Bu fazın amacı, hastanın insanı predatör olarak algılamasıyla devreye giren maskeleme davranışını kırarak gerçek klinik postürünü uzaktan gözlemlemek ve ardından en az manipülasyonla hedefe yönelik klinik tanı adımlarını tamamlamaktır.

4. **Uzaktan davranış gözlemi ve objektif görsel skorlama (Kritik Aşama):** Hekim kuşu doğrudan rahatsız etmeden; bir kamera, ayna veya kutu üzerindeki küçük bir gözetleme deliği vasıtasıyla uzaktan inceler. İnsan tehdidi algılamayan kuş, maskeleme davranışını bırakarak gerçek beden duruşunu (postür) sergiler.[7,9] Bu aşamada kuşun tüneğe tutunma durumu, asimetrik kanat duruşları (kanat düşüklüğü), tüy kabartma (piloereksiyon), gözlerin kısılması veya kapalı tutulması ve ağız açık soluma gibi doğrudan gözlenebilir davranışsal göstergeler kayıt altına alınarak, doğrudan temastan kaçınan ve ileride valide edilerek standardize edilebilecek yapılandırılmış bir görsel stres/ağrı değerlendirmesi için klinik bir temel oluşturulur.[7,9,14]
5. **Görme duyusunun kapatılması ve önleyici (pre-emptive) analjezi:** Yakalanma ve tutulma süreci, kuşlarda fizyolojik dengeleri hızla bozarak ölümcül yakalama miyopatisi (capture myopathy) krizlerini tetikleyebilir.[10] Bunu önlemek amacıyla, kuşa müdahale edilmeden önce kalın bir havlu örtülür veya şahin başlığı (falconry hood) takılarak görme duyusu tamamen kapatılır. Fiziksel kısıtlama (zapturapt) başlar başlamaz, ağrı kaynaklı şoku ve kas yıkımını bloke etmek amacıyla hızlı etkili analjezikler (örn: butorphanol 1-2 mg/kg IM) veya meloksikam (0.5-1.0 mg/kg IM) uygulanarak önleyici analjezi protokolü derhal devreye sokulur.[6,7,9]

FAZ III: Rehabilitasyon ve Salım Öncesi Değerlendirme (Rehabilitation and Pre-release Assessment)

Modelin son fazı, klinik tedavisi tamamlanan yırtıcı kuşların doğada tek olarak hayatta kalabilecek fizyolojik ve avlanma kondisyonuna ulaştıklarının uluslararası standartlara göre doğrulanmasını ve salınmasını kapsar.

6. **Hedefe yönelik ve "tek seferlik temas" (single-handling) klinik muayene:** Kuşun enerji rezervlerini tüketecek tekrarlı zapturapt stresinden kaçınmak için bu aşamada tüm tanısal araçlar hazır bulundurulmalıdır. Kuş şahin başlığı ile sınırlandırılmış ve analjezisi sağlanmışken; hedefe yönelik kısa klinik fiziksel muayene, tanısal radyografi ve laboratuvar analizleri için kan örneğinin (*Vena basilica*) alınması gibi tüm invaziv işlemler mümkün olan en kısa sürede ve tek bir seans halinde tamamlanarak hayvanın maruz kaldığı iatrojenik stresörler önemli bir şekilde sınırlandırılır.[7,8,9]
7. **Tedavi ve besleme stratejisi:** Davranışsal ve hedefe yönelik fiziksel muayene bulgularıyla planlanan medikal tedavi protokolleri hızla uygulanır. Dehidrasyona bağlı gelişen prerenal azotemi tablosuna karşı yavaş rehidrasyon (tercihen SQ sıvı tedavisi) ile başlanır. Hidrasyonu sağlanan kuş için sindirim sistemini yormayacak, tüysüz/kemiksiz bütün gıdalar veya kolay sindirilebilir enteral beslenme formülleriyle nütrisyonel destek kademeli olarak başlatılır.[6,7,9]
8. **Doğaya salım öncesi kondisyonlama ve "canlı av" testi:** Stres faktörlerinden uzak bir iyileşme sürecinin ardından kuş, uçuş yeteneğini geri kazanması için kademeli olarak dış uçuş kafeslerine alınır.[7] Salım kararı öncesinde temel klinik değerlerin normal aralıkta olması ve yeterlik uçuş kondisyonu ile birlikte manevra kapasitesi teyit edilmelidir. Bununla birlikte, özellikle genç yaşta rehabilitasyona kabul edilen kuşlarda doğada hayatta kalabilmesi için mevzuat ve hayvan refahı koşullarına uygun olduğu süreçte avlanma becerisinin değerlendirilmesi amacıyla "canlı av yakalama becerisi" (live-prey testing) objektif olarak test edilebilir. Avlanma yeteneği olan, klinik ve gerekli durumlarda laboratuvar değerlendirmeleriyle yeterli iyileşmenin doğrulandığı bireyler, kendi sirkadiyen ritimlerine ve mevsimsel göç takvimlerine uygun en doğru saatte ve bölgede doğaya salınır.[3,5,15]



Şekil 1. GÖKY (OFCA) algoritması akış diyagramı

2.3. Tartışma

Yaban hayatı rehabilitasyon merkezlerine kabul edilen apeks predatör yırtıcı kuşlarda ilk triyaj ve tanının, hastayı doğrudan zapturapt altına alarak yapılan uzun süreli fiziksel muayeneye dayandırılması, hasta yönetimi açısından büyük bir risk barındırmaktadır. Bu çalışmada kavramsallaştırılan maskeleme fenomeni, kuşun o anki gerçek fizyolojik durumunu yansıtmaz; aksine zayıflığını predatörlerden gizlemeye çalışan evrimsel bir savunma stratejisinin ürünüdür.[5,7] GÖKY, hastanın klinikteki ilk kabul anından itibaren bu katekolaminerjik savunma stratejisini tetikleyen stresörleri ortadan kaldırmayı, erken ve gereksiz manipülasyonları engelleyerek maskeleme refleksini sürdürebilmek amacıyla harcadığı kritik enerji tüketimini durdurmayı ve potansiyel olarak ölümcül yakalama miyopatisi (capture myopathy) riskini minimize etmeyi amaçlamaktadır.[10-13]

Klinik saha deneyimleri, düşük uyaranlı barındırma uygulamalarının yalnızca davranışsal stresin azaltılması açısından değil, aynı zamanda rehabilitasyon başarısı açısından da hayati olduğunu göstermektedir. Özellikle geniş aralıklı tel kafeslerde barındırılan yırtıcı kuşlarda panik halindeki kanat çırpmalar sırasında primer ve sekonder uçuş teleklerinde mekanik hasar oluşabilmektedir. Bu durum telek kırıkları veya deformasyonları nedeniyle kuşun tamamen iyileşse bile uçuş performansını kaybederek doğaya dönüş sürecinin ciddi ölçüde gecikmesine neden olmaktadır. Buna karşılık GÖKY'nin temelini oluşturan opak, düz tabanlı ve yumuşak yüzeyli taşıma kutularının kullanılması, hem çevresel uyaranları azaltarak maskeleme refleksini kırmakta hem de telek bütünlüğünü korumaktadır.

GÖKY'nin etkinliğine dair doğrudan ampirik karşılaştırmalar mevcut olmasa da, bu yaklaşım yaban kuşlarında fatal sonuçlar doğurabilen ekzersiyonel miyopati (exertional myopathy) patofizyolojisini engellemek adına kanatlı tıbbının kabul görmüş fizyolojik gerçekleri üzerine inşa edilmiş güçlü bir mantıksal sistemdir.[6,8,13] Önerilen bu klinik algoritma; Uluslararası Yaban Hayatı Rehabilitasyon Konseyi (IWRC) ve Ulusal Yaban Hayatı Rehabilitatörleri Birliği (NWRA) tarafından yayımlanan, yaban hayvanlarının ilk kabul ve triyajında stresi, iatrojenik hasarları ve gereksiz temasları en aza indirme konusundaki uluslararası minimum standartlarla tam bir paralellik göstermektedir.[3,7,9] Ayrıca uluslararası rehabilitasyon rehberlerinde ve yaban hayatı literatüründe de önemle vurgulandığı üzere; başarılı bir rehabilitasyon süreci yalnızca klinik/anatomik bir iyileşmeyle sınırlı kalmayıp, hayvanın doğaya salındıktan sonra insan desteğine ihtiyaç duymadan kendi başına tam fonksiyon gösterebilmesi (özellikle avlanma ve hayatta kalma becerisi) şartına bağlıdır.[3,5,15] Klasik klinik değerlendirmelerin neden olduğu hekim yanılgılarını önlemesi ve hayvan refahını merkeze alması açısından GÖKY, yaban hayatı hekimliğinde pratik bir klinik çerçeve olma potansiyeli taşımaktadır. Bu kavramsal yaklaşımın, gelecekte farklı merkezlerde yürütülecek prospektif saha çalışmaları ve vaka serileri ile desteklenmesi, etkinliğini istatistiksel olarak da kanıtlayacaktır. Bu nedenle GÖKY (OFCA), mevcut aşamada farklı yaban hayatı rehabilitasyon merkezlerinde yürütülecek prospektif çalışmalarla doğrulanması gereken kavramsal bir klinik yaklaşım olarak değerlendirilmelidir. Bu yaklaşımın klinik etkinliği ve rehabilitasyon sonuçlarına olan katkısı, gelecekte gerçekleştirilecek çok merkezli çalışmalarla ortaya konulabilecektir.

3. Sonuç

Maskeleme fenomeni yalnızca doğal bir davranışsal adaptasyon olarak değil, yaban hayatı hekimliğinde ilk klinik kararları doğrudan ve yanıltıcı şekilde etkileyen temel bir hasta yönetimi sorunu olarak değerlendirilmelidir. Bu sorunun çözümüne yönelik olarak geliştirilen GÖKY (OFCA), hekimleri "görünürde stabil olma" yanılgısından korumak amacıyla düşük stresli, uzaktan gözlem odaklı ve pratik saha tecrübesine dayalı bir klinik yaklaşım sunmaktadır. GÖKY'nin yaban hayatı kliniklerince pratik bir yaklaşım olarak benimsenmesinin, hayvan refahını artırarak gereksiz iatrojenik ölümleri azaltması ve rehabilitasyon başarısını artırması beklenmektedir. Düşük uyaranlı ve telek bütünlüğünü koruyan uygun barındırma uygulamalarının ilk kabulden rehabilitasyonun sonuna kadar sürdürülmesi, hem stresin azaltılması hem de fonksiyonel iyileşmenin desteklenmesi açısından GÖKY yaklaşımının temel bileşenlerinden biridir.

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EXAMINING POSTGRADUATE THESES INVOLVING LAUGHTER YOGA INTERVENTIONS IN TURKIYE: A DOCUMENT ANALYSIS

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ABSTRACT

Objective: This study aimed to examine completed postgraduate theses on laughter yoga in Türkiye, identify current research trends, and provide a framework for future research.

Materials and Methods

This descriptive study was conducted using the document analysis method. Data were obtained by searching the Council of Higher Education (CoHE) National Thesis Center database using the keywords *"laughter yoga"* and *"laughter therapy."* All completed postgraduate theses on laughter yoga identified through the search were evaluated in terms of publication year, thesis type, academic discipline, study design, sample characteristics, intervention protocols, data collection instruments, and main findings.

Results

A total of 35 completed postgraduate theses on laughter yoga in Türkiye were identified. Of these, 88.6% were conducted in 2022 or later, 88.6% were conducted in the field of nursing, and 82.9% employed randomized controlled experimental design. The studies included healthcare professionals, nursing and midwifery students, women's health groups, individuals with chronic diseases, and various special populations. The most frequently used data collection instruments were the Perceived Stress Scale, the Pittsburgh Sleep Quality Index, and various quality-of-life measures. Overall, the findings indicated that laughter yoga had positive effects in reducing stress, anxiety, depression, pain, and sleep problems and in improving quality of life, psychological well-being, and spiritual well-being. However, findings regarding biochemical markers were limited and heterogeneous.

Conclusion

The reviewed postgraduate theses suggest that laughter yoga is a complementary nursing intervention that can be applied to diverse populations and may have positive effects, particularly on psychosocial health outcomes. Nevertheless, further multicenter randomized controlled studies with standardized intervention protocols, long-term follow-up, and mixed-methods designs incorporating participants' experiences are needed.

Keywords: Laughter yoga, postgraduate theses, nursing, complementary therapy, document analysis.

Introduction

As an expression of humor, laughter is not merely an expression of emotion but a multidimensional human behavior that has been regarded as a good medicine for centuries (Kramer & Leitao, 2023). Laughter yoga/laughter therapy is a structured mind–body practice developed by Dr. Madan Kataria in India in 1995, which combines voluntary/simulated laughter exercises with yogic breathing techniques and is generally practiced in a group setting.

The practice involves initiating laughter through exercise without requiring a humorous stimulus, humor, or a joke, and sustaining it through interactions such as deep breathing, rhythmic movements, eye contact, and childlike play (Kataria, 2002; Bressington et al., 2019). According to Kataria, laughter initiated voluntarily can gradually develop into spontaneous laughter through eye contact and playful interactions within the group; this process is combined with breathing exercises (Kataria, 2002). Therefore, laughter yoga is considered not merely an activity based on producing laughter, but rather a holistic practice in which laughter, breathing, movement, and social interaction are used together.

Although the emergence of laughter yoga is rooted in a modern health practice, the functions of laughter and humor in human behavior have been examined from philosophical and psychological perspectives since much earlier periods. In ancient Greek thought, Plato's and Aristotle's considerations of laughter formed the background to later superiority and incongruity approaches, while in the modern period, the views of Spencer and Freud sought to explain the relationship between laughter and processes of tension and relief. Classical theories of laughter are approaches aimed at explaining the emergence and functions of laughter. In the literature, these approaches are generally discussed under the theories of superiority, incongruity, and relief/tension release. Superiority theory explains laughter in terms of an individual perceiving themselves as superior to others or to a previous state; incongruity theory explains it in terms of the mismatch between expectations and the situation encountered; and relief theory explains it in terms of the reduction or release of accumulated psychological tension. However, each of these approaches focuses on a different dimension of laughter and cannot, on its own, explain all aspects of the phenomenon of laughter (Morreall, 1986; Wilkins & Eisenbraun, 2009).

The social dimension of laughter has been examined in greater detail through contemporary neuroscientific approaches. The frequent occurrence of laughter in social settings and its contagious nature suggest that it serves an important function in interpersonal interaction and social bonding. In this context, it has also been proposed that mirror neuron mechanisms may play a role in the perception of others' laughter and the accompanying behavioral responses (Gervais & Wilson, 2005; Palagi et al., 2022).

From the perspective of laughter yoga, approaches suggesting that voluntary laughter may influence physiological and psychological processes, that breathing and bodily movements may regulate mood, and that laughter performed within a group may support social interaction become more important than classical theories of laughter. Therefore, the theoretical foundations of laughter yoga should not be limited to a single theory of laughter but should instead be considered within a multidimensional framework in which biological, psychological, and social mechanisms are evaluated together (Kataria, 2018).

Laughter yoga is practiced in the form of sessions that include warm-up, breathing, and laughter exercises accompanied by songs and clapping. The sessions, which can be conducted individually or in groups, consist of sessions lasting 30–45 minutes. Laughter yoga has four main components: warm-up exercises, deep breathing exercises, childlike playfulness, and laughter exercises (Kataria, 2018).

- ***Hand Clapping and Warm-Up Exercises:*** The hands are held parallel to each other and clapped so that the fingertips touch each other. To increase the group's energy level and synchronize the group, hand clapping is generally accompanied by a rhythm such as 1-2, 1-2-3. These activities engage group participants mentally and physically, preparing them for the subsequent laughter exercises (Kataria, 2011, 2012).
- ***Deep Breathing Exercises:*** The arms are raised toward the sky while taking a breath as deeply as possible. Following deep inhalation, the breath is held for 4–5 seconds. Exhalation is performed slowly and rhythmically. Depending on the group dynamics, deep breathing exercises are practiced for approximately 10–15 minutes (Kataria, 2011).
- ***Childlike Playfulness:*** Group members hold their arms upward in the shape of the letter "Y," with their palms facing the sky. The yoga leader uses motivational words such as "very good–very good–yes" between breathing exercises and yoga sessions to increase the enthusiasm and energy of the group (Kataria, 2011, 2012).
- ***Laughter Exercises:*** At this stage, participants continuously laugh through different laughter exercises without any particular reason and are encouraged to laugh. In the final stage, verbal suggestions are given to the group by saying, "Place your hand on your heart, feel your heartbeat, exhale with a smile, pray or make a wish, and smile as if your wish has come true," and the session is concluded (Öztürk & Tezel, 2021).

Laughter yoga has been reported to have physiological and psychological effects on individuals (Çakar et al., 2021). When these effects are examined, it can be stated that laughter yoga increases the release of dopamine and endorphins, decreases cortisol levels, regulates sleep, improves mood, increases pain tolerance, regulates memory and interpersonal relationships, and improves stress (Decaro & Constantine Brown, 2016; Fujisawa et al., 2018; Kashdan et al., 2014; Kurtz & Algoe, 2015; Namazinia et al., 2023; Özer & Ateş, 2021). The relevant literature also indicates that laughter yoga has beneficial effects on glycemic control (Hirosaki et al., 2023), depression levels (Bressington et al., 2019), pregnancy (Ağapınar Şahin & Bekar, 2023) and menopausal symptoms (Koca et al., 2024), blood pressure (Marisa & Danismaya, 2024), exercise capacity in patients with lung cancer (Han et al., 2023), chemotherapy-induced symptoms (Namazinia et al., 2024; Uğur et al., 2025), and renal function in patients with chronic kidney failure (Sharma, 2018).

Laughter and humor can be described as natural emotional expressions that create a mutual, sincere, and humanistic interaction between patients and nurses, offering authenticity and genuineness. By reducing patients' anxiety, increasing their participation in self-care, and enhancing positive levels of interaction, they can be used as a highly beneficial tool for resolving and managing complex processes (Çevik Aktura et al., 2021).

The fact that laughter yoga is an easy-to-implement, group-based, and relatively low-cost complementary practice is considered among the characteristics that support its use in healthcare services (Ağapınar Şahin & Bekar, 2023). In nursing care, laughter and humor are considered as tools that may support humanistic and therapeutic interaction between patients and nurses. The potential of laughter yoga to reduce patients' anxiety, support positive affect, and increase participation in care processes allows this practice to be considered as a complementary intervention in nursing care (Çevik Aktura et al., 2021). Therefore, the increasing attention given to laughter yoga in nursing research is important for advancing the evidence-based use of this practice.

It is noteworthy that research on laughter yoga in Türkiye has increased markedly, particularly in recent years. Nevertheless, there is a need for a comprehensive evaluation of the areas in which existing research has focused, the populations in which it has been conducted, the research designs and measurement tools used, and the extent to which the implementation protocols are similar. In particular, postgraduate theses constitute an important source for monitoring the trends in academic research and the development of scientific knowledge generated within a field. A systematic examination of postgraduate theses conducted on laughter yoga in Türkiye may contribute to identifying the strengths and limitations of the existing body of research and to determining priorities for future research.

Accordingly, the aim of this study is to examine completed postgraduate theses on laughter yoga in Türkiye, identify current research trends, and provide a framework for future research.

Materials and Methods

Research Design

This study is a descriptive study conducted using the document analysis method. In the study, the characteristics of the included postgraduate theses were systematically examined according to predetermined categories, the obtained data were coded, and analyzed using descriptive statistics.

Scope of the Study and Identification of Theses

The scope of the study consisted of postgraduate theses in which laughter yoga/laughter therapy was implemented as an intervention in Türkiye. To identify the theses, a search was conducted on June 18, 2026, through the National Thesis Center of the Council of Higher Education (YÖK) using the keywords *"laughter yoga"* and *"laughter therapy."* No date restriction was applied to the search, and the aim was to identify all completed postgraduate theses on the subject in Türkiye. As a result of the search, the full texts of 34 theses were accessed, while only the abstract of one thesis was accessible; however, since all the necessary information was provided in the abstract, all 35 theses identified through the search were included in the evaluation. Therefore, no separate sample selection was performed in the study. The titles, abstracts, and full texts of the theses identified through the search were examined, and theses in which laughter yoga/laughter therapy was implemented as an intervention within the scope of the research were included in the study.

Data Collection Instrument

The "Thesis Review and Data Collection Form," developed by the researchers in accordance with the aim of the study, was used to examine the theses. For each thesis, the following information was recorded:

- Author and publication year
- University where the thesis was conducted
- Department
- Postgraduate education level
- Research type/design
- Sample group
- Sample size
- Characteristics of the laughter yoga/therapy intervention
- Intervention duration and total number of sessions
- Mode of implementation
- Scales and other data collection instruments used
- Main findings of the study

Data Analysis

The data obtained from the 35 theses examined were analyzed using descriptive statistics. The characteristics of the theses were presented using frequency (n) and percentage (%) values. Quantitative characteristics such as sample size, intervention duration, and number of sessions were evaluated based on the values reported in the theses. The results of the studies were classified and presented according to the main findings reported in the theses examined. Thus, an overview of the postgraduate theses conducted in the field of laughter yoga/laughter therapy in Türkiye was provided in terms of publication year, postgraduate education level, research design, sample characteristics, intervention characteristics, measurement instruments used, and main research findings.

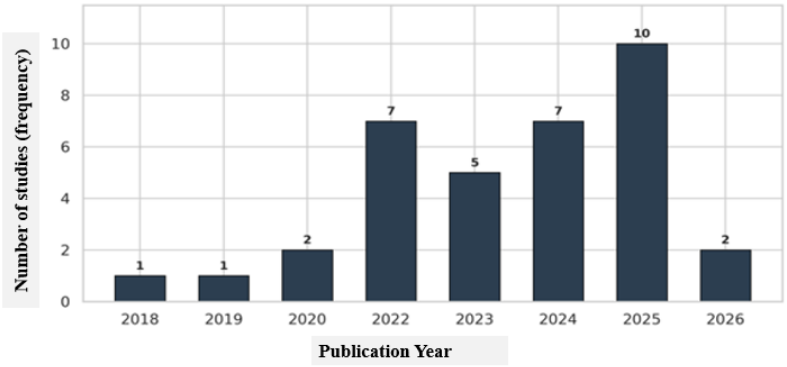
Ethical Considerations

As this study does not involve the collection of primary data from human participants and is based on the document analysis of postgraduate theses made publicly accessible through a publicly available database, ethical committee approval is not required. The information obtained from the theses examined in the study was evaluated solely for scientific purposes, and the findings were presented collectively. Personal information regarding the thesis authors was not used within the scope of the study; data security and the principles of academic ethics were observed.

Results

When the postgraduate theses related to laughter yoga were examined, it was determined that the first thesis on the subject in Türkiye was conducted in 2018 and that a total of 35 theses were completed between 2018 and 2026 (Figure 1). It was observed that 88.6% (n = 31) of the theses examined were conducted in 2022 or later.

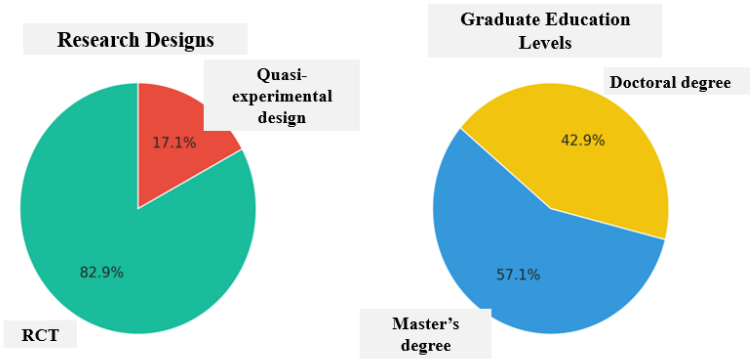
Figure 1. Distribution of Laughter Yoga Studies by Year (2018–2026)



Of the theses, 88.6% (n = 31) were conducted in the field of nursing, whereas 11.4% (n = 4) were conducted in the field of midwifery. It was determined that 57.1% (n = 20) of the theses were master's theses, while 42.9% (n = 15) were doctoral dissertations.

Regarding the research designs, 82.9% (n = 29) of the theses employed a randomized controlled design, while 17.1% (n = 6) used a quasi-experimental design (Figure 2). Detailed data on postgraduate theses involving laughter yoga interventions in Türkiye are presented in Table 1.

Figure 2. Methodological and Academic Distribution of the Studies (N = 35)



Sample Characteristics and Intervention Protocols of the Theses

When the theses included in the review were evaluated in terms of their sample characteristics, it was observed that the studies were conducted across diverse populations. Seven theses involved healthcare professionals (e.g., nurses and personnel of the National Medical Rescue Team [UMKE]), seven involved nursing and midwifery students, 10 involved clinical populations and individuals with chronic diseases (e.g., patients undergoing hemodialysis and those with cancer, diabetes, chronic obstructive pulmonary disease [COPD], or undergoing bariatric surgery), five involved women's health populations (e.g., pregnant women, postpartum women, women with infertility, and women during breastfeeding or menopause), and six involved special and vulnerable populations (e.g., individuals aged 65 years and older, individuals with visual impairments, adolescents, and mothers of children with special needs).

Regarding sample sizes, the smallest sample consisted of 40 participants (experimental = 20, control = 20) and was recruited from mothers of children with special needs, whereas the largest sample consisted of 144 participants (experimental = 71, control = 73) and comprised women in the postpartum period.

When the number of sessions in the laughter yoga intervention was examined, it was found that a total of eight sessions were implemented in 60% of the theses, with the intervention generally structured as two sessions per week over a period of four weeks. The lowest number of sessions was two, which was implemented in a study examining the effects of laughter yoga on premenstrual symptoms among nursing and midwifery students during the luteal phase. The highest number of sessions was 16, which was implemented in three theses. In these studies, the samples consisted of hemodialysis patients, nurses, and patients with breast cancer undergoing chemotherapy.

Data Collection Instruments and Measurement Characteristics

An evaluation of the data collection instruments used across the 35 postgraduate theses included in the review revealed that the studies predominantly focused on assessing variables such as psychological well-being, stress, sleep quality, and quality of life. In all theses, a Personal Information Form was used to collect participants' sociodemographic and descriptive characteristics.

Among the standardized measurement instruments used, the Perceived Stress Scale (PSS) was identified as the most frequently used instrument (n = 11), followed by the Pittsburgh Sleep Quality Index (PSQI) (n = 5) and various quality-of-life scales (n = 5). The quality-of-life scales were used across different contexts, including kidney disease, cancer, menopause, work life, and general quality of life.

In addition, instruments such as the Visual Analog Scale (VAS) and the Numeric Pain Rating Scale were used to assess pain, various scales were employed to evaluate spiritual and psychological well-being, and biochemical measures, such as salivary cortisol levels, were used to assess physiological variables. Less frequently used instruments included the Maslach Burnout Inventory, the Hospital Anxiety and Depression Scale, the General Health Questionnaire, the Warwick–Edinburgh Mental Well-being Scale, and the Depression Anxiety Stress Scales. Similarly, scales assessing spirituality and spiritual care were also utilized.

It was also observed that measurement instruments specific to the characteristics of the study samples were used.

Among student populations, instruments assessing test anxiety, self-reflection, and problem-solving skills were preferred, whereas among women's health populations, instruments evaluating prenatal attachment, pregnancy-related symptoms, premenstrual syndrome, and breastfeeding self-efficacy were used. In clinical populations, instruments assessing illness perception, COPD symptoms, and caregiver burden were employed, while in occupational groups, instruments measuring job performance, mindfulness, and professional resilience were used.

Overall, it was determined that the measurement instruments used in the theses predominantly focused on stress, sleep, and quality of life; psychological variables were assessed more frequently than physiological measures; and measurement instruments tailored to the characteristics of the respective sample groups were also widely used.

Research Findings on the Effects of Laughter Yoga

Among the 35 theses included in the review, only 8 studies (22.9%) conducted follow-up assessments after the post-test, whereas in 27 studies (77.1%), the effects of the intervention were evaluated solely based on pre-test and post-test measurements. The reported findings indicated that laughter yoga was generally associated with positive psychological, physical, and social health outcomes across different populations.

In terms of psychological variables, particularly in studies conducted among nursing students, healthcare professionals, and women's health populations, laughter yoga was found to significantly reduce levels of stress, anxiety, and depression. For example, randomized controlled trials involving nursing students reported reductions in psychological symptom levels; some studies also reported concomitant decreases in salivary cortisol levels. Similarly, studies conducted among healthcare professionals indicated that laughter yoga may reduce burnout and occupational stress while improving attention and job performance. However, some studies found no significant changes in certain variables, particularly work motivation.

Among women's health populations, laughter yoga was found to reduce stress and anxiety levels and enhance prenatal attachment among pregnant women. Among women in the menopausal period, it was found to alleviate the severity of menopausal symptoms and improve quality of life. However, some postpartum studies found no significant effect on specific outcomes, such as breastfeeding self-efficacy.

Among clinical patient populations, the findings also demonstrated the potential benefits of laughter yoga as a complementary intervention. Studies conducted among patients with cancer reported reductions in anxiety and depression levels, improvements in quality of life, and alleviation of symptoms such as chemotherapy-induced nausea and vomiting. Among individuals with chronic conditions such as hemodialysis, diabetes, and COPD, reductions in pain levels, improvements in sleep quality, and, in some studies, favorable changes in blood glucose levels were reported.

In terms of physiological and biochemical parameters, some studies reported favorable changes, such as reductions in salivary cortisol levels and increases in oxygen saturation. However, physiological and biochemical outcomes were not fully consistent across studies, and some studies found no statistically significant differences in these parameters.

When symptom- and functioning-related outcomes such as sleep quality, pain, and quality of life were evaluated, laughter yoga was found to produce positive outcomes, particularly in terms of improving sleep quality and reducing pain. These effects were reported in both healthy individuals and diverse clinical populations.

Overall, the majority of postgraduate theses conducted in Türkiye demonstrated that laughter yoga produced positive outcomes in terms of reducing stress, supporting psychological well-being, improving sleep quality and quality of life, and alleviating certain physical symptoms. In contrast, findings regarding physiological and, particularly, biochemical measures were more limited and heterogeneous, and no significant effects were observed for some outcome variables. Furthermore, the limited number of theses that included follow-up assessments indicates that the effects of laughter yoga have predominantly been evaluated based on short-term outcomes.

Table 1. Summary of Postgraduate Theses Involving Laughter Yoga Interventions in Türkiye (N = 35)

No	Author, Year, University & Degree	Sample Population & Sample Size (N)	Intervention Protocol Characteristics	Measurement Scales/ Parameters	Pretest–Posttest–Follow-up Assessment Timing	Key Findings and Clinical Implications
1	Öztürk, 2018 Ankara University (Doctoral)	Nursing Students (1st Year) Experimental: 38 Control: 37	Experimental group: 2 sessions/week for 4 weeks (40 min/session); 8 sessions in total. Control group: No intervention.	Descriptive Characteristics Questionnaire, Brief Symptom Inventory, Salivary Cortisol Level	Pretest: Before the intervention Posttest: At the end of Week 4 Follow-up assessment: None	Among first-year nursing students at the Department of Nursing, Faculty of Health Sciences, Ankara University, the laughter yoga intervention was found to be effective in reducing psychological symptoms and salivary cortisol levels.
2	Özer, 2019 Üsküdar University (Doctoral)	Hemodialysis Patients Experimental: 34 Control: 34	Experimental group: 2 sessions/week for 8 weeks (30 min/session); 16 sessions in total. Control group: No intervention.	Sociodemographic Information Form, Beta-Endorphin Level, Visual Analog Scale (VAS), Pittsburgh Sleep Quality Index (PSQI)	Pretest: Before the intervention Posttest: At the end of Weeks 4 and 8 Follow-up assessment: None	Although laughter yoga did not increase beta-endorphin levels in patients undergoing hemodialysis, it was found to be effective in reducing the severity of pain, the most commonly experienced symptom, and improving sleep quality. Laughter yoga may be recommended as a cost-effective and easily accessible nursing intervention for managing these two symptoms.
3	Şahin, 2020 Sivas Cumhuriyet University (Doctoral)	Pregnant Women Enrolled in a Childbirth Preparation Class Experimental: 43 Control: 42	Experimental group: 2 sessions/week for 4 weeks (approximately 45 min/session); 8 sessions in total. Control group: Routine pregnancy education.	Pregnancy Information Form, Pregnancy Symptom Inventory, Warwick–Edinburgh Mental Well-being Scale, Prenatal Attachment Inventory	Pretest: Before the intervention Posttest: At the end of Week 4 Follow-up assessment: None	Laughter yoga reduced the frequency of pregnancy symptoms and the extent to which these symptoms interfered with daily activities, while increasing pregnant women's levels of mental well-being and prenatal attachment. Laughter yoga may be used during pregnancy to alleviate pregnancy symptoms and enhance mental well-being and prenatal attachment.
4	Karali, 2020 Marmara University (Master's)	Midwifery and Nursing Students Experimental: 32	Experimental group: Two 30-minute sessions per week during the luteal phase; 2	Descriptive Information Form, Premenstrual Syndrome Symptom Scale,	Pretest: Before the intervention Posttest: After	The findings suggest that laughter yoga has positive effects both in reducing

		Control: 48	sessions in total. Control group: No intervention.	"How Do You Feel?" Questionnaire, and Visual Analogue Scale (VAS)	the intervention (a few days before the expected menstrual period) Follow-up assessment: None	PMS symptoms and in promoting participants' subjective well-being, including enthusiasm, energy level, mood, optimism, stress level, sense of friendship with group members, awareness of breathing, level of muscle relaxation, mental relaxation, and the desire to laugh spontaneously without an apparent reason.
5	Kızılkaya, 2022 İnönü University (Doctoral)	Bariatric Surgery Patients Experimental: 31 Control: 31	Experimental group: 2 sessions/week for 5 weeks (50 min/session); 10 sessions in total. Control group: No intervention.	Patient Information Form, Beck Depression Inventory, Serotonin Level Recording Form	Pretest: Before the intervention Posttest: At the end of Week 5 Follow-up assessment: None	Laughter yoga was found to reduce depression following bariatric surgery and to decrease serotonin levels; however, the decrease in serotonin levels was not statistically significant compared with the control group.
6	Bedez, 2022 Dokuz Eylül University (Master's)	Hematological Cancer Patients Experimental: 30 Control: 30	Experimental group: 3 sessions/week for 2 weeks (45 min/session); 6 sessions in total. Control group: Routine clinical care.	Patient Information Form, Eastern Cooperative Oncology Group (ECOG) Performance Status Scale, Index of Nausea and Vomiting Scale, Hospital Anxiety and Depression Scale (HADS), Patient Satisfaction Scale	Tests were administered at different time points. Rhodes Index of Nausea, Vomiting and Retching: Pretest: After the first intervention session Follow-up assessment: Daily at the same time throughout the two-week period Hospital Anxiety and Depression Scale: Pretest: After the first intervention session Posttest: After the intervention (at the end of Week 2) Patient Satisfaction Scale: Single assessment: After the intervention (at the end of Week 2)	Laughter yoga was found to reduce symptom distress related to nausea, vomiting, and anxiety among patients with hematological cancer. Accordingly, integrating laughter yoga into the treatment process is recommended to support patients' adherence to and continuity of treatment.
7	İnce, 2022 İstanbul Okan University (Master's)	Women Diagnosed with Gynecological Cancer	Experimental group: 2 sessions/week for 6 weeks (35 min/session); 12	Introductory Information Form and Psychological Well-being Scale	Pretest: Before the intervention Posttest: At	The mean pretest scores on the Psychological Well-being Scale were similar

		Experimental: 35 Control: 35	sessions in total (online). Control group: Routine nursing care.		Week 6, at the end of the 12th session Follow-up assessment: None	between the intervention and control groups. In the control group, the posttest Psychological Well-being Scale scores decreased significantly compared with the pretest scores, whereas in the intervention group, the posttest scores increased significantly compared with the pretest scores. Based on the findings, laughter yoga is recommended for integration into routine nursing care to enhance the psychological well-being of oncology patients. It is also recommended that designated spaces be established in hospital oncology outpatient clinics and Cancer Early Diagnosis, Screening and Education Centers (KETEM) for nurses who have received laughter yoga certification.
8	Kaba, 2022 Karadeniz Teknik University (Doctoral)	Nurses Laughter Yoga Group: 33 Mindfulness Group: 34 Control Group: 34	Experimental group: 2 sessions/week for 8 weeks (30–45 min/session); 16 sessions in total. Control group: No intervention.	Personal Information Form, Chalder Fatigue Scale, Computerized Sustained Attention Test, Stroop Test Victoria Version, and Individual Work Performance Questionnaire (IWPQ)	Pretest: Before the intervention Interim assessment: During the intervention, at the end of Week 4 or after the 8th session Posttest: At the end of Week 8 Follow-up assessment: One month after the posttest	During the intervention period, laughter therapy and mindfulness practices reduced nurses' perceived fatigue while improving their levels of sustained attention and perceived individual work performance. The sustainability of these positive effects of laughter and mindfulness practices could be investigated through booster sessions, such as follow-up interventions conducted every two weeks.
9	Üner, 2022 Marmara University (Doctoral)	Nursing Students Experimental: 35 Control: 35	Experimental group: 2 sessions/week for 4 weeks (45 min/session); 8 sessions in total (online).	Introductory Information Form, General Health Questionnaire-28 (GHQ-28), Pittsburgh Sleep Quality Index (PSQI), and Perceived Stress Scale (PSS)	Pretest: Before the intervention Posttest: At the end of Week 8 Follow-up assessment: None	Laughter therapy had a substantial effect on improving perceived stress, general health status, and sleep quality. It may be considered an intervention that can be implemented by school health

						nurses among university students to help regulate perceived stress, general health status, and sleep quality.
10	Şahin, 2022 Atatürk University (Doctoral)	Postpartum Women Experimental: 71 Control: 73	Experimental group: 2 sessions/week for 4 weeks (45 min for the first session and 30 min for subsequent sessions); 8 sessions in total (online).	Survey Form, Postpartum Specific Anxiety Scale (PSAS), and Perceived Stress Scale (PSS)	Pretest: Before the intervention Posttest: At the end of Week 4 Follow-up assessment: None	Laughter yoga was found to reduce anxiety and stress levels among women in the postpartum period.
11	Kuzu, 2022 İstanbul Medipol University (Master's)	Hematological Cancer Patients Experimental: 22 Control: 22	Experimental group: Laughter yoga was administered daily for 14 consecutive days. Control group: No intervention.	Patient Information Form, Pittsburgh Sleep Quality Index (PSQI), Visual Analog Pain Scale (VAS), Spielberger State-Trait Anxiety Inventory (STAI), and Physiological Parameters Monitoring Form.	Pretest: Before the intervention Posttest: At the end of the 7th and 14th sessions Follow-up assessment: None	Significant changes were observed in sleep quality, state anxiety levels, pain, diastolic blood pressure, oxygen saturation, respiratory rate, and pulse rate among patients in the intervention group. Sleep quality and oxygen saturation increased, whereas pain levels, state anxiety, respiratory rate, and pulse rate decreased significantly. No change was observed in body temperature.
12	Yılmaz, 2023 Manisa Celal Bayar University (Master's)	Intensive Care Nurses Experimental: 33 Control: 33	Experimental group: 2 sessions/week for 4 weeks (30–40 min/session); 8 sessions in total.	Nurse Information Form, Nurse Work Motivation Scale, Perceived Stress Scale (PSS), and Warwick–Edinburgh Mental Well-being Scale.	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	Laughter yoga administered to intensive care nurses was found to have no significant effect on perceived stress levels or work motivation; however, a statistically significant difference was observed in the mean mental well-being scores of the intervention group.
13	Bilgihan, 2023 İstanbul Medipol University (Master's)	Psychiatric Nurses Experimental: 35 Control: 35	Total of 8 sessions (30 min/session).	Nurse Information Form, Maslach Burnout Inventory, Perceived Stress Scale (PSS), and General Health Questionnaire (GHQ).	Pretest: Before the intervention Posttest: At the end of the 8th session Follow-up assessment: None	Laughter yoga administered to psychiatric nurses was found to have positive effects on general health status, perceived stress levels, and burnout. Given its reported and demonstrated positive effects on the maintenance and promotion of mental health, integrating laughter yoga into

						the healthcare system as a complementary practice and promoting its wider implementation is considered important.
14	Diril, 2023 Atatürk University (Master's)	Women with Primary Infertility Experimental: 40 Control: 41	Experimental group: 2 sessions/week for 4 weeks (30–40 min/session); 8 sessions in total.	Survey Form and Infertility Stress Scale	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	Based on the posttest mean scores for all subscales of the Infertility Stress Scale, the differences between the experimental and control groups were statistically significant. Accordingly, women in the experimental group who participated in laughter yoga experienced a statistically significant reduction in stress levels across all domains following the intervention. Laughter yoga is an effective method that can be used to reduce stress levels among women with primary infertility.
15	Akçin, 2023 İnönü University (Master's)	Patients with Type 2 Diabetes Experimental: 50 Control: 50	Experimental group: 2 sessions/week for 4 weeks (30–45 min/session); 8 sessions in total (online; individual and group sessions).	Patient Information Form, Brief Illness Perception Questionnaire (BIPQ), and Perceived Stress Scale (PSS).	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	Laughter yoga was found to reduce postprandial blood glucose levels, improve illness perception, and decrease stress levels among patients with type 2 diabetes mellitus.
16	Eraydın, 2023 Marmara University (Doctoral)	Hemodialysis Patients Experimental: 40 Control: 40	Experimental group: 3 sessions/week for 4 weeks (50 min/session); 12 sessions in total (online).	Introductory Characteristics Information Form, Depression Anxiety Stress Scales (DASS), Kidney Disease Quality of Life Form, and Cortisol Levels.	Pretest: Before the intervention Posttest: At the end of Week 4, after the 12th session Follow-up assessment: None	Although laughter therapy did not affect serum cortisol levels in hemodialysis patients, it was found to be effective in reducing depression, anxiety, and stress levels and improving quality of life.
17	İnanç, 2024 Ege University (Master's)	Third-age university students (individuals aged 60 years and older) Experimental: 30 Control: 30	Experimental group: 1 session/week for 8 weeks (40 min/session); 8 sessions in total.	Introductory Characteristics Information Form, Pittsburgh Sleep Quality Index (PSQI), Oxford Happiness Questionnaire, and Positive and	Pretest: Before the intervention Posttest: At the end of Week 8 Follow-up	In the laughter yoga group, the posttest mean scores for sleep quality, happiness, and positive affect were higher than those in the control group. In addition, the

				Negative Affect Schedule (PANAS).	assessment: None	posttest scores for negative affect were higher in the control group than in the intervention group. Laughter yoga was found to be effective in improving sleep quality and happiness. Based on the findings of the study, laughter yoga is recommended for use among older adults as an effective, non-pharmacological, and easily applicable intervention.
18	Ataş, 2024 İzmir Bakırçay University (Master's)	Final-year nursing students Experimental: 39 Control: 20	Experimental group: 2 sessions/week for 4 weeks (45 min/session); 8 sessions in total.	Introductory Information Form, Perceived Stress Scale (PSS), and Pittsburgh Sleep Quality Index (PSQI).	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	There was a statistically significant difference in the posttest mean scores on the Perceived Stress Scale (PSS) and Pittsburgh Sleep Quality Index (PSQI) between the two groups. A moderate positive correlation was found between the posttest mean scores on the PSQI and PSS among students in the intervention and control groups. Laughter yoga can be safely implemented to reduce perceived stress levels and improve sleep quality among final-year nursing students.
19	Erdenilgen, 2024 Manisa Celal Bayar University (Master's)	Breastfeeding Women Experimental: 52 Control: 62	Experimental group: 2 sessions/week for 5 weeks (40 min for the first session and 30 min for subsequent sessions); 10 sessions in total (online).	Introductory Information Form, Perceived Stress Scale (PSS), and Breastfeeding Self-Efficacy Scale.	Pretest: Before the intervention Posttest: At the end of Week 5, after the 10th session Follow-up assessment: When the women reached 6 months postpartum	Laughter yoga was found to have no significant effect on perceived stress or breastfeeding self-efficacy among breastfeeding women.
20	Çoktay, 2024 Kafkas University (Doctoral)	Women with Breast Cancer Receiving Chemotherapy Laughter Yoga Group: 30 MBSR Group: 30 Control: 30	Laughter Yoga: 2 sessions/week for 8 weeks; MBSR: 2 sessions/week for 8 weeks (40–60 min/session); 16 sessions in total (hybrid).	Semi-Structured Survey Form, Hospital Anxiety and Depression Scale (HADS), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire	Pretest: Before the intervention Posttest: At Weeks 4 and 8 Follow-up assessment: Four weeks after the final	In both intervention groups, anxiety and depression levels were significantly lower, while quality of life and spiritual well-being levels were significantly

				(EORTC QLQ), and Spiritual Well-being Scale.	intervention (Week 12)	higher compared with the control group. In addition, at Week 12, the depression level in the laughter yoga group was statistically significantly lower than that in the MBSR group. Based on the findings of the study, it is recommended that nurses integrate laughter yoga and MBSR into standard hospital care to support patients with cancer, including those diagnosed with breast cancer.
21	Kayserilioğlu, 2024 Ankara Yıldırım Beyazıt University (Doctoral)	Bariatric Surgery Patients Experimental: 33 Control: 33	Preoperatively, two sessions per week for a total of six sessions.	Patient Information Form, Salivary Cortisol–Blood Glucose–Oxygen Level Monitoring Form, Perceived Stress Scale-14 (PSS-14), Numeric Pain Rating Scale, and General Comfort Questionnaire.	Pretest: Before the intervention Posttest: At the end of Week 3, after the 6th session (on the morning of surgery) Follow-up assessment: Postoperative Day 1	Patients who received laughter therapy based on Kolcaba's Comfort Theory had statistically significantly lower postoperative blood glucose and pain levels and significantly higher comfort and oxygen saturation levels compared with patients in the control group. However, laughter therapy was found to have no statistically significant effect on postoperative perceived stress scores or salivary cortisol levels between the groups. Based on these findings, laughter therapy based on Kolcaba's Comfort Theory is recommended for use by surgical nurses during the preoperative physiological preparation of bariatric surgery patients as a cost-free, easily applicable, readily accessible, and side-effect-free non-pharmacological intervention.
22	Çelik, 2024 Atatürk University (Master's)	Women in the Menopausal Period Experimental: 64 Control: 64	Experimental group: 2 sessions/week for 4 weeks (45 min for the first session and 30 min for subsequent	Personal Information Form, Menopause Rating Scale (MRS), and Menopause-Specific Quality of Life Questionnaire (MENQOL).	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session	Laughter yoga was found to reduce menopausal symptoms and improve quality of life among women in the menopausal period. Its implementation by

			sessions); 8 sessions in total.		Follow-up assessment: None	nurses as an alternative intervention is recommended.
23	Aldan, 2024 Hacettepe University (Doctoral)	Individuals with Chronic Obstructive Pulmonary Disease (COPD) Pursed-Lip Breathing Exercise Group: 21 Laughter Therapy Group: 21 Control: 21	Intervention group: Participants received training and practiced the intervention during the initial session and were provided with an instructional video. They were then instructed to perform the intervention three days per week for 8 weeks. On one of the three days each week, the intervention was conducted via video call.	Dyspnea-12 Scale, COPD Assessment Test (CAT), and Care Dependency Scale.	Pretest: Before the intervention Posttest: At Weeks 4 and 8 Follow-up assessment: At Week 12	The study found that both pursed-lip breathing exercises and laughter therapy were effective in reducing dyspnea severity and improving health status among patients with COPD. Furthermore, the positive effects on dyspnea severity were maintained after a four-week intervention-free period. However, neither pursed-lip breathing exercises nor laughter therapy had an effect on care dependency.
24	Gür, 2025 Ege University (Doctoral)	Individuals with Visual Impairments Experimental: 33 Control: 33	Experimental group: 2 sessions/week for 4 weeks (40 min/session); 8 sessions in total.	UCLA Loneliness Scale, Trait Anger Scale, and Salivary Cortisol Levels.	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	Laughter yoga was effective in reducing loneliness and anger levels among individuals with visual impairments. Although a significant decrease in salivary cortisol levels over time was observed in the intervention group, no statistically significant difference was found in the between-group comparison. These findings support the consideration of laughter yoga as a complementary method in psychosocial support programs.
25	Tiftikci, 2025 Kırıkkale University (Master's)	Second-year nursing students Experimental: 40 Control: 40	Experimental group: 2 sessions/week for 4 weeks (40 min/session); 8 sessions in total.	Introductory Characteristics Form, Test Anxiety Scale, and Spirituality Scale.	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	In the experimental group that received laughter yoga, test anxiety levels decreased significantly, while spirituality levels increased significantly. In the control group, no significant changes were observed in terms of test anxiety or spirituality levels. Based on these findings, laughter yoga is recommended as an effective intervention for

						reducing test anxiety and enhancing spirituality among nursing students.
26	Güler, 2025 İzmir Demokrasi University (Master's)	Third- and fourth-year nursing students Experimental: 30 Control: 30	Experimental group: 2 sessions/week for 4 weeks (30 min/session); 8 sessions in total.	Personal Information Form, Spirituality and Spiritual Care Rating Scale, and Three-Factor Spiritual Well-being Scale.	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	The study findings indicated that laughter yoga increased scores on both scales in the experimental group. However, compared with the control group, no statistically significant differences were found in scores on the Spirituality and Spiritual Care Rating Scale or the Three-Factor Spiritual Well-being Scale. Laughter yoga is considered to have positive contributions to self-awareness and spiritual relaxation; therefore, its integration into nursing education as a supportive intervention is recommended.
27	Akdeniz, 2025 İzmir Demokrasi University (Master's)	National Medical Rescue Team (UMKE) Personnel Experimental: 32 Control: 32	10 sessions in total (40 min for the first session and 30 min for subsequent sessions; online).	Descriptive Characteristics Form, Quality of Life Scale for Employees, and Perceived Stress Scale (PSS).	Pretest: Before the intervention Posttest: One month after the completion of the intervention Follow-up assessment: None	Laughter yoga was found to significantly reduce perceived stress and discomfort and to decrease burnout levels. However, no significant changes were observed in the areas of inadequate self-efficacy, professional satisfaction, or compassion fatigue. Laughter yoga is recommended as a complementary stress management tool for National Medical Rescue Team (UMKE) personnel working in disaster and crisis situations.
28	Uncu, 2025 İstanbul University-Cerrahpaşa (Doctoral)	Midwifery students KIPT: 12 Laughter Yoga: 12 Placebo: 12; Control: 12	All participants: 3 individual sessions KIPT: 8 weeks (60 min/session) Laughter Yoga: 8 sessions (60 min/session) Placebo group: Group interaction for 8 weeks Control group: No intervention	Student Information Form, Interpersonal Relationship Dimension Scale, Problem-Solving Inventory, Interpersonal Problem-Solving Inventory, and Self-Reflection Scale for Health Sciences Students.	Pretest: Before the intervention Interim assessment: At Week 4 Posttest: At the end of Week 8 Follow-up	In Group 1 (KIPT), significant improvements were observed in KIBO (trust in others), PEI (planned approach), KPEI (failure to take responsibility), and SRHS (reflection-in-action and

					assessment: At Week 12	reflection-for-action) scores. In Group 2 (Laughter Therapy), improvements were observed in KIBO (empathy, trust in others, and emotional awareness), total PEI, and KPEI (persistent approach) scores. In Group 3 (Placebo), significant improvements were recorded in KIBO (trust in others and emotional awareness), total PEI, KPEI (negative approach to the problem, constructive problem solving, lack of self-confidence, and failure to take responsibility), and SRHS (reflection-for-action) scores.
29	Van, 2025 İzmir Demokrasi University (Master's)	Intensive Care Nurses Experimental: 34 Control: 36	Experimental group: 2 sessions/week for 4 weeks (45 min for the first session and 30 min for subsequent sessions); 8 sessions in total.	Descriptive Characteristics Form, Maslach Burnout Inventory, and Spiritual Well-being Scale.	Pretest: Before the intervention Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	Laughter yoga did not significantly reduce burnout but was found to have an effect on self-efficacy. A significant, moderate, positive correlation was found between burnout, spiritual well-being, and the life plan subdimension of spiritual well-being.
30	Karaca, 2025 İstanbul University-Cerrahpaşa (Master's)	Older adults aged 65 years and older living in a nursing home Experimental: 35 Control: 35	Experimental group: 2 sessions/week for 6 weeks (45 min/session); 12 sessions in total.	Descriptive Information Form, Psychological Well-being Scale for Older Adults, Life Satisfaction Scale for Older Adults, and Depression Anxiety Stress Scales (DASS).	Pretest: Before the intervention Posttest: At the end of Week 6, after the 12th session Follow-up assessment: One month after the completion of the intervention	Laughter therapy was found to have a large positive effect on the psychological well-being, life satisfaction, and mental health of older adults living in nursing homes, with these effects largely maintained at the one-month follow-up assessment.
31	Ertürk Balcı, 2025 Karabük University (Master's)	Midwives and Nurses Experimental: 45 Control: 41	Experimental group: 2 sessions/week for 6 weeks (35–45 min/session); 12 sessions in total.	Descriptive Information Form, Quality of Work Life Scale in Nursing, and Minnesota Job Satisfaction Questionnaire.	Pretest: Before the intervention Posttest: At the end of Week 6, after the 12th session Follow-up assessment:	Laughter yoga did not result in a significant increase in overall job satisfaction or overall quality of work life compared with the control group. However, the fact that scores in the experimental

					Six weeks after the posttest assessment	group remained largely stable throughout the study, while a decline was observed in the control group, suggests that laughter yoga may play a protective role rather than having a direct enhancing effect.
32	Erdem, 2025 Selçuk University (Doctoral)	Mothers of children with special needs Experimental: 20 Control: 20	Laughter Yoga-Based Mental Health Promotion Training: 1 session/week for 8 weeks (45–50 min/session); 8 sessions in total.	Personal Information Form, Zarit Burden Interview (ZBI), Positive Mental Health Scale, and Perceived Stress Scale (PSS).	Pretest: Before the intervention Posttest: At the end of Week 8, after the 8th session Follow-up assessment: None	The "Laughter Yoga-Based Mental Health Promotion Training" was found to be effective in reducing mothers' caregiving burden. However, no significant change was observed in mothers' perceived stress levels. The statistically significant group × time interaction observed for Positive Mental Health and salivary cortisol levels indicates that the mental health promotion training provided to the mothers had positive effects over time.
33	İnan, 2025 Düzce University (Master's)	Nurses Experimental: 36 Control: 36	Experimental group: 1 session/week for 8 weeks (30–45 min/session); 8 sessions in total.	Personal Information Form, Five Facet Mindfulness Questionnaire (FFMQ), and Skovholt Practitioner Professional Resiliency and Self-Care Inventory (SPRSI).	Pretest: Before the intervention Posttest: At the end of Week 8, after the 8th session Follow-up assessment: None	The findings indicate that laughter yoga can be used as an intervention to enhance and support nurses' levels of mindfulness, professional resilience, and self-care.
34	Tamaddon, 2026 Health Sciences University (Doctoral)	Adolescents aged 10–15 years Four groups: 21 participants per group; 84 participants in total	Experimental group: One session of health education followed by 12 weeks of laughter yoga Control group: Standard education	Descriptive Information Form, Adolescent Stress Questionnaire, Digital Game Addiction Scale for Children, and Satisfaction Questionnaire.	Pretest: Before the intervention Posttest: At Week 8 Follow-up assessment: None	The health education-based laughter yoga program for adolescents was found to reduce overall stress levels and the risk of digital game addiction. Systematically implemented in the school setting using active teaching methods, this program is considered an effective model for developing stress-coping skills and an easily applicable, low-cost intervention for reducing the risk of digital game addiction.

35	Bakırlıoğlu, 2026 Pamukkale University (Doctoral)	Parents of children with moderate to severe intellectual disabilities Experimental: 30 Control: 32	Experimental group: Laughter yoga, 2 sessions/week for 4 weeks; 8 sessions in total.	Descriptive Information Form, Parenting Self-Efficacy Scale, Maslach Burnout Inventory, Perceived Stress Scale-14 (PSS-14), and Salivary Cortisol Levels.	Pretest: Before the intervention Interim assessment: Conducted Posttest: At the end of Week 4, after the 8th session Follow-up assessment: None	Laughter yoga was found to be an effective intervention for reducing perceived stress and salivary cortisol levels, a biological indicator of stress, among mothers of children with intellectual disabilities. At the same time, laughter yoga can be used as a complementary and feasible method in psychosocial support programs for parents.

Discussion and Conclusion

In this study, the characteristics and reported outcomes of postgraduate theses conducted on laughter yoga in Türkiye were examined. The first postgraduate thesis on the topic in Türkiye was conducted in 2018, and a marked increase in the number of theses has been observed, particularly since 2022. This increase indicates that laughter yoga has increasingly attracted research interest as a complementary and supportive intervention. This finding is particularly noteworthy when considered alongside early systematic reviews in the international literature, which reported that studies on laughter yoga were limited in number and varied in methodological quality (Bressington et al., 2018; Üner et al., 2022). Indeed, in recent years, the evidence on laughter yoga and laughter-based interventions has been re-evaluated through systematic reviews and meta-analyses (Erkin & Kocaçal, 2024; Li et al., 2024; Li et al., 2026). Therefore, the increase in the number of theses in Türkiye, particularly in recent years, may indicate not only growing academic interest but also that the international trend toward strengthening the empirical evidence base for laughter yoga has found resonance in Türkiye.

It is noteworthy that the vast majority of the theses examined in this study employed randomized controlled designs and were conducted within the field of nursing. This suggests that laughter yoga has been considered in Türkiye particularly as a complementary intervention that can be incorporated into nursing care, with a focus on evaluating its effects through experimental research. Similarly, a systematic review of 16 randomized controlled trials evaluating the effects of laughter therapy in individuals with various health conditions reported that this intervention could be considered a simple, low-cost, and non-pharmacological approach that can be incorporated into nursing care (Üner et al., 2022). However, the use of a randomized controlled design alone does not necessarily indicate a high level of evidence quality. Indeed, although a recent meta-analysis of 15 randomized controlled trials demonstrated that laughter interventions significantly reduced stress, the high level of heterogeneity across studies ($I^2 = 95.8\%$) and variability in methodological quality indicate that these findings should be interpreted with caution (Li et al., 2026). Therefore, although the predominance of randomized controlled designs among theses conducted in Türkiye is a positive feature, future research should strengthen not only the study design but also methodological aspects such as randomization, allocation concealment, blinding, sample size, and follow-up.

In the theses examined, laughter yoga was most frequently implemented as two sessions per week over a four-week period, with a total of eight sessions. Although this pattern may suggest that a specific mode of implementation is beginning to emerge in Türkiye, the variation in intervention duration from two to 16 sessions, together with differences in delivery format, including online versus face-to-face and individual versus group-based sessions, indicates that intervention protocols have not yet been fully standardized. The literature similarly reports considerable variation in laughter yoga interventions in terms of the number and duration of sessions. In the systematic review by Üner et al. (2022), the number of sessions was reported to range from one to 16, whereas Erkin and Kocaçal (2024) identified intervention protocols ranging from five to 24 sessions. Although this variability supports the applicability of laughter yoga across diverse populations, it also indicates that the questions of "which population, at what frequency, for how many sessions, and for what duration laughter yoga should be

implemented to achieve greater effectiveness" have not yet been conclusively answered. Therefore, future research should clearly define the core components of laughter yoga, provide a rationale for the intervention dose, and, whenever possible, employ standardized intervention protocols.

The more frequent use of measurement instruments assessing psychosocial variables and quality of life in the theses examined indicates that laughter yoga research in Türkiye has primarily focused on its effects on individuals' subjective health and psychosocial outcomes. The findings reported in the theses suggest that laughter yoga generally demonstrates a positive trend in terms of stress, anxiety, depression, psychological well-being, sleep quality, pain, and quality of life. Despite the use of different measurement instruments, these findings are largely consistent with the results of systematic reviews and meta-analyses in the international literature (Erkin & Kocaçal, 2024; Li et al., 2024; Li et al., 2026; Üner et al., 2022). In particular, laughter yoga has been reported to reduce stress and burnout, alleviate symptoms of depression and anxiety, and support psychological well-being among nurses and nursing students (Erkin & Kocaçal, 2024). Similarly, improvements have been reported in various outcomes among hemodialysis patients, including quality of life, pain, sleep quality, and psychological well-being (Li et al., 2024). However, the limited number of theses that included follow-up assessments also indicates that the effects of laughter yoga have predominantly been evaluated based on short-term outcomes. In addition to short-term outcomes, long-term follow-up assessments are needed to determine how long the effects persist after the intervention has been discontinued.

The integration of group interaction, voluntary laughter, rhythmic breathing, physical movement, and playful interaction in laughter yoga provides a multidimensional structure that may help explain its potential effects on psychosocial outcomes. Increased eye contact and social interaction within the group, promotion of positive affect, and the contribution of breathing exercises and physical movements to relaxation processes may be among the possible explanations for the positive changes observed in outcomes such as stress and psychological well-being. However, these observations do not imply that the underlying mechanisms have been definitively established. Therefore, research employing physiological and biological indicators in addition to self-report measures is important for determining the mechanisms through which laughter yoga may influence psychosocial outcomes.

In our study, it is noteworthy that findings related to physiological and biochemical indicators were more limited and heterogeneous than those concerning psychosocial outcomes. Although some theses reported favorable changes in biological indicators such as salivary cortisol, other studies found no statistically significant differences. Similarly, the absence of significant changes in work motivation, breastfeeding self-efficacy, burnout, or certain biological indicators in some studies suggests that laughter yoga may not be equally effective across all outcomes. This finding is also largely consistent with the international literature. Üner et al. (2022) reported that the evidence regarding the effects of laughter therapy on blood glucose, blood pressure, endorphin, and cortisol levels was limited. In contrast, a systematic review and meta-analysis by Kramer and Leitao (2023), which included eight intervention studies and 315 participants, demonstrated that laughter interventions resulted in a significant reduction in cortisol levels compared with control groups. Although this finding suggests a potential association between laughter and the biological stress response, it also indicates that effects specific to laughter yoga need to be distinguished from those of other laughter-based interventions. Indeed, the review evaluated humor/comedy videos, therapist-delivered laughter sessions, and individual laughter programs together (Kramer & Leitao, 2023). From this perspective, our study demonstrated that although postgraduate theses on laughter yoga in Türkiye showed a relatively consistent positive trend in psychosocial outcomes, uncertainty remains regarding physiological and biochemical outcomes. Therefore, future research should move beyond the question of "Is laughter yoga effective?" and instead investigate in which populations, at what intervention dose and duration, for which outcomes, and through which mechanisms laughter yoga is effective. In particular, conducting multicenter randomized controlled trials, standardizing intervention protocols, implementing long-term follow-up assessments, and supplementing self-report measures with objective biomarkers such as cortisol will contribute to strengthening the level of evidence. The high level of heterogeneity reported in the meta-analysis by Li et al. (2026) further supports this need.

Some methodological limitations were also noteworthy in the theses examined. Relatively small sample sizes, generally short follow-up periods, variations in intervention protocols, and the assessment of biological outcomes in only a limited number of studies may constrain the comparability and generalizability of the existing evidence.

In addition, the lack of qualitative data on participants' experiences of laughter yoga in the majority of the theses reviewed represents an important gap in knowledge regarding how the intervention is perceived by individuals, which aspects are considered beneficial or challenging, and how participation in the intervention translates into daily life. Therefore, mixed-methods research may contribute to understanding not only the quantitative outcomes of laughter yoga but also participants' experiences and the feasibility of implementing the intervention.

In conclusion, laughter yoga research in Türkiye has emerged as a rapidly developing area of research, particularly in recent years, especially within the field of nursing. The existing theses are largely based on experimental designs and demonstrate a generally positive trend in the evidence, particularly regarding psychosocial outcomes such as stress, psychological well-being, sleep, and quality of life. However, the diversity of intervention protocols and the heterogeneity of physiological and biochemical outcomes indicate that the current evidence is not yet sufficient to support a standardized clinical practice recommendation. Therefore, further methodologically rigorous and standardized studies evaluating long-term outcomes are needed to establish more robust evidence for the potential of laughter yoga as a complementary intervention in nursing care. In this regard, the following recommendations can be proposed:

1. Studies incorporating long-term follow-up assessments should be planned to evaluate the sustainability of the effects of laughter yoga.
2. Multicenter randomized controlled trials involving participants from different regions and healthcare centers should be increased.
3. Standardized laughter yoga protocols should be developed, specifying the number and duration of sessions, frequency of implementation, and core components of the intervention.
4. Studies using appropriate biomarkers, particularly cortisol, should be increased to investigate the potential biological mechanisms underlying the effects of laughter yoga.
5. The effects of laughter yoga should be investigated across diverse populations, including individuals with psychiatric disorders, caregivers, healthcare professionals, and individuals with chronic diseases.
6. Qualitative and mixed-methods studies may also be conducted to explore the feasibility and acceptability of laughter yoga and to gain a deeper understanding of participants' experiences.

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AKUT KORONER SENDROM DÜŞÜNÜLEN ACIL BAŞVURULARINDA TROPONIN T DÜZEYI ILE PLATELET VE PLATELET İNDEKSLERI ARASINDAKI İLIŞKININ İNCELENMESI

INVESTIGATION OF THE RELATIONSHIP BETWEEN TROPONIN T LEVEL AND PLATELET AND PLATELET INDICES IN EMERGENCY DEPARTMENT ADMISSIONS WITH SUSPECTED ACUTE CORONARY SYNDROME

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Amaç
Bu çalışma, Akut Koroner Sendrom (AKS) şüphesi olan hastalarda trombosit sayısı (PLT) ve indekslerinin (MPV, PCT, PDW) yüksek duyarlılıklı kardiyak troponin T (hs-cTnT) düzeyiyle ilişkisini inceleyerek trombotik süreçleri değerlendirmeyi ve hs-cTnT düzeylerinin mevsimsel değişimini belirleyerek klinik farkındalığı artırmayı amaçlamıştır.

Gereç ve Yöntem
Düzce Üniversitesi Tıp Fakültesi Acil Servisi'ne son bir yılda başvurup kardiyolojiye konsülte edilen ve eş zamanlı hs-cTnT ile tam kan sayımı (TKS) yapılan hastalar geriye dönük incelendi. Mükerrer kayıtlar çıkarılarak ilk başvurusu olan 2074 hasta çalışmaya dahil edildi. Cinsiyet karşılaştırmalarında Mann-Whitney U ve yaşa göre düzeltilmiş ANCOVA, mevsimsel karşılaştırmalarda Kruskal-Wallis ve Bonferroni düzeltmeli post-hoc analizi, değişkenler arası ilişkide ise Spearman korelasyon analizi kullanıldı.

Bulgular
Hastaların yaş ortalaması 65,95±15,08 olup %56,7'si erkekti. hs-cTnT düzeyleri erkeklerde kadınlara göre anlamlı derecede yüksek bulunurken (27,47 ng/L'ye karşı 21,65 ng/L; $p<0,001$), tüm trombosit indeksleri (PLT, MPV, PCT, PDW) kadınlarda erkeklerden anlamlı derecede yüksek saptandı ($p<0,001$). hs-cTnT ile PLT ($r=-0,071$) ve PCT ($r=-0,066$) arasında zayıf negatif; PDW ile ($r=0,049$) zayıf pozitif korelasyon izlendi; MPV ile anlamlı ilişki saptanmadı. hs-cTnT seviyelerinde mevsimsel olarak anlamlı farklılık görüldü ($p=0,004$); en yüksek ortanca değer kışın (28,84 ng/L), en düşük ise sonbaharda (20,40 ng/L) kaydedildi. Post-hoc analizde yalnızca kış ile sonbahar arasındaki fark istatistiksel olarak anlamlıydı ($p<0,001$).

Sonuç
Hs-cTnT ile trombosit indeksleri arasındaki zayıf ilişki, bu parametrelerin AKS değerlendirmesinde tek başlarına yeterli olmadığını göstermektedir. Ancak Trop T düzeylerinde gözlenen mevsimsel dalgalanmalar (kışın en yüksek, sonbaharda en düşük) klinik uygulamada göz önünde bulundurulmalıdır.
Anahtar Kelimeler: Troponin T, trombosit indeksleri, mevsimsel değişim, akut koroner sendrom, acil servis.

Objective
This study aimed to evaluate thrombotic processes by investigating the relationship between platelet count (PLT) and platelet indices (MPV, PCT, PDW) and high-sensitivity cardiac troponin T (hs-cTnT) levels in patients with suspected Acute Coronary Syndrome (ACS), and to raise clinical awareness by determining the seasonal variation of hs-cTnT levels.

Materials and Methods
Patients who presented to the Emergency Department of Düzce University Faculty of Medicine within the last year, were consulted to cardiology, and had simultaneous hs-cTnT and complete blood count (CBC) measurements were retrospectively reviewed.

After excluding duplicate records, 2074 patients with their first admission were included in the study. The Mann-Whitney U test and age-adjusted ANCOVA were used for sex comparisons, the Kruskal-Wallis test with Bonferroni-corrected post-hoc analysis was used for seasonal comparisons, and Spearman correlation analysis was used to assess relationships between variables.

Results
The mean age of the patients was 65.95±15.08 years, and 56.7% were male. hs-cTnT levels were significantly higher in men than in women (27.47 ng/L vs 21.65 ng/L; p<0.001), whereas all platelet indices (PLT, MPV, PCT, PDW) were significantly higher in women than in men (p<0.001). Weak negative correlations were observed between hs-cTnT and PLT (r=-0.071) and PCT (r=-0.066), and a weak positive correlation with PDW (r=0.049); no significant correlation was found with MPV. hs-cTnT levels showed a statistically significant seasonal variation (p=0.004), with the highest median value recorded in winter (28.84 ng/L) and the lowest in autumn (20.40 ng/L). In the post-hoc analysis, only the difference between winter and autumn was statistically significant (p<0.001).

Conclusion
The weak relationship between hs-cTnT and platelet indices indicates that these parameters are not sufficient on their own for the evaluation of ACS. However, the seasonal fluctuations observed in Trop T levels (highest in winter, lowest in autumn) should be taken into consideration in clinical practice.
Keywords: Troponin T, platelet indices, seasonal variation, acute coronary syndrome, emergency department.

1. GİRİŞ
Akut koroner sendrom (AKS), koroner arter hastalığının ölümcül seyredebilen ve acil serviste sık karşılaşılan bir klinik tablosudur; ST-segment yükselmeli miyokard enfarktüsü (STEMI), ST-segment yükselmesiz miyokard enfarktüsü (NSTEMI) ve kararsız anjina pektorisi (UA) kapsamaktadır. Kardiyak troponinler, miyokard hasarının özgül ve duyarlı biyobelirteçleri olarak AKS tanısında önemli bir yer tutmaktadır (1). Yüksek duyarlılıklı troponin T (hs-cTnT) testleri, düşük düzeylerdeki miyokard hasarını dahi saptayabilmeleri nedeniyle güncel klinik uygulamada yaygın olarak kullanılmaktadır (2).
AKS'nin patofizyolojisinin temelinde aterosklerotik plak rüptürü/erozyonu sonrasında gelişen trombosit aktivasyonu ve trombüs oluşumu yer almaktadır (3). Bu nedenle, AKS'nin patofizyolojisinde santral rol oynayan trombosit aktivasyonunu ve fonksiyonel durumunu yansıttığı öne sürülen trombosit sayısı (PLT) ile trombosit indeksleri -ortalama trombosit hacmi (MPV), plateletkrit (PCT) ve trombosit dağılım genişliği (PDW)-, kolay ulaşılabilir ve ucuz olan rutin tam kan sayımı (TKS) ile birlikte otomatik olarak raporlanabilmeleri nedeniyle trombotik süreçlerin değerlendirilmesinde potansiyel belirteçler olarak araştırılmaktadır. Literatürde MPV ve PDW'nin daha büyük, daha aktif ve daha trombojenik trombositleri yansıttığı ve bu nedenle AKS'li hastalarda kontrol gruplarına kıyasla yükseldiği bildirilmektedir (4).
Ayrıca kardiyovasküler olayların mevsimsel bir dağılım gösterdiği; kış aylarında soğuğa bağlı hemokonsantrasyon ve artmış trombotik eğilim nedeniyle kardiyovasküler mortalite ve morbiditenin arttığı bilinmektedir (5). Bununla birlikte, literatürde hs-cTnT düzeylerinin mevsimsel değişimi ile trombosit indeksleri ve hs-cTnT arasındaki ilişkiyi inceleyen çalışmalarda farklı sonuçlar elde edilmiştir Bu çalışmada, AKS şüphesiyle acil servise başvuran hastalarda PLT ve trombosit indekslerinin (MPV, PCT, PDW) hs-cTnT düzeyi ile ilişkisini inceleyerek trombotik süreçleri değerlendirmek ve hs-cTnT düzeylerinin mevsimsel değişimini belirleyerek klinik farkındalığı artırmak amaçlanmıştır.

2. GEREÇ VE YÖNTEM
2.1. Çalışma Tasarımı ve Popülasyonu
Bu çalışma, Düzce Üniversitesi Tıp Fakültesi Acil Servisi'ne son bir yıl içinde başvuran (Mart 2025-Şubat 2026) ve kardiyolojiye konsülte edilen, eş zamanlı hs-cTnT ile TKS ölçümü yapılan hastaların verilerinin geriye dönük olarak incelendiği tanımlayıcı bir çalışmadır. Mükerrer başvuru kayıtları veri setinden çıkarılarak yalnızca hastaların ilk başvurusuna ait kayıtlar değerlendirmeye alınmış ve toplam 2074 hasta çalışmaya dahil edilmiştir.

2.2. Laboratuvar Ölçümleri

hs-cTnT ölçümleri cobas 6000 tam otomatik analizörü (Roche Diagnostics, Mannheim, Almanya) kullanılarak gerçekleştirilmiştir. TKS ölçümleri (PLT, MPV, PCT ve PDW dahil) Dymind H800 tam otomatik hematoloji analizörü (Shenzhen Dymind Biotechnology Co., Ltd., Shenzhen, Çin) ile yapılmıştır.

2.3. İstatistiksel Analiz

Veriler SPSS (Statistical Package for the Social Sciences) 25.0 programı kullanılarak analiz edilmiştir. Sürekli değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov ve Shapiro-Wilk testleri ile değerlendirilmiş; normal dağılım göstermeyen sürekli değişkenler ortanca ve çeyrekler arası aralık (IQR: 25.-75. persentil) olarak, kategorik değişkenler ise sayı ve yüzde (%) olarak ifade edilmiştir. İkiden fazla bağımsız grup arasındaki farklılıkların değerlendirilmesinde Kruskal-Wallis testi kullanılmış, anlamlı bulunan karşılaştırmalarda Bonferroni düzeltmeli Mann-Whitney U testi post-hoc analiz olarak uygulanmıştır. Cinsiyetler arası karşılaştırmalarda yaş farklılığının olası karıştırıcı etkisini kontrol etmek amacıyla yaş kovaryant olarak alınarak tek yönlü kovaryans analizi (ANCOVA) uygulanmıştır. Değişkenler arasındaki ilişkiler Spearman korelasyon analizi ile değerlendirilmiştir. Tüm analizlerde istatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edilmiştir.

3. BULGULAR

Çalışmaya dahil edilen 2074 hastanın yaş ortalaması 65.95 ± 15.08 yıl olup yaşlar 18 ile 100 arasında dağılım göstermektedir. Hastaların 897'si (%43.3) kadın, 1177'si (%56.7) erkek cinsiyetindeydi. Laboratuvar bulgularında PLT ortancası 247 (IQR: 201–303), MPV ortancası 10.9 (IQR: 10.1–11.8), PCT ortancası 0.270 (IQR: 0.221–0.327), PDW ortancası 12.0 (IQR: 10.8–13.3) ve Troponin T ortancası 24.85 (IQR: 12.70–60.98) olarak saptanmıştır.

Cinsiyete göre yapılan karşılaştırmada erkeklerde Troponin T düzeyi kadınlara kıyasla anlamlı düzeyde daha yüksek bulunurken (Erkek: Medyan = 27.47, IQR = 50.63; Kadın: Medyan = 21.65, IQR = 42.71; $p < 0.001$), trombosit indekslerinde ise kadınların değerleri erkeklere göre anlamlı düzeyde daha yüksek saptanmıştır (PLT: 259 vs. 239; MPV: 11.0 vs. 10.8; PCT: 0.284 vs. 0.259; PDW: 12.1 vs. 12.0; tüm karşılaştırmalar için $p < 0.001$, Table 1). Cinsiyet grupları arasındaki yaş farkı göz önünde bulundurularak yaş kovaryat olarak alındığında, yaş düzeltmesi sonrasında da tüm değişkenlerde cinsiyet farklılıklarının istatistiksel olarak anlamlılığını koruduğu görüldü ($p<0.001$).

Table 1. Comparison of demographic and laboratory findings by sex

	Woman	Man	p
	Median (IQR)	Median ((IQR)	
Age (years)	71.00 (61.00 - 80.00)	65.00 (54.00 - 75.00)	**<0.001**
PLT	259.00 (209.00 - 315.00)	239.00 (195.00 - 292.00)	
MPV	11.00 (10.30 - 11.80)	10.80 (10.00 - 11.70)	
PCT	0.28 (0.23 - 0.34)	0.26 (0.21 - 0.31)	
PDW	12.10 (10.90 - 13.40)	12.00 (10.80 - 13.20)	
Troponin T	21.65 (11.58 - 54.27)	27.47 (13.45 - 63.96)	

Spearman korelasyon analizi sonuçlarına göre yaş ile Troponin T arasında pozitif yönlü, orta düzeyde ve istatistiksel olarak anlamlı bir ilişki saptandı ($r = 0,364$; $p < 0,001$). Yaş ile PLT arasında negatif yönlü zayıf bir ilişki ($r = −0,100$; $p < 0,001$), yaş ile PCT arasında negatif yönlü zayıf bir ilişki ($r = −0,093$; $p < 0,001$) ve yaş ile PDW arasında pozitif yönlü zayıf bir ilişki ($r = 0,049$; $p = 0,025$) gözlemlendi. Yaş ile MPV arasında istatistiksel olarak anlamlı bir ilişki saptanmadı ($r = 0,028$; $p = 0,208$).

PLT ile PCT arasında pozitif yönlü çok güçlü bir ilişki ($r = 0,929$; $p < 0,001$), PLT ile PDW arasında negatif yönlü orta düzeyde bir ilişki ($r = −0,381$; $p < 0,001$) ve PLT ile MPV arasında negatif yönlü orta düzeyde bir ilişki ($r = −0,336$; $p < 0,001$) tespit edildi. PLT ile Trop_T arasında negatif yönlü zayıf ancak anlamlı bir ilişki mevcuttu ($r = −0,071$; $p = 0,001$, Table 2).

MPV ile PDW arasında pozitif yönlü çok güçlü bir ilişki saptandı (r = 0,891; p < 0,001). MPV ile PCT (r = −0,009; p = 0,689) ve MPV ile Troponin T (r = 0,020; p = 0,363) arasında ise istatistiksel olarak anlamlı bir ilişki gözlemlenmedi (Table 2).
PCT ile PDW arasında negatif yönlü zayıf ancak anlamlı bir ilişki (r = −0,085; p < 0,001), PCT ile Trop_T arasında negatif yönlü zayıf bir ilişki (r = −0,066; p = 0,003) tespit edildi. PDW ile Trop_T arasında pozitif yönlü zayıf bir ilişki saptandı (r = 0,049; p = 0,025, Table 2).

Table 2. Spearman correlation analysis between age, platelet indices, and Troponin T levels

		Age (years)	PLT	MPV	PCT	PDW	Troponin T
Age (years)	r		**-0.100****	0.028	**-0.093****	**0.049***	**0.364****
	p		**<0.001**	0.208	**<0.001**	**0.025**	**<0.001**
PLT	r	**-0.100****		**-0.336****	**0.929****	**-0.381****	**-0.071****
	p	**<0.001**		**<0.001**	**<0.001**	**<0.001**	**0.001**
MPV	r	0.028	**-0.336****		-0.009	**0.891****	0.020
	p	0.208	**<0.001**		0.689	**<0.001**	0.363
PCT	r	**-0.093****	**0.929****	-0.009		**-0.085****	**-0.066****
	p	**<0.001**	**<0.001**	0.689		**<0.001**	**0.003**
PDW	r	**0.049***	**-0.381****	**0.891****	**-0.085****		**0.049***
	p	**,025**	**<0.001**	**<0.001**	**<0.001**		**0.025**
Troponin T	r	**0.364****	**-0.071****	0.020	**-0.066****	**0.049***	
	p	**<0.001**	**0.001**	0.363	**0.003**	**0.025**	

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Troponin T düzeylerinin mevsimsel medyan değerleri incelendiğinde en yüksek değerin Kış mevsiminde (Medyan = 28.84, IQR = 48.63), bunu sırasıyla Yaz (Medyan = 26.52, IQR = 52.29), İlkbahar (Medyan = 24.95, IQR = 45.61) ve Sonbahar (Medyan = 20.40, IQR = 41.33) mevsimlerinin izlediği görülmüştür. Kruskal-Wallis testi, Troponin T düzeylerinin mevsimlere göre istatistiksel olarak anlamlı farklılık gösterdiğini ortaya koymuştur (p = 0.004). Bonferroni düzeltmeli Mann-Whitney U post hoc analizinde yalnızca Kış (Medyan = 28.84, IQR = 48.63) ile Sonbahar (Medyan = 20.40, IQR = 41.33) arasındaki fark istatistiksel olarak anlamlı bulunmuştur (U = 101576, p < 0.001).

4. TARTIŞMA

Bu çalışmada, AKS şüphesiyle acil servise başvuran ve kardiyolojiye konsülte edilen hastalarda hs-cTnT düzeyi ile PLT ve trombosit indeksleri (MPV, PCT, PDW) arasında istatistiksel olarak anlamlı ancak klinik açıdan zayıf düzeyde korelasyonlar saptanmıştır. Bu bulgu, trombosit indekslerinin AKS'nin tanısal değerlendirmesinde tek başına güvenilir bir belirteç olarak kullanılamayacağını, ancak troponin ile birlikte tamamlayıcı bilgi sağlayabileceğini düşündürmektedir.
Literatürde AKS tanılı hastalar ile sağlıklı kontrol grupları karşılaştırıldığında trombosit indekslerinin anlamlı derecede yüksek bulunduğu bildirilmiştir. Mir ve ark. AKS grubunda ortalama MPV, PDW ve PCT değerinin kontrol grubuna göre anlamlı derecede yüksek olduğunu, bu değerlerin STEMI grubunda NSTEMI ve kararsız anjina gruplarına kıyasla daha yüksek seyrettiğini bildirmiştir (6). Benzer şekilde Wang ve ark., AKS grubunda MPV düzeyinin kontrol grubuna göre anlamlı derecede yüksek olduğunu ve ayrıca akut miyokard enfarktüsü grubunda kararsız anjina grubuna göre anlamlı derecede yüksek seyrettiğini göstermiştir. Artmış MPV'nin akut miyokard enfarktüsü için erken ve bağımsız bir öngörücü olabileceği, troponin I ile birlikte değerlendirildiğinde tanısal performansı artırabileceği öne sürülmüştür (7). Buna karşın Krishnan ve ark. çalışmasında, MPV'nin AKS grubunda kontrole göre anlamlı derecede yüksek bulunmasına rağmen troponin T ile anlamlı olmayan zayıf pozitif korelasyon gösterdiği; PCT ve PDW'nin de AKS grubunda daha yüksek olmakla birlikte bu farkın istatistiksel olarak anlamlı olmadığı ve her iki parametrenin de troponin T ile anlamlı olmayan pozitif korelasyon gösterdiği bildirilmiştir (8). Bu bulgu, mevcut çalışmadaki anlamlı olmayan MPV-hs-cTnT ilişkisi ve PCT-hs-cTnT, PDW-hs-cTnT arasındaki zayıf korelasyonlarla kısmen örtüşmektedir.

Çalışmalar arasındaki bu farklılığın; kullanılan çalışma tasarımından, örneklem büyüklüğünden, hasta popülasyonunun klinik özelliklerinden ve kullanılan troponin izoformu ile ölçüm yönteminden kaynaklanabileceği düşünülmektedir. Nitekim mevcut çalışmada hastalar AKS tanısı almış bir grubu değil, AKS şüphesiyle değerlendirilen ve kardiyolojiye konsülte edilen geniş bir acil servis popülasyonunu temsil etmektedir.

Çalışmamızda kadınların yaş ortancasının erkeklerden anlamlı derecede yüksek olmasına karşın hs-cTnT düzeylerinin erkeklerde anlamlı derecede yüksek saptanması dikkat çekicidir. Yaş ile hs-cTnT arasında saptanan orta düzeyde pozitif korelasyon (r=0,364) göz önüne alındığında, kadınlarda ileri yaşa rağmen daha düşük hs-cTnT düzeylerinin gözlenmesi, cinsiyete özgü kas kütlesi farklılıkları, kardiyak yapısal ve fonksiyonel farklılıklar ile olası hormonal etkiler gibi yaşın etkisinden bağımsız faktörlerle ilişkili olabileceği düşünülmüştür (9–12). Buna karşın trombosit indekslerinin (PLT, MPV, PCT, PDW) tamamının kadınlarda erkeklerden anlamlı derecede yüksek bulunması, cinsiyete bağlı trombosit fizyolojisi farklılıklarının klinik yorumlamada dikkate alınması gerektiğine işaret etmektedir (13,14).

hs-cTnT düzeylerinde saptanan mevsimsel değişim -kışın en yüksek, sonbaharda en düşük- literatürle nispeten uyumludur. Mikić ve ark., Doğu Hırvatistan popülasyonunda pozitif yüksek duyarlılıklı troponin I test sonuçlarının en fazla Aralık ayında, en az ise Ocak-Şubat ve ardından Nisan-Ağustos aylarında görüldüğünü bildirmiştir. Aralık ayındaki artışın bayram/kutlama dönemine bağlı davranışsal faktörler ya da kıtasal iklimde bu aya özgü kısa süreli ve değişken sıcaklık dalgalanmalarıyla açıklanabileceğini öne sürmüştür (15). Çalışmamızda mevsim bazında yapılan değerlendirmede kış mevsiminin en yüksek hs-cTnT düzeyleriyle ilişkili bulunması, soğuk havaya bağlı hemokonsantrasyon ve artmış trombotik/kardiyovasküler yük hipotezini desteklemektedir. Bu bulgu, kış aylarında AKS şüphesiyle başvuran hastalarda troponin yüksekliğinin yorumlanmasında ve klinik risk değerlendirmesinde mevsimsel farkındalığın önemine dikkat çekmektedir.

Bu çalışmanın bazı kısıtlılıkları bulunmaktadır. Çalışmanın tek merkezli ve retrospektif olması genellenebilirliği sınırlandırmaktadır. Hastaların AKS tanısının (STEMI, NSTEMI, kararsız anjina) veya nihai klinik sonlanımının veri setinde ayrı ayrı sınıflandırılmamış olması, bulguların AKS alt tipleri özelinde yorumlanmasını güçleştirmektedir. Ayrıca sağlıklı bir kontrol grubunun bulunmaması, saptanan korelasyonların AKS'ye özgü olup olmadığının değerlendirilmesini sınırlamaktadır. Bununla birlikte, çalışmanın geniş örneklem büyüklüğü (n=2074) ve rutin klinik pratiği yansıtan gerçek yaşam verisi niteliği, bulguların güvenilirliği açısından önemli bir güç oluşturmaktadır.

5. SONUÇ

Bu çalışmada, AKS şüphesiyle acil servise başvuran hastalarda hs-cTnT ile trombosit indeksleri arasında saptanan zayıf korelasyonlar, bu parametrelerin AKS değerlendirmesinde tek başına yeterli olmadığını düşündürmektedir. Bununla birlikte, hs-cTnT düzeylerinde gözlenen mevsimsel dalgalanmaların -kışın en yüksek, sonbaharda en düşük düzeylerde seyretmesi- klinik uygulamada göz önünde bulundurulabilir. Trombosit indekslerinin AKS'deki rolünün netleştirilmesi için, klinik tanı alt gruplarını (STEMI/NSTEMI/UA) ve kontrol gruplarını içeren, ileriye dönük ve çok merkezli çalışmalara ihtiyaç duyulmaktadır.

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ASSOCIATIONS AMONG SURGICAL FEAR, PAIN CATASTROPHIZING, AND EARLY MOBILIZATION EXPERIENCES IN PATIENTS UNDERGOING LAPAROSCOPIC ABDOMINAL SURGERY

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Abstract

Objective: This study examined the associations among surgical fear, pain catastrophizing, and pain and difficulty during early mobilization in patients undergoing laparoscopic abdominal surgery.

Materials and Methods

This descriptive, prospective, observational, correlational study was conducted between June 25 and August 2, 2026, in the surgical units of a state training and research hospital in southeastern Türkiye. The sample comprised 51 eligible patients who consented to participate. Data were collected face-to-face using a Patient Information Form, the Surgical Fear Questionnaire, the Pain Catastrophizing Scale, and the Patient Mobility Scale. The Surgical Fear Questionnaire was administered on the morning of surgery before the procedure; the other scales were administered on postoperative day 2. Normality was evaluated using skewness and kurtosis coefficients and the Shapiro-Wilk test. Because the scale scores were non-normally distributed, the Mann-Whitney U test and Spearman's rank-order correlation analysis were used. Statistical significance was set at $p<0.05$.

Results

Participants' mean age was 39.76±12.11 years; 51.0% were male, 58.8% were married, and 52.9% had no previous surgical experience. Married patients had higher surgical fear and pain catastrophizing scores than single patients (both $p<0.001$). Patients without previous surgical experience had higher surgical fear ($p=0.002$), pain catastrophizing ($p<0.001$), and Patient Mobility Scale scores ($p<0.001$). Surgical fear was positively correlated with pain catastrophizing ($r_s=0.783$), while Patient Mobility Scale scores were positively correlated with surgical fear ($r_s=0.569$) and pain catastrophizing ($r_s=0.573$) (all $p<0.001$).

Conclusion

Greater surgical fear and pain catastrophizing were associated with greater pain and difficulty during early postoperative mobilization. Preoperative assessment of surgical fear, particularly among patients without previous surgical experience, and individualized nursing interventions incorporating education, psychological support, and mobilization preparation are recommended.

Keywords: Early mobilization, laparoscopic surgery, nursing, pain catastrophizing, surgical fear

1. Introduction

Contemporary Enhanced Recovery After Surgery pathways address postoperative recovery after abdominal surgery through coordinated perioperative care and include early mobilization alongside effective analgesia, early oral intake, appropriate fluid management, and timely removal of tubes and catheters.[1] Early mobilization is intended to limit the adverse effects of bed rest and facilitate a return to functional independence. However, the evidence for its isolated effect on clinical outcomes remains incomplete. A systematic review of eight studies in abdominal and thoracic surgery found marked variation in mobilization protocols and insufficient, often conflicting evidence for improved postoperative outcomes.[2] A later systematic review and meta-analysis of 15 studies involving 3,538 patients undergoing gastrointestinal surgery found that early mobilization shortened time to gastrointestinal recovery by a mean of 11.53 hours, but did not significantly reduce morbidity or hospital length of stay.[3] These findings identify mobilization as an important recovery process while showing that its benefits cannot be inferred without considering protocol intensity, adherence, and patients' ability to participate.

Evidence specific to laparoscopic abdominal surgery indicates that structured preparation can improve mobilization. In a randomized controlled trial of 78 patients, preoperative early-mobilization training increased postoperative mobilization duration and was accompanied by lower pain, greater comfort, better sleep quality, and shorter hospitalization.[4] Implementation nevertheless remains difficult. In a prospective feasibility study after high-risk abdominal surgery, 92% of patients were mobilized within 24 hours, yet fatigue, pain, and dizziness were the main barriers to participation.[5] Among 470 patients undergoing gastrointestinal surgery, only 53.6% met the study's early-mobilization criterion; older age, female sex, lower educational attainment, and the presence of four or more catheters were associated with failure to mobilize early.[6] Qualitative interviews after abdominal surgery further showed that patients' motivation, previous experiences, preparation, and confidence in competent caregivers shaped their willingness to get out of bed.[7] Early mobilization is therefore more than a binary record of whether a patient stood or walked. The pain and difficulty perceived during specific activities provide clinically relevant information about how the patient experiences and tolerates mobilization.

Surgical fear may influence this experience before postoperative movement begins. It is a procedure-specific emotional response that can encompass immediate concerns about anesthesia, pain, or the operation as well as concerns about longer-term recovery and health consequences. The Surgical Fear Questionnaire was validated in 3,233 adults awaiting elective surgery and demonstrated two related dimensions concerning short-term and long-term consequences. Surgical fear also correlated with state anxiety, pain catastrophizing, and preoperative pain.[8] Direct evidence linking fear with mobility is emerging. In 125 patients undergoing laparoscopic cholecystectomy, higher preoperative surgical fear was associated with greater postoperative anxiety, pain, and difficulty during mobilization.[9] A study of 205 abdominal surgery patients likewise reported a moderate positive association between surgical fear and Patient Mobility Scale scores, for which higher scores reflect greater pain and difficulty during postoperative activities.[10] Because both studies were observational, they do not establish that fear causes impaired mobility, but they show that preoperative fear remains clinically relevant during early recovery.

Pain catastrophizing is a related but distinct psychological construct. It describes an exaggerated negative orientation toward actual or anticipated pain and comprises rumination, magnification, and helplessness.[11] A systematic review and meta-analysis of 53 publications identified catastrophizing as the psychological factor most strongly associated with acute postsurgical pain.[12] The wider evidence is not uniform. A systematic review and meta-analysis of 33 studies involving 53,362 patients did not find pain catastrophizing to be a significant pooled predictor of poor acute postoperative pain control,[13] whereas a review of 29 studies found that preoperative anxiety and catastrophizing were associated with chronic postsurgical pain, although effect estimates varied across procedures and methods.[14] These differences indicate that the importance of catastrophizing may depend on the surgical population, outcome definition, and timing of measurement.

Abdominal surgery studies provide more direct evidence for the relationship among pain-related cognitions, pain, and movement. In 246 patients undergoing abdominal surgery, pain catastrophizing was positively associated with acute postoperative pain and partly mediated the relationship between pain sensitivity and acute pain.[15] In a prospective correlational study of 92 patients undergoing laparoscopic abdominal surgery, pain intensity, pain catastrophizing, and body mass index jointly explained 56% of the variance in Patient Mobility Scale scores. The presence of catheters or drains was also associated with greater catastrophizing, pain, and mobility difficulty.[16] These findings support assessment of postoperative mobility as a multidimensional experience influenced by symptoms, treatment-related restrictions, and patients' interpretations of pain.

Surgical fear and pain catastrophizing overlap, but they are not interchangeable. Surgical fear concerns the operation and its possible consequences, whereas catastrophizing concerns the meaning and expected course of pain. Their documented correlation suggests that they may operate together during recovery,[8] but existing mobility studies have generally examined surgical fear or pain catastrophizing separately.[9,10,16] The available evidence is also concentrated in single procedures or heterogeneous abdominal surgery samples. Consequently, the concurrent relationships among preoperative surgical fear, postoperative pain catastrophizing, and early mobilization experiences in patients undergoing laparoscopic abdominal surgery remain insufficiently characterized. Examining all three constructs in the same cohort can clarify whether they identify overlapping or complementary psychological barriers to early movement.

This study therefore aimed to examine the associations among preoperative surgical fear, postoperative pain catastrophizing, and early mobilization experiences in adults undergoing laparoscopic abdominal surgery. It specifically evaluated whether greater surgical fear was associated with greater pain catastrophizing and more difficult or painful mobilization, and whether pain catastrophizing was associated with patients' mobilization experiences. Because the study was observational, the analysis was intended to identify associations rather than causal pathways. An integrated assessment may help define targets for preoperative education, perioperative psychological support, and individualized mobilization strategies that can be tested in subsequent intervention studies.

Materials and Methods

1.1.Study Design and Aim

This descriptive, prospective, observational, correlational study was conducted among patients undergoing laparoscopic abdominal surgery. The study aimed to examine the associations between patients' preoperative surgical fear and their pain catastrophizing and perceived pain and difficulty during early mobilization on postoperative day 2.

1.2.Study Setting and Time

The study was conducted in the surgical units of a state training and research hospital located in southeastern Türkiye. Data were collected between June 25 and August 2, 2026.

1.3.Study Population and Sample

The study population comprised patients who underwent laparoscopic abdominal surgery in the surgical units of the study hospital during the data collection period. A census approach was attempted during the study period: all patients who met the eligibility criteria were invited, and those who voluntarily agreed were enrolled. The final sample consisted of 51 patients.

1.4.Data Collection

Data were collected by the researchers through face-to-face interviews at two time points. On the morning of surgery and before the surgical procedure, patients completed the Patient Information Form and the Surgical Fear Questionnaire. On postoperative day 2, the Pain Catastrophizing Scale was administered, and the pain and difficulty experienced by patients during four basic mobilization activities were evaluated using the Patient Mobility Scale.

1.5.Data Collection Instruments

Data were collected using the Patient Information Form, Surgical Fear Questionnaire, Pain Catastrophizing Scale, and Patient Mobility Scale.

1.5.1. Patient Information Form

Developed by the researchers based on the relevant literature, this form consisted of questions assessing patients' sociodemographic and clinical characteristics, including age, sex, marital status, educational level, perceived income level, previous surgical experience, medical diagnosis, and type of surgical procedure.

1.5.2. Surgical Fear Questionnaire

The Surgical Fear Questionnaire (SFQ) was developed by Theunissen et al to assess adult patients' fears concerning the short- and long-term consequences of elective surgery.[8] The validity and reliability of the Turkish version were established by Bağdigen and Karaman Özlü.[17]

The SFQ consists of 8 items, each rated from 0 ("not at all afraid") to 10 ("very afraid"). The first 4 items assess short-term fears, including fear of the surgical procedure, anesthesia, postoperative pain, and adverse effects of surgery. The remaining 4 items assess long-term fears, including deterioration in health, surgical failure, incomplete recovery, and prolonged rehabilitation. The total score ranges from 0 to 80, with higher scores indicating greater surgical fear. The Cronbach α coefficient for the total Turkish version was 0.93.[17] In the present study, the Cronbach α coefficient was 0.92.

1.5.3. Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) was developed by Sullivan et al. to assess exaggerated negative cognitive and emotional responses to actual or anticipated pain.[11] The validity and reliability of the Turkish version were established by Ugurlu et al.[18] The scale consists of 13 items encompassing three subscales: rumination, magnification, and helplessness. Each item is rated on a 5-point Likert scale

ranging from 0 ("not at all") to 4 ("all the time"). Item scores are summed to obtain a total score ranging from 0 to 52, with higher scores indicating greater pain-related catastrophic thinking. The Turkish validation study reported a Cronbach's alpha coefficient of 0.955.[18] In the present study, the Cronbach's alpha coefficient was 0.79.

1.5.4. Patient Mobility Scale

The Patient Mobility Scale (PMS) was developed by Heye et al. to assess the pain and difficulty experienced by patients while performing postoperative mobility activities.[19] The validity and reliability of the Turkish version were established by Ayoğlu and Akyolcu.[20] The scale assesses four activities: turning from side to side in bed, sitting at the bedside, standing at the bedside, and walking in the patient's room. For each activity, pain and difficulty are evaluated separately using 15-cm visual analogue scales, resulting in eight item scores. Each item is scored from 0 to 15 by measuring the distance between the zero point and the patient's mark. The eight item scores are summed to obtain a total score ranging from 0 to 120, with higher scores indicating greater pain and difficulty during postoperative mobility. In the present study, the validated Turkish 15-cm visual analogue scale version was administered and scored without modification. The Cronbach's alpha coefficient was 0.81 in the present sample.

1.6.Study Variables

The primary variables of interest were preoperative surgical fear, pain catastrophizing on postoperative day 2, and perceived pain and difficulty during early mobilization on postoperative day 2, assessed using the total Patient Mobility Scale score. The analyses evaluated associations among these variables and did not test causal effects.

1.7.Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as numbers and percentages. Continuous variables were summarized using the mean and standard deviation, as well as the median, first and third quartiles, and minimum and maximum values, as appropriate. Normality was assessed using skewness and kurtosis coefficients and the Shapiro–Wilk test. Because the scale scores were non-normally distributed, two-group comparisons were performed using the Mann–Whitney U test, and relationships among scale scores were examined using Spearman's rank-order correlation analysis. All tests were two-sided, and statistical significance was set at $p < 0.05$

1.8.Ethical Considerations

The necessary institutional permission was obtained from the relevant hospital administration, and ethical approval was granted by the ethics committee of the relevant university (Approval No: 2026/02/07/6). The study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical principles governing scientific research. Participants were informed about the purpose of the study, the data collection process, the voluntary nature of participation, and their right to withdraw from the study at any time without providing a reason. Informed consent was obtained from all participants before data collection, and the confidentiality of their personal information was maintained.

Results

Table 1. Sociodemographic and clinical characteristics of the participants (n=51)

Descriptive and clinical characteristics	Mean ± SD / n	Median (Min–Max) / %
Age (years)	39.76 ± 12.11	34 (20–58)
Sex		
Female	25	49.0
Male	26	51.0
Marital status		

Descriptive and clinical characteristics	Mean ± SD / n	Median (Min–Max) / %
Married	30	58.8
Single	21	41.2
Education level		
Illiterate	2	3.9
Literate	10	19.6
Primary school	7	13.7
Secondary school	5	9.8
High school	14	27.5
University or higher	13	25.5
Perceived income level		
Income lower than expenses	29	56.9
Income equal to expenses	14	27.5
Income higher than expenses	8	15.7
History of previous surgery		
Yes	24	47.1
No	27	52.9
Medical diagnosis		
Hernia	21	41.2
Cholecystitis	6	11.8
Cholelithiasis	10	19.6
Appendicitis	8	15.7
Splenomegaly	1	2.0
Splenic rupture	1	2.0
Obesity	4	7.8
Surgical procedure performed		
Laparoscopic cholecystectomy	16	31.4
Laparoscopic appendectomy	8	15.7
Laparoscopic hernia repair	21	41.2
Laparoscopic bariatric surgery	4	7.8
Laparoscopic splenectomy	2	3.9

SD: Standard deviation; Min: Minimum; Max: Maximum.

The participants' mean age was 39.76±12.11 years, with a median age of 34 years (range, 20–58 years). Of the participants, 25 (49.0%) were female, 26 (51.0%) were male, and 30 (58.8%) were married. Regarding educational level, 14 participants (27.5%) were high school graduates, and 13 (25.5%) had a university-level or higher education. Twenty-nine participants (56.9%) reported that their income was lower than their expenses, and 27 (52.9%) had no previous surgical experience.

The most common medical diagnosis was hernia (n=21; 41.2%), followed by cholelithiasis (n=10; 19.6%), appendicitis (n=8; 15.7%), cholecystitis (n=6; 11.8%), and obesity (n=4; 7.8%). Splenomegaly and splenic rupture were each diagnosed in 1 patient (2.0%). Regarding the surgical procedures performed, 21 patients (41.2%) underwent laparoscopic hernia repair, 16 (31.4%) underwent laparoscopic cholecystectomy, 8 (15.7%) underwent laparoscopic appendectomy, 4 (7.8%) underwent laparoscopic bariatric surgery, and 2 (3.9%) underwent laparoscopic splenectomy.

Table 2. Distribution of the patients' total scale scores (n = 51)

Scales	Mean ± SD	Median (Q1–Q3)	Min–Max
Surgical Fear Questionnaire total score	21.78 ± 16.20	17 (7–31)	0–66
Pain Catastrophizing Scale total score	25.65 ± 14.17	27 (13–36)	0–66
Patient Mobility Scale total score	23.76 ± 11.45	32 (8–32)	8–36

SD: Standard deviation; Q1: First quartile; Q3: Third quartile; Min: Minimum; Max: Maximum.

As shown in Table 2, the median total score on the Surgical Fear Questionnaire was 17 (Q1–Q3: 7–31), with scores ranging from 0 to 66. The median total score on the Pain Catastrophizing Scale was 27 (Q1–Q3: 13–36), with a range of 0–66. The median total score on the Patient Mobility Scale was 32 (Q1–Q3: 8–32), and the scores ranged from 8 to 36. The corresponding mean total scores were 21.78 ± 16.20, 25.65 ± 14.17, and 23.76 ± 11.45, respectively.

Table 3. Comparison of the patients' total scale scores according to their descriptive and clinical characteristics (n = 51)

Characteristics	n	Surgical Fear Questionnaire	Pain Catastrophizing Scale	Patient Mobility Scale
Sex		**243.00 (0.108)**	**273.00 (0.308)**	**267.00 (0.250)**
Female	25	31.00 (7.00-31.00)	31.00 (13.00-36.00)	32.00 (8.00-32.50)
Male	26	17.00 (7.00-31.00)	27.00 (13.00-36.00)	30.00 (8.00-32.00)
Marital status		**125.00 (<0.001)**	**115.00 (<0.001)**	**226.00 (0.073)**
Married	30	31.00 (17.00-31.00)	36.00 (27.00-36.00)	32.00 (26.50-32.00)
Single	21	7.00 (7.00-16.00)	13.00 (13.00-22.00)	8.00 (8.00-33.00)
Previous surgery		**170.00 (0.002)**	**128.00 (<0.001)**	**94.00 (<0.001)**
Yes	24	7.00 (7.00-31.00)	13.00 (13.00-22.00)	8.00 (8.00-32.00)
No	27	31.00 (17.00-31.00)	36.00 (27.00-36.00)	32.00 (32.00-33.00)

For characteristic rows, values are Mann-Whitney U statistics (p values); for category rows, values are median (25th-75th percentile). Statistical significance was set at p<0.05.

As shown in Table 3, the total scores of the Surgical Fear Questionnaire, Pain Catastrophizing Scale, and Patient Mobility Scale did not differ significantly according to sex (p = 0.108, p = 0.308, and p = 0.250).

Married patients had significantly higher Surgical Fear Questionnaire and Pain Catastrophizing Scale total scores than single patients (both p<0.001). However, Patient Mobility Scale total scores did not differ significantly according to marital status (p=0.073).

Patients with no history of previous surgery had significantly higher Surgical Fear Questionnaire (p=0.002), Pain Catastrophizing Scale (p<0.001), and Patient Mobility Scale total scores (p<0.001) than those who had previously undergone surgery.

Table 4. Relationships among the total scale scores (n = 51)

Scales	1	2	3
1. Surgical Fear Questionnaire	1.000		
2. Pain Catastrophizing Scale	0.783**	1.000	
3. Patient Mobility Scale	0.569**	0.573**	1.000

Values are presented as Spearman's rank correlation coefficients (r_s). *$p < 0.001$.

The relationships among the total scale scores were examined using Spearman's rank-order correlation analysis. A statistically significant, strong positive correlation was found between surgical fear and pain catastrophizing (r_s=0.783, p<0.001). Surgical fear was also significantly and positively correlated with Patient Mobility Scale scores (r_s=0.569, p<0.001). Similarly, pain catastrophizing was significantly and positively correlated with Patient Mobility Scale scores (r_s=0.573, p<0.001).

Discussion

This study showed that preoperative surgical fear, postoperative pain catastrophizing, and pain and difficulty during early mobilization were closely related in adults undergoing laparoscopic abdominal surgery. Surgical fear had a strong positive association with pain catastrophizing and moderate positive associations with Patient Mobility Scale scores; pain catastrophizing was also moderately associated with Patient Mobility Scale scores. Married patients reported greater surgical fear and pain catastrophizing than single patients, whereas patients without previous surgical experience reported higher scores on all three measures. These findings identify a cluster of psychological and experiential factors associated with a more difficult early-mobilization experience. They do not, however, establish that fear or catastrophizing caused mobility difficulty.

The mean Surgical Fear Questionnaire score in this study (21.78±16.20) was close to the 19.90±17.85 reported among 125 patients undergoing laparoscopic cholecystectomy[9] and lower than the 25.95±16.33 reported among 205 patients undergoing mixed abdominal surgery[10] and the 31.83±13.83 reported among 111 day-surgery patients.[22] Differences in procedure mix, clinical setting, perioperative information, and the distribution of patient characteristics may account for variation across studies. The wide dispersion and the median of 17 in the present sample also indicate substantial between-patient heterogeneity. Because the Surgical Fear Questionnaire does not provide a universally accepted diagnostic cutoff, these scores should be interpreted comparatively rather than labeled as a clinical category.

Surgical fear, pain catastrophizing, and mobility scores did not differ by sex in the present study. This differs from the original validation work, which detected variation in Surgical Fear Questionnaire scores by sex and other demographic characteristics,[8] and from observational studies identifying sex among the factors associated with surgical fear.[22,23] The absence of a sex difference here may reflect the nearly balanced sex distribution, the small sample, or procedure-specific factors. Married participants had higher surgical fear and pain catastrophizing scores, consistent with evidence that marital status can be associated with surgical fear,[22] but marital status itself should not be interpreted as a mechanism. It may represent differences in age, family responsibilities, social roles, or other unmeasured characteristics. Because the comparisons were unadjusted, residual confounding is a plausible explanation.

Patients without previous surgical experience reported more surgical fear, greater pain catastrophizing, and a more painful or difficult mobilization experience. A first operation may involve greater uncertainty about anesthesia, postoperative pain, and the expected sensations of movement, which is compatible with qualitative evidence that previous experiences and preparation shape willingness to mobilize.[7] Nevertheless, previous surgery is not uniformly protective. In a study of 100 hospitalized surgical patients, previous surgery and prior anesthesia exposure independently predicted greater rather than lower surgical fear.[24] The contrast suggests that the quality and emotional meaning of prior experience may be more important than whether surgery occurred previously.

The present finding should therefore support targeted assessment of first-time surgical patients without implying that all previously operated patients are at low risk.

The strong correlation between surgical fear and pain catastrophizing (r_s=0.783) is consistent with the convergent-validity evidence for the Surgical Fear Questionnaire, in which surgical fear correlated with pain catastrophizing and state anxiety.[8] It is also compatible with broader evidence linking catastrophizing to acute postsurgical pain[12] and with abdominal surgery research showing that catastrophizing can contribute to the relationship between pain sensitivity and acute postoperative pain.[15] Surgical fear and catastrophizing may share an appraisal of threat while remaining conceptually distinct: one concerns the operation and its consequences, whereas the other concerns anticipated or experienced pain. In this study, surgical fear was assessed preoperatively, but catastrophizing was assessed on postoperative day 2. The observed association may therefore reflect continuity in negative threat appraisal across the perioperative period, although the design cannot determine whether preoperative fear preceded an increase in catastrophizing.

The positive association between surgical fear and Patient Mobility Scale scores (r_s=0.569) agrees with findings in laparoscopic cholecystectomy patients[9] and in a larger mixed abdominal surgery sample,[10] both of which reported more pain and difficulty during mobilization among patients with greater surgical fear. The present study extends this pattern to a sample that included laparoscopic hernia repair, cholecystectomy, appendectomy, bariatric surgery, and splenectomy. Importantly, the Patient Mobility Scale is a patient-reported measure of pain and difficulty during four activities. A higher score therefore indicates a more burdensome mobilization experience, not necessarily less walking, delayed first ambulation, or lower objectively measured activity. Previous work showing that many postoperative patients require verbal or physical assistance during basic movement further supports interpreting mobility as a multidimensional care need.[21]

Pain catastrophizing was also positively associated with Patient Mobility Scale scores (r_s=0.573). This finding closely supports a prospective study of 92 laparoscopic abdominal surgery patients in which pain intensity, catastrophizing, and body mass index together explained 56% of the variance in Patient Mobility Scale scores; catheters and drains were additionally associated with greater pain, catastrophizing, and mobility difficulty.[16] Evidence from 673 abdominal surgery patients monitored with wearable devices likewise showed that higher postoperative pain was associated with less time spent sitting or standing, independent of opioid consumption.[25] Related research in 330 postoperative patients found that pain anxiety and fear-avoidance beliefs were associated with kinesiophobia, with perceived stress contributing to these relationships.[26] Together, these studies support a biopsychosocial interpretation in which pain intensity, pain-related cognitions, stress, and treatment-related restrictions may jointly shape early movement. However, catastrophizing and mobility experience were measured at the same postoperative assessment in the present study. Reverse directionality and shared self-report variance are therefore possible, and mediation should not be inferred from the correlations.

1.9.Limitations

This study has several limitations. It was conducted in a single hospital with a small, nonprobability sample of 51 patients, which limits precision and generalizability. The sample combined several laparoscopic procedures, but the analyses did not adjust for procedure type, urgency, anesthesia, preoperative pain, analgesic exposure, body mass index, catheters or drains, complications, or other clinical factors that may influence both psychological scores and mobilization. Group comparisons were unadjusted and multiple comparisons were performed, so statistically significant demographic findings should be considered exploratory. Surgical fear was measured preoperatively, whereas pain catastrophizing and mobility experience were measured concurrently on postoperative day 2; consequently, the temporal direction between catastrophizing and mobility cannot be established. The Patient Mobility Scale assessed perceived pain and difficulty rather than objective activity duration, distance, timing, or assistance. Larger multicenter studies with repeated psychological assessments, objective mobility measures, and multivariable analysis are needed.

1.10. Implications for Nursing Practice and Research

The findings support brief preoperative assessment of surgical fear and focused preparation for patients who are unfamiliar with surgery. Nursing care can include clear information about expected postoperative sensations, analgesia plans, the purpose and sequence of early-mobilization activities, and the assistance available during movement.

These recommendations are supported by a randomized trial in laparoscopic abdominal surgery in which preoperative early-mobilization training increased mobilization duration and was accompanied by lower pain, greater comfort, better sleep quality, and shorter hospitalization.[4] Pain catastrophizing may also be a modifiable target, although a scoping review found clinically important reductions in only a minority of intervention studies, indicating that the effective components and timing remain uncertain.[27] Future trials should test integrated interventions that combine expectation-setting, pain-management education, cognitive and emotional support, and rehearsed mobility, while measuring fear, catastrophizing, pain, and objective mobility at prespecified time points.

Conclusion

Among adults undergoing laparoscopic abdominal surgery, greater preoperative surgical fear was associated with greater postoperative pain catastrophizing and a more painful or difficult early-mobilization experience. Pain catastrophizing was also associated with mobilization-related pain and difficulty. Patients without previous surgical experience reported higher scores across all three measures, but the small sample and unadjusted observational analyses require cautious interpretation. These findings support individualized perioperative assessment and preparation and justify prospective intervention studies; they do not demonstrate causal effects.

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SUBCRITICAL WATER-DERIVED CERATONIA SILIQUA L. SEED EXTRACT AS A NATURAL ANTIMICROBIAL AGENT AGAINST PATHOGENIC BACTERIA AND FUNGI

SUBKRİTİK SU EKSTRAKSİYONU İLE ELDE EDİLEN CERATONİA SİLİQUA L. ÇEKİRDEK EKSTRAKTININ PATOJEN BAKTERİ VE MANTARLARA KARŞI DOĞAL ANTİMİKROBİYAL AJAN OLARAK DEĞERLENDİRİLMESİ

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ABSTRACT

Background and Aim: The global rise of antimicrobial resistance (AMR) has significantly threatened and limited the clinical efficacy of currently available antimicrobial therapies. This growing crisis highlights the urgent need to discover novel alternative antimicrobial agents with high phytotherapeutic potential. This study aimed to investigate the antimicrobial potential of an extract obtained from *Ceratonia siliqua* L. seeds (CsLSE) against bacterial and fungal pathogens.

Methods
The carob seeds were first dried, ground and then extracted using the method of subcritical water extraction for obtaining the extract. The reference microbial strains employed against the extracted antimicrobial were *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATTC 14579, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Candida glabrata* ATCC 90030 and *Candida albicans* ATCC 90028. Antimicrobial activity of the CsLSE was measured via the agar well diffusion method at the extract concentration of 100 mg/mL. Minimum inhibitory concentration (MIC) as well as minimum bactericidal/fungicidal concentration (MBC/MFC) values were determined using the broth micro-dilution method in 96-well plates as per the CLSI guidelines.

Results
CsLSE exhibited inhibitory activity against all tested pathogenic microorganisms. The diameters of inhibition zone of CsLSE against the tested microorganisms ranged from 15 to 30 mm. The extract showed the highest antimicrobial activity against Gram-negative bacteria *Escherichia coli* (30 ± 0.5 mm) and *Pseudomonas aeruginosa* (29 ± 0.4 mm) with significantly larger zones of inhibition compared to the positive control, gentamicin (*E. coli*: 21.0 ± 0.9 mm; *P. aeruginosa*: 19.0 ± 0.8 mm). MBC/MFC analysis revealed bactericidal activity only against *E. coli*, with an MBC value of 12.5 mg/mL, whereas MBC/MFC values for the remaining microorganisms exceeded 100 mg/mL.

Conclusion
CsLSE demonstrated notable antimicrobial activity against the tested pathogens, particularly exhibiting strong inhibitory and bactericidal effects against *E. coli*. These findings suggest that *Ceratonia siliqua* L. seed extract represents a promising natural-source antimicrobial candidate, especially against Gram-negative bacterial pathogens and warrants further investigation for potential biomedical applications.
Keywords: *Ceratonia siliqua* L.; antibacterial; antifungal; minimum inhibitory concentration (MIC); minimum bactericidal/fungicidal concentration (MBC/MFC)

ÖZET

Giriş ve Amaç
Küresel ölçekte artan antimikrobiyel direnç (AMD), mevcut antimikrobiyel tedavi seçeneklerinin klinik etkinliğini ciddi derecede tehdit etmekte ve sınırlandırmaktadır. Bu kriz, patojenlere karşı yeni

fitoterapötik potansiyeli yüksek alternatif antimikrobiyel ajanların keşfini zorunlu kılmaktadır. Bu çalışmada, keçiboynuzu (*Ceratonia siliqua L.*) çekirdeklerinden (CsLSE) elde edilen ekstraktların bakteriyel ve fungal izolatlar üzerindeki antimikrobiyel potansiyelinin belirlenmesi amaçlanmıştır.

Yöntem
İlk olarak keçiboynuzu çekirdekleri kurutulup öğütülerek, alt-kritik su ekstraksiyonu ile ekstrakte edilmiştir. Elde edilen ekstraktın antimikrobiyel aktivitesi Gram pozitif, Gram negatif ve mayalara karşı değerlendirilmiştir. CsLSE, mikrobiyal referans suşlar (*S. aureus* ATCC 25923, *B. cereus* ATTC 14579, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *C. glabrata* ATCC 90030 and *C. albicans* ATCC 90028) kullanılarak standart mikrobiyolojik prosedürlere uygun olarak kültüre edilmiştir. Ekstraktların antimikrobiyel duyarlılığı için agar kuyu difüzyon metodu (100 mg/ml); minimum inhibitör konsantrasyonu (MİK) ve minimum bakterisidal/fungisidal konsantrasyonu (MBK/MFC) değerlerinin tespiti için ise CLSI protokollerine uygun 96 kuyucuklu plakalarda sıvı mikrodilüsyon yöntemi kullanılmıştır.

Bulgular
CsLSE, test edilen tüm patojenik mikroorganizmalara karşı inhibitör aktivite göstermiştir. En düşük MIC değeri *Escherichia coli* için 6, 25 mg/mL olarak belirlenirken, bunu *Bacillus cereus* ve *Pseudomonas aeruginosa* (12, 5 mg/mL), *Staphylococcus aureus* (25 mg/mL) ve *Candida glabrata* (50 mg/mL) izlemiştir. MBC/MFC analizinde yalnızca *E. coli* için bakterisidal aktivite gözlenmiş (MBC: 12, 5 mg/mL), diğer mikroorganizmalar için MBC/MFC değerleri > 100 mg/mL olarak belirlenmiştir.

Sonuç
CsLSE, özellikle *E. coli* başta olmak üzere test edilen patojenlere karşı belirgin inhibitör aktivite sergilemiştir. Sonuçlar CsLSE'nin *E. coli* üzerinde bakterisidal etki göstererek önemli veri elde edildiğini göstermektedir. Ayrıca, CsLSE'nin doğal kaynaklı bir antimikrobiyel ajan olarak özellikle Gram-negatif bakterilere karşı potansiyel taşıdığı ve ileri biyolojik değerlendirmeler için umut verici bir aday olabileceği düşünülmektedir.
Keywords: Ceratonia siliqua L.; carob seed extract; antibacterial activity; antifungal activity; minimum inhibitory concentration (MIC); minimum bactericidal/fungicidal concentration (MBC/MFC);

GİRİŞ
Antimikrobiyel direnç, 21. yüzyılın en kritik küresel halk sağlığı sorunlarından biri olarak kabul edilmektedir (EClinicalMedicine, 2021). AMR'nin küresel sağlık gündeminde bu denli belirgin bir yer edinmesi; sağlık sistemlerindeki bilimsel, teknolojik ve kurumsal ilerlemelere paralel bir seyir izlemekte ve son yüzyılda yaşanan köklü sosyoekonomik dönüşümleri yansıtmaktadır. Farklı disiplinlerden yürütülen araştırmalar; hasta güvenliği ve enfeksiyon kontrolünden (Gradmann, 2017), bulaşma yolları ve patojen rezervuarlarının moleküler epidemiyolojisine (Mughini-Gras et al., 2019), toplum düzeyindeki yükünün halk sağlığı boyutundan (Baquero et al., 2015), sağlık ekonomisi kapsamında yönetimi ve maliyet analizlerine (Roope et al., 2019) kadar AMR probleminin muhtelif yönlerini kapsamlı biçimde incelemiştir. Son dönemlerde bu küresel sorunun görünürdeki kötüleşmesine rağmen, yeni antibiyotiklerin geliştirilmesinin yüksek maliyetleri ve antimikrobiyel dirençlerin (AMR) kaçınılmaz olarak ortaya çıkması nedeniyle antibiyotik geliştirmenin ilaç endüstrisi için ekonomik açıdan cazip olmamasına ve yeni farmösitik ajan arayışına yönelmeye neden olmuştur. *Pseudomonas aeruginosa, Acinetobacter baumannii* veya *Klebsiella pneumoniae* kaynaklı olanlar başta olmak üzere çoklu ilaç direnci (MDR) gösteren enfeksiyonlar, tarihsel olarak çoğunlukla nosokomiyal (hastane kaynaklı) ve sağlık kuruluşlarıyla ilişkili vakalar biçiminde değerlendirilmiştir. Sonuç olarak AMR'nin küresel ölçekte yayılması, yüksek mortalite oranları ve yeni antibiyotik geliştirme çalışmalarındaki yetersizlikler, MDR bakterileri modern tıbbın karşı karşıya kaldığı en kritik tehditlerden biri hâline getirmektedir (Alós, 2015). Antibiyotik dirençli bakteriyel patojenlerle mücadelede etkili yeni antibakteriyel ajanların keşfi, güncel bilimsel araştırmalarda öncelikli bir çalışma alanını oluşturmaktadır. Bu doğrultuda, bitkisel kaynaklı biyoaktif bileşikler, yüksek terapötik potansiyelleri sayesinde gelecek vaat edici alternatifler olarak öne çıkmaktadır. Keçiboynuzu (*Ceratonia siliqua* L.), Akdeniz bölgesinde yaygın olarak yetiştirilen bir ağaç olarak baklagiller (Leguminoseae) familyasının Caesalpinaceae alt familyasına ait olarak uzun süredir bilinen bir türdür (Yousif & Alghzawi, 2000).

Keçiboynuzu meyvesinin kabuk kısmı; yüksek şeker içeriği ve ekonomik bir hammadde olması sebebiyle uzun süredir hayvan yemi olarak değerlendirilmesinin yanı sıra tatlı, bisküvi ve işlenmiş içecekler başta olmak üzere insan beslenmesinde de yaygın kullanım alanına sahiptir.
Ayrıca söz konusu meyvenin antioksidan, antiinflamatuar, antidiyabetik özellikleri, tekstil ve kozmetik endüstrileride kullanımı, dondurma, tatlı ve çorba gibi çeşitli gıda ürünlerinde nitelikli bir doğal kıvam artırıcı ve stabilizör katkı maddesi olarak kullanımı araştırılmıştır (Darwish et al., 2021; Santos et al., 2005). Son dönemlerde ise keçiboynuzu özütlerinin bazı bakteri ve mantar türlerine karşı çok güçlü antimikrobiyel etki göstermesi nedeniyle önemli ölçüde ilgi görmüştür (Hsouna et al., 2011a; Ibrahim & Auer, 2013). Bu çalışmada asıl amaç, keçiboynuzu tohumlarının ekstrakte edilerek çeşitli mikroorganizmalar üzerindeki etkinliği analiz etmektir.

MATERYAL VE METOD

Malzemeler

Bu çalışmada kullanılan keçiboynuzu tohumları Mersin Üniversitesi'den toplanmıştır. Numunelerin öğütülmesinde laboratuvar tipi bir öğütücüden (Retsch RS200) yararlanılmıştır. Ekstraksiyon ve analiz süreçlerinde kullanılan etanol, diklorometan, Gram-pozitif (*Staphylococcus aureus* ATCC 25923 ve *Bacillus cereus* ATTC 14579), Gram-negatif (*Pseudomonas aeruginosa* ATCC 27653 ve *Escherichia coli* ATCC 25922) bakteriler ve mayalardan (*C. glabrata* ATCC 90030 and *C. albicans* ATCC 90028*)* suşları, Mueller-Hinton Broth (MHB, Merck, Almanya) besiyeri, Patates Dekstroz Agar (PDA, BD Difco, ABD), gentamisin (10 µg/disk, Oxoid, İngiltere), amfoterisin B (20 µg/disk, Oxoid, İngiltere) ve negatif kontrol olarak kullanılan %10 DMSO (dimetil sülfoksit, Sigma-Aldrich, ABD) çeşitli firmalardan tedarik edilmiştir. Ayrıca alt-kritik su ekstraksiyon sistemi (yüksek basınçlı çelik reaktör), santrifüj, UV-Vis spektrofotometresi, analitik terazi, manyetik karıştırıcı, filtre kağıdı ve kurutma fırını (etüv) kullanılmıştır.

Numune Hazırlama

Keçiboynuzu meyvelerinden çekilerek ayrılan tohumlar distile su ile yıkanmış ve etüvde 80 °C'de 24 saat süreyle kurutulmuştur. Kurutulan tohumlar halkalı öğütücü (Retsch RS200) yardımıyla öğütüldükten sonra 500 µm'lik analitik elekten geçirilmiş ve homojen hale getirilmiştir. Hazırlanan numuneler, ekstraksiyon aşamasına kadar 4 °C'de soğuk ortamda muhafaza edilmiştir.

Alt-Kritik Su Ekstraksiyonu

Alt-kritik su ekstraksiyonu için 10 g öğütülmüş keçiboynuzu numunesi tartılarak yüksek basınçlı reaktöre aktarılmıştır. Üzerine 160 mL saf su ilave edildikten sonra reaktör sızdırmaz şekilde kapatılmıştır. Ardından sisteme yaklaşık 10 bar basınç uygulanmıştır. Isıtma ünitesine alınan reaktör hedef sıcaklıklara erişene kadar ısıtılmış ve numuneler bu sıcaklıkta 1 saat boyunca tutulmuştur. İşlem tamamlandıktan sonra reaktör soğutulmuş ve numune filtre kağıdı ile süzülmüştür. Elde edilen sıvı faz, döner buharlaştırıcı kullanılarak deriştirilmiştir. Balon çeperinde biriken kalıntı 20 mL etanol ve 5 mL diklorometan (DCM) ile çözülmüş, takiben DCM ortamdan uzaklaştırılmıştır. Son hacim etanol ilavesiyle yaklaşık 30 mL'ye tamamlanmıştır.

Antibakteriyel Aktivite

Mikrobiyal Suşlar ve Kültür Koşulları

CSLE'nin antibakteriyel aktivitesi; Gram-pozitif (*Staphylococcus aureus* ATCC 25923 ve *Bacillus cereus* ATCC 14579), Gram-negatif (*Pseudomonas aeruginosa* ATCC 27653 ve *Escherichia coli* ATCC 25922) bakterilerden ve mayalardan (*C. glabrata* ATCC 90030 and *C. albicans* ATCC 90028*)* oluşan bir panel üzerinde değerlendirilmiştir. Bakteri kültürleri, Mueller-Hinton Broth (MHB) besiyerinde 37ºC'de 24 saat süreyle inkübe edilmiş ve nihai inokulum yoğunlukları 1 x 10^8 CFU/mL (0,5 McFarland standart eşdeğeri) olacak şekilde ayarlanmıştır. Mayalar ise Patates Dekstroz Agar (PDA) ortamında 30ºC'de 24 saat süreyle inkübe edilmiş ve nihai Tüm analizler, her bir bakteri suşu için bağımsız olarak üçer paralel (triplikat) hâlinde gerçekleştirilmiştir.

Agar Kuyu Difüzyon İnhibisyon Zonlarının Belirlenmesi

25 mL Mueller-Hinton Agar (MHA) içeren petri kapları aseptik koşullarda hazırlanarak etiketlenmiştir. Hazırlanan bakteriyel inokulumlar, steril eküvyon yardımıyla agar yüzeyine homojen bir şekilde ekilmiştir; homojen bir dağılım sağlamak amacıyla her sürme işleminden sonra plaklar 90° döndürülmüştür. Plaklarda, steril bir delgi (steril mantar delici) kullanılarak 4 mm çapında kuyucuklar

oluşturulmuştur. Ardından, 100 mg/mL konsantrasyonda hazırlanan bitki ekstraktından 100 µL'lik alikotlar kuyucuklara yüklenmiştir. Aynı işlemler mayalar için Patates Dekstroz Agarda ortamında gerçekleştirilmiştir. Gözlemlenen antimikrobiyel aktivitenin çözücü etkisinden bağımsız olduğunu doğrulamak amacıyla, sırasıyla pozitif kontrol olarak gentamisin (10 µg/disk) ve Amfoterisin B (20 µg/disk) ve negatif kontrol olarak %10 DMSO (dimetil sülfoksit) kullanılmıştır. Plaklar, ekstraktın agar matrisine ön difüzyonunu sağlamak amacıyla oda sıcaklığında 30 dakika bekletildikten sonra 37 °C'de inkübe edilmiştir. İnkübasyon süresi sonunda kuyucukların çevresinde oluşan şeffaf inhibisyon zonları milimetre (mm) cinsinden ölçülmüş ve antimikrobiyel aktivite derecesini belirlemek üzere ortalama zon çapları hesaplanmıştır.

MİK ve MBK/MFK Düzeylerinin Belirlenmesi

CsLSE'nin minimum inhibitör konsantrasyonu (MİK) ve minimum bakterisidal konsantrasyonu (MBK), Klinik ve Laboratuvar Standartları Enstitüsü (CLSI) protokollerinde bazı modifikasyonlar yapılarak 96 kuyucuklu mikrotitrasyon plakalarında sıvı mikrodilüsyon yöntemiyle belirlenmiştir. CsLSE, stok çözeltiler elde edilmek üzere distile suda çözülmüştür. Bu stok çözeltilerden MHB kullanılarak seri iki katlı seyreltmeler hazırlanmış ve değişen nihai test konsantrasyonlar elde edilmiştir. Mikrobiyal kültürler, kuyucuklarda 5 x 10^5 CFU/mL'lik nihai bakteri yoğunluğu sağlanacak şekilde aşılanmıştır. Tüm deneysel kurulumlar duplikat olarak yürütülmüş; yalnızca MHB ve PDB içeren üreme kontrolleri ile MHB ve distile su karışımını içeren negatif kontroller ortama dâhil edilmiştir. Gentamisin ve Amfoterisin B, pozitif referans standart olarak kullanılmıştır. 24 saatlik inkübasyon periyodunun ardından MİK, makroskobik olarak gözle görülür bakteriyel gelişimi tamamen engelleyen en düşük ekstrakt konsantrasyonu olarak kaydedilmiştir. MBK değerini belirlemek amacıyla, berrak görünüm sergileyen tüm MİK kuyucuklarından alınan 20 µL'lik hacimler agar plakalarına pasajlanmıştır. MBK, başlangıç inokulumunun %99,9'unu katleden en düşük bitki ekstraktı konsantrasyonu olarak tanımlanmıştır. Tüm tayinler üç bağımsız deneysel tekrarda gerçekleştirilmiş ve ortalama sonuçlar hesaplanmıştır.

İstatistiksel veriler

İstatiksel analiz parametreleri eklenerek, verilerin birbiriyle olan anlamlılık düzeylerinin p değerleri ($p < 0,05$) ve harflendirme sistemi (ANOVA / Tukey Testi) ile ifade edilmiştir.

Bulgular Ve Tartışma

CsLSE ile pozitif kontrollerin (Gentamisin ve Amfoterisin B) mikroorganizmalar üzerindeki inhibisyon zon çapları Tek Yönlü Varyans Analizi (One-Way ANOVA) ve ardından Tukey testi uygulanarak analiz edilmiştir ($p < 0,05$). Elde edilen veriler, farklılıkların istatistiksel önemini belirten harflendirmelerle birlikte Tablo 1'de sunulmuştur. CsLSE'nin oluşturduğu inhibisyon zonları 15-30 mm arasında değişmiştir. En yüksek antimikrobiyel aktivite *Escherichia coli* ve *Pseudomonas aeruginosa* üzerinde gözlenmiş olup, sırasıyla 30 ± 0, 5 mm ve 29 ± 0, 4 mm inhibisyon zonları oluşturmuştur. Bu değerler, pozitif kontrol olarak kullanılan gentamisinin inhibisyon zonlarından (*E. coli*: 21, 0 ± 0, 9 mm; *P. aeruginosa*: 19, 0 ± 0, 8 mm) daha yüksek bulunmuştur. Bu durum, CsLSE'nin özellikle Gram-negatif bakterilere karşı güçlü bir inhibitör etkiye sahip olduğunu göstermektedir. Gram-pozitif bakteriler değerlendirildiğinde, CsLSE *Bacillus cereus* üzerinde 21 ± 1, 2 mm ve *Staphylococcus aureus* üzerinde 18 ± 0, 2 mm inhibisyon zonu oluşturmuştur. *S. aureus* için CsLSE aktivitesi gentamisin kontrolüne (17, 0 ± 0, 3 mm) göre daha yüksek bulunurken, *B. cereus* için gentamisin (23, 0 ± 0, 4 mm) CsLSE'den daha yüksek aktivite göstermiştir. Bu sonuçlar, ekstraktın Gram-pozitif bakterilere karşı da etkili olduğunu, ancak etkinliğin bakteri türüne bağlı olarak değişebileceğini göstermektedir. Maya türleri değerlendirildiğinde, CsLSE *Candida glabrata* ve *Candida albicans* üzerinde sırasıyla 16 ± 0, 7 mm ve 15 ± 1, 0 mm inhibisyon zonları oluşturmuştur. Antifungal kontrol olarak kullanılan amfoterisin B ile karşılaştırıldığında, CsLSE'nin aktivitesi *C. glabrata* (16 mm ve 15 mm) ve *C. albicans* (15 mm ve 14 mm) için hafif daha yüksek bulunmuştur. Bu sonuç, CsLSE'nin Candida türlerine karşı da antifungal potansiyele sahip olduğunu göstermektedir.

Tablo 1. CsLSE ve standart kontrol antibiyotiklerinin inhibisyon zon çapları (mm) ve istatistiksel karşılaştırması

Patojenik mikroorganizma	**İnhibisyon Zon (mm)**		
	(CsLSE) (100 mg/mL)	**Pozitif kontrol**	
		Gentamisin (10 µg/disk)	**Amfoterisin B** (20 µg/disk)
Staphylococcus aureus	18 ± 0, 2[a]	17, 0 ± 0, 3[b]	0
Bacillus cereus	21 ± 1, 2[a]	23, 0 ± 0, 4[b]	0
Escherichia coli	30 ± 0, 5[a]	21, 0 ± 0, 9[b]	0
Pseudomonas aeruginosa	29 ± 0, 4[a]	19, 0 ± 0, 8[b]	0
Candida glabrata	16 ± 0, 7[a]	0	15, 0 ± 0, 7
Candida albicans	15 ± 1, 0[a]	0	14, 0 ± 0, 3

* Veriler 3 bağımsız tekrarın ortalaması ± standart sapma (Ortalama ± SD) olarak verilmiştir. * Aynı satırdaki farklı küçük harfler ([a, b, c]), gruplar arasındaki farkın istatistiksel olarak anlamlı olduğunu gösterir ($p < 0,05$). * U.D.: Uygulanmadı / Zon Oluşmadı (0 mm). Negatif kontrol (%10 DMSO) hiçbir grupta inhibisyon göstermemiştir.

CsLSE patojenik mikroorganizmalar üzerindeki antimikrobiyel aktivitesi, minimum inhibitör konsantrasyon (MIC) ve minimum bakterisidal/fungisidal konsantrasyon (MBC/MFC) değerleri belirlenerek değerlendirilmiştir (Tablo 2). Elde edilen sonuçlara göre CsLSE'nin tüm test edilen mikroorganizmalar üzerinde inhibitör aktivite göstermiştir. En düşük MIC değeri *Escherichia coli* için 6, 25 mg/mL olarak belirlenmiş ve bu mikroorganizmanın CsLSE'ye karşı en duyarlı patojen olduğu görülmüştür. *Bacillus cereus* ve *Pseudomonas aeruginosa* için MIC değerleri 12, 5 mg/mL, *Staphylococcus aureus* için 25, 0 mg/mL olarak saptanmıştır. Maya türleri içerisinde *Candida glabrata* en yüksek MIC değerine sahip olup (50, 0 mg/mL), CsLSE'ye karşı bakteriyel türlere kıyasla daha düşük duyarlılık göstermiştir. MBC/MFC sonuçları değerlendirildiğinde, *E. coli* için MBC değeri 12, 5 mg/mL olarak belirlenmiş ve ekstraktın bu suşa karşı bakterisidal aktivite gösterdiği tespit edilmiştir. *E. coli* için hesaplanan MBC/MIC oranı 2 olup, bu değer bakterisidal etki kriterleri ile uyumludur. Buna karşın, *S. aureus*, *B. cereus* ve *P. aeruginosa* için MBC değerleri 100 mg/mL'nin üzerinde bulunmuş, bu mikroorganizmalarda test edilen konsantrasyon aralığında öldürücü aktivite gözlenmemiştir. Benzer şekilde, *C. glabrata* için MFC değerinin > 100 mg/mL olması, CsLSE'nin bu maya türüne karşı fungisidal etkisinin sınırlı olduğunu göstermiştir. Genel olarak değerlendirildiğinde, CsLSE özellikle *E. coli* üzerinde güçlü inhibitör ve bakterisidal aktivite gösterirken, diğer test edilen mikroorganizmalarda ağırlıklı olarak büyümeyi baskılayıcı (bakteriyostatik/fungistatik) etki sergilemiştir. CsLSE Gram-negatif bakterilere karşı umut verici antimikrobiyel potansiyele sahip olduğunu ortaya koymaktadır.

Tablo 2. CsLSE patojenik mikroorganizmalar üzerindeki MİK ve MBK/MFK değerleri (mg/mL)

Patojenik mikroorganizma	**MIC (mg/mL)**	**MBC/MFC (mg/mL)**
Staphylococcus aureus	25, 0	> 100
Bacillus cereus	12, 5	> 100
Escherichia coli	6, 25	12, 5
Pseudomonas aeruginosa	12, 5	> 100
Candida glabrata	50, 0	> 100
Candida albicans	50, 0	> 100

Elde edilen veriler, keçiboynuzu çekirdeği ekstraktının özellikle *E. coli* ve *P. aeruginosa* gibi Gram-negatif bakterilere karşı belirgin düzeyde antibakteriyel ve antimikrobiyal etki gösterdiğini ortaya koymaktadır. Söz konusu antibakteriyel aktivitenin konsantrasyona bağlı bir seyir izlemesi, bitkisel kaynaklı ekstraktların sentetik antibiyotiklere kıyasla daha düşük yan etki profili sunan potansiyel birer

alternatif olabileceğine işaret etmektedir. Farklı literatürler incelendiğinde, Hsouna ve ark. (2011) keçiboynuzu meyve kabuğu uçucu yağının antimikrobiyal ve sitotoksik niteliklerini rapor etmiş olup; bu veriler mevcut çalışmanın bulgularıyla paralellik göstermektedir (Hsouna et al., 2011). Benzer şekilde Meziani ve ark. (2015), keçiboynuzu yaprak ve meyve kabuklarından elde edilen aseton ve etanol ekstraktlarının Gram-negatif patojenler üzerinde kayda değer bir inhibisyon sağladığını bildirmişlerdir (Meziani et al., 2015). Bunun yanı sıra Aissani ve ark. (2012), keçiboynuzu yapraklarına ait metanolik ekstraktların *Listerioides monocytogenes* (veya *L. monocytogenes*) gelişimi üzerindeki baskılayıcı etkisini ortaya koymuştur (Aissani et al., 2012). Farklı olarak yapılan bir çalışmada, Alshareef ve ark. (2025), Filistin keçiboynuzu (*Ceratonia siliqua*) ekstraktlarının antimikrobiyal aktivitesini kuyu difüzyon yöntemi kullanarak *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* ve *Klebsiella pneumoniae* bakterilerine karşı değerlendirmiştir. Elde edilen bulgular; yaprak ekstraktlarının (300 mg/mL) özellikle *S. aureus* üzerinde en güçlü antibakteriyel etkiyi sergilediğini ve ortaya çıkan inhibisyon zonu çapının (23,67 ± 0,57 mm), pozitif kontrol olarak kullanılan antibiyotiğin (vankomisin 30 µg/mL) inhibisyon zonunu (18 mm) geride bıraktığını göstermiştir (Alshareef et al., 2025). Söz konusu bileşiklerin antibakteriyel etkinliklerini birden fazla etki mekanizması üzerinden gerçekleştirdikleri öngörülmektedir. İlk olarak; gallik asit ve kafeik asit gibi fenolik bileşiklerin, mikrobiyal hücre zarlarının bütünlüğünü bozduğu bilinmektedir (Oulahal & Degraeve, 2022). Zar yapısında meydana gelen bu destabilizasyon; membran geçirgenliğinin artmasına, sitoplazmik bileşenlerin hücre dışına sızmasına ve nihayetinde hücre ölümünün gerçekleşmesine yol açmaktadır (Wong et al., 2021). Buna ek olarak; kuersetin ve rutin gibi flavonoid bileşiklerin, enerji metabolizması ve hücre bölünmesinde kritik rol oynayan temel enzimleri inhibe etmek suretiyle bakteriyel metabolik süreçleri baskıladığı, dolayısıyla bakteriyel üreme ve çoğalmayı engellediği düşünülmektedir (Ullah et al., 2020). Sonuç olarak; mevcut çalışmada elde edilen veriler ile literatürdeki benzer bulgular birlikte değerlendirildiğinde, keçiboynuzu (*Ceratonia siliqua*) çekirdek ekstraktlarının sahip olduğu zengin içeriği sayesinde Gram-negatif patojenlere karşı çoklu etki mekanizmaları üzerinden güçlü bir antimikrobiyal potansiyel sergilediği anlaşılmaktadır. Bu durum, keçiboynuzunun sentetik antibiyotiklere karşı güvenilir, düşük yan etkili ve doğal bir biyoterapötik alternatif olarak tıp ve gıda sektörlerinde kullanım olanağını güçlü bir şekilde desteklemektedir.

Sonuç

Bu çalışmada, CsLSE'nin çeşitli patojenik mikroorganizmalar üzerindeki antimikrobiyel potansiyeli, inhibisyon zon çapları ile MİK ve MBK/MFK parametreleri üzerinden değerlendirilmiştir. Elde edilen bulgular, CsLSE'nin test edilen tüm patojenler üzerinde değişen derecelerde antimikrobiyel aktiviteye sahip olduğunu göstermektedir. Ekstrakt, özellikle Gram-negatif bakterilere karşı dikkat çekici ve güçlü bir etkinlik sergilemiştir. *E. coli* (30 ± 0,5 mm) ve *P. aeruginosa* (29 ± 0,4 mm) üzerinde oluşturduğu inhibisyon zonları, pozitif kontrol olarak kullanılan gentamisin antibiyotiginden (sırasıyla 21,0 mm ve 19,0 mm) istatistiksel olarak anlamlı derecede daha yüksek bulunmuştur ($p < 0,05$). Ayrıca *E. coli* için tespit edilen 6,25 mg/mL MİK ve 12,5 mg/mL MBK değerleri (MBK/MİK = 2), CsLSE'nin bu suş üzerinde güçlü bir bakterisidal etki gösterdiğini kanıtlamaktadır. Gram-pozitif bakteriler (*B. cereus* ve *S. aureus*) ile Candida türlerinde (*C. glabrata* ve *C. albicans*) da belirgin inhibisyon zonları gözlenmiş; Candida türlerindeki zon çapları antifungal kontrol amfoterisin B'den hafifçe daha yüksek saptanmıştır. Ancak bu gruplar için MİK değerlerinin daha yüksek (12,5 - 50,0 mg/mL) ve MBK/MFK değerlerinin >100 mg/mL olması, ekstraktın bu patojenler üzerinde temel olarak büyümeyi baskılayıcı (bakteriyostatik/fungistatik) bir etki mekanizmasına sahip olduğunu ortaya koymaktadır. Özetle, CsLSE başta Gram-negatif patojenler (özellikle *E. coli*) olmak üzere geniş bir antimikrobiyel spektruma sahiptir. Bu sonuçlar, CsLSE'nin doğal bir antimikrobiyel ajan olarak potansiyelini vurgulamakta ve ileride aktif bileşenlerinin izolasyonu ile etki mekanizmalarının aydınlatılmasına yönelik daha ileri çalışmaların yapılması gerektiğini desteklemektedir.

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INVESTIGATION OF THE EFFICACY OF AVOCADO SEED EXTRACTS IN PREVENTING, INHIBITING AND ERADICATING S. AUREUS AND P. *AERUGINOSA* BIOFILMS

AVOKADO ÇEKİRDEĞİ ÖZÜTÜNÜN S. AUREUS VE P. AERUGINOSA BİYOFİLMLERİNİN ÖNLENMESİ, ENGELLENMESİ VE ORTADAN KALDIRILMASINDAKİ ETKİNLİĞİNİN ARAŞTIRILMASI

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Abstract

Background and Aim: Biofilms formed by *Staphylococcus aureus* ATCCC 25923 and *Pseudomonas aeruginosa* ATCCC 27853, which are frequently associated with chronic wounds and medical devices, exhibit high tolerance to antimicrobial treatments due to their protective extracellular matrix structure. Therefore, the discovery of innovative natural bioactive agents capable of preventing biofilm attachment, inhibiting biofilm development, and reducing established biofilms has become increasingly important. This study aimed to investigate the antibiofilm potential of an extract obtained from avocado (*Persea americana* Mill.) seeds (ASE) against *S. aureus* and *P. aeruginosa* biofilms.

Methods

ASE were initially dried, powdered and extracted using the Soxhlet extraction method. Biofilm inhibition activity was assessed using the crystal violet staining assay by determining the minimum biofilm prevention concentration (MBPC), minimum biofilm inhibitory concentration (MBIC) and minimum biofilm eradication concentration (MBEC). Culture medium and chlorhexidine were used as negative and positive controls, respectively.

Results

The antibiofilm activity of the avocado seed extract increased in a concentration-dependent manner against both tested strains. At %10, the highest inhibition of initial attachment was observed as 81.34% for *S. aureus* and 63.97% for *P. aeruginosa*. The extract inhibited biofilm formation by 79.28% and 65.09% and reduced established biofilms by 87.54% and 61.35% for *S. aureus* and *P. aeruginosa*, respectively. Significant differences were observed between the extract-treated groups and the negative control ($p < 0.05$), whereas no significant difference was detected between the extract and chlorhexidine treatments ($p > 0.05$).

Conclusion

Avocado seed extract demonstrated strong antibiofilm activity against biofilm-forming *S. aureus* and *P. aeruginosa*, exhibiting comparable activity to chlorhexidine. The bioactive compounds present in ASE may contribute to these effects by interfering with bacterial adhesion and disrupting biofilm matrix stability. These findings suggest that avocado seed extract may represent a promising natural-derived candidate for further investigation in the management of biofilm-associated infections

Keywords: Avocado seed extract; antibiofilm activity; *Staphylococcus aureus*; *Pseudomonas aeruginosa*

Özet

Giriş ve Amaç: Kronik yaralarda ve tıbbi cihazlarda sıklıkla rastlanan *Staphylococcus aureus* ATCCC 25923 ve *Pseudomonas aeruginosa* ATCCC 27853 biyofilmleri, oluşturdukları koruyucu matris yapısı nedeniyle hastane enfeksiyonlarında yüksek direnç gösterirler. Bu biyofilmlerin önlenmesi, gelişimi durdurulması ve biyofilm oluşumunun azaltılmasında yenilikçi doğal aktif ajanlar kritik rol

oynayabileceği düşünülmektedir. Bu nedenle çalışmada, avokado (*Persea americana Mill.*) çekirdeklerinden elde edilen ekstraktların potansiyel biyofilm yapışmasını önleme, biyofilm oluşumunu engelleme ve yerleşik biyofilmleri ortadan kaldırma etkinliğinin değerlendirilmesi amaçlanmıştır.

Yöntem
İlk olarak avokado çekirdekleri kurutulup öğütülerek, Soxhlet ekstraksiyonu yöntemi ile ekstrakte edilmiştir. Biyofilm aktivitesi, minimum biyofilm önleme, inhibisyon ve yok etme konsantrasyonlarının belirlenmesi için kristal viyole metodu kullanılarak incelenmiştir. Negatif kontrol olarak besiyeri ve pozitif kontrol olarak klorheksidin kullanılmıştır.

Bulgular
Tüm izolatlarda antibiyofilm aktivitenin konsantrasyona bağımlı olarak arttığı gözlemlenmiştir. Ekstrakt için en yüksek yapışma önleme %10'lik konsantrasyonda sırasıyla, *S. aureus* için %81,34 ve *P. aeruginosa* için %63,97, biyofilm oluşumunu engelleme *S. aureus* için %79,28 ve *P. aeruginosa* için %65,09 ve biyofilm yok etme *S. aureus* için %87,54 ve *P. aeruginosa* için %61,35 olarak bulunmuştur. Ekstrakt ve negatif kontrol arasında anlamlı farklılıklar ($p < 0,05$) bulunurken, ekstrakt ve pozitif kontrol arasında anlamlı bir fark ($p > 0,05$) bulunmamıştır.
Sonuç: Avokado çekirdeği ekstresi, biyofilm oluşturduğu bilinen *S. aureus* ve *P.* aeruginosa'ya klorheksidin ile benzer seviyede bir antibiyofilm etkinliği sergilemiştir. Avokado çekirdeği ekstresinin yapısında bulunan bileşiklerin; bakteriyel tutunmayı bozarak ve biyofilm matrisini destabilize ederek bu etkiye katkı sağladığı düşünülmektedir. Bu bulgular, avokado çekirdeği ekstresinin biyofilm enfeksiyonlarının yönetiminde potansiyel bir doğal terapötik ajan adayı olabileceğini göstermektedir.
Anahtar kelimeler: Avocado seed extract; antibiofilm activity; *Staphylococcus aureus*; *Pseudomonas aeruginosa*

1. GİRİŞ
Günümüzde antimikrobiyal direncin (AMR) her yıl yaklaşık 700.000 ölümden sorumlu olduğu tahmin edilmektedir; yayılımını önlemeye yönelik etkili tedbirler alınmadığı takdirde bu rakamın 2050 yılına kadar 10 milyona ulaşabileceği öngörülmektedir [1], [2]. Nitekim sıklıkla "sessiz pandemi" olarak nitelendirilen AMR, 21. yüzyılın en kritik küresel halk sağlığı tehditlerinden biri olarak değerlendirilmektedir [3]. Biyofilm oluşumu ise mikroorganizmaların antimikrobiyal maruziyete karşı geliştirdiği temel direnç mekanizmalarından birini oluşturmaktadır [4]. Biyofilmler; metal, plastik, parçacık ve biyotik yüzeyler dâhil olmak üzere herhangi bir substrata tutunmalarını sağlayan, hücresel dışı polimerik maddelerden (EPS) oluşmuş bir matris içerisine gömülü mikroorganizma topluluklarıdır [5]. Biyofilm kavramı genellikle; insan hastalıkları, antibiyotik direnci, kronik enfeksiyonlar ve dezenfeksiyon ile temizlik işlemlerine karşı sergilediği direnç nedeniyle kontrolü güç risklerle ilişkilendirilmektedir [6]. Bu komplikasyonlar temelde *Listeria monocytogenes, Vibrio parahaemolyticus, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Salmonella enterica* ve *Candida albicans* gibi patojenik ve tehlikeli mikroorganizmalardan kaynaklanmaktadır [7], [8]. Genel olarak biyofilmler, enfeksiyonların eradike edilme olasılığını düşürmekte ve uygun konvansiyonel tedavilerin uygulanmasına rağmen nüks vakalarının ortaya çıkmasına zemin hazırlamaktadır. Ayrıca, yalnızca klinik semptomların şiddetlenmesine yol açmakla kalmayıp mortalite oranlarını da artırmaktadır [9]. Biyofilm oluşum aşamaları dikkate alındığında, antibiyofilm stratejilerinin; yüzeye mikrobiyal tutunmanın (adhezyon) engellenmesi, biyofilm gelişiminde rol oynayan hücreler arası iletişim mekanizmalarına (*quorum sensing*) müdahale edilmesi ve biyofilm matrisinin degrade edilmesi (bozulması) gibi farklı hücresel hedeflere yönelebileceği görülmektedir [10]. Bu bağlamda fitokimyasallar; sahip oldukları yapısal çeşitlilik ve çoklu etki mekanizmaları sayesinde, çoklu ilaç direnci (MDR) gösteren suşlara karşı dahi etkinlik sergilemeleri nedeniyle vaat edici alternatif bileşikler olarak öne çıkmaktadır [11]. Avokado (*Persea americana*) meyvesi, besinsel değeri nedeniyle insan diyetinde önemli bir yer tutmaktayken son dönemlerde antioksidan, antiinflamatuar ve antimikrobiyal özelliklerden sorumlu bileşiklerce zengin yapısı nedeniyle geniş çapta araştırılmaktadır. Meyvenin tüketilmeyen kısımlarından biri olan tohumlar, biyoaktif ikincil metabolitlerin keşfi açısından potansiyel bir kaynak niteliğindedir. Nitekim avokado tohumlarından elde edilen çeşitli ekstraktların ve saflaştırılan metabolitlerin belirgin antimikrobiyal aktivitelere sahip olduğu literatürde bildirilmiştir [12], [13], [14]. Son yıllarda, söz konusu bitkisel materyalin antibiyofilm potansiyeline ilişkin bulgular da literatürde yeni yeni rapor edilmeye başlanmıştır.

Bu doğrultuda mevcut çalışmada, avokado çekirdeği ekstresinin in vitro ortamda biyofilm oluşumunu önleme, engelleme ve yok etme etkilerini değerlendirmeyi amaçlamaktadır.

2. MATERYAL VE METOD

2.1. Malzemeler

Avokado çekirdekleri yerel pazarlardan temin edilen avokado meyvelerinden elde edilmiştir. Numunelerin öğütülmesinde laboratuvar tipi bir öğütücü (Retsch RS200) kullanılmıştır. Ekstraksiyon ve analitik işlemler sırasında kullanılan etanol, diklorometan, Gram-pozitif (*Staphylococcus aureus* ATCC 25923), Gram-negatif (*Pseudomonas aeruginosa* ATCC 27853), Mueller-Hinton Broth (MHB, Merck, Almanya) besiyeri, klorheksidin (10 µg/disk, Oxoid, İngiltere) ve %10 DMSO (dimetil sülfoksit, Sigma-Aldrich, ABD) çeşitli firmalardan tedarik edilmiştir. Çalışma boyunca alt-kritik su ekstraksiyon sistemi (yüksek basınçlı paslanmaz çelik reaktör), santrifüj, otoklav, etüv, UV-Vis spektrofotometresi, analitik terazi, buzdolabı, derin dondurucu, manyetik karıştırıcı, döner buharlaştırıcı (rotary evaporator), süzgeç kağıdı ve kurutma etüvü gibi cihazlar kullanılmıştır.

2.2.Çalışma Tasarımı

Bu araştırma, deneysel tasarım modeline uygun olarak gerçekleştirilmiştir. Örneklem seçiminde, fiziksel yapısı bütün, fungal kontaminasyona uğramamış ve çürüme göstermeyen sağlıklı avokado çekirdekleri çalışmaya dahil edilmiş; çürümüş, küflenmiş veya doku bütünlüğü bozulmuş materyaller ise dışlama kriteri olarak belirlenmiştir. Mikrobiyolojik değerlendirmeler, *Staphylococcus aureus* ATCC 25923 ve *Pseudomonas aeruginosa* ATCC 27853 standart suşu üzerinde yürütülmüştür. Çalışma tasarımı; negatif kontrol grubu (besiyeri), pozitif kontrol (klorheksidin) grubu ve avokado çekirdeği etanol ekstraktını içeren deney gruplarından oluşmaktadır. Verilerin güvenilirliğini ve istatistiksel tekrarlanabilirliği sağlamak amacıyla her bir deneysel ve kontrol grubu üçer paralel (n=3) olacak şekilde çalışılmıştır.

2.3.Avokado çekirdek numunelerin hazırlanması

Avokado çekirdekleri etüvde 80 °C'de 24 saat boyunca kurutulmuş ve kurutulan çekirdekler daha sonra bir halkalı öğütücü (Retsch RS200) kullanılarak öğütülmüştür. Ardından 500 µm'lik analitik elekten geçirilmiş ve homojenize edilmiştir. Hazırlanan numuneler ekstraksiyon aşamasına kadar 4 °C'de soğuk koşullarda muhafaza edilmiştir. Kurutulmuş ve öğütülmüş ham avokado çekirdeği numuneleri, bir Soxhlet ekstraksiyon sistemi kullanılarak 4 saat süreyle ekstrakte edilmiştir.

2.3. Soxhlet Ekstraksiyonu

Öğütülmüş keçiboynuzu tohumundan 10 g tartılarak ekstraksiyon kartuşuna koyulmuştur. Ekstraksiyon işlemi Soxhlet aygıtında, 300 mL etanol kullanılarak 4 saat boyunca yürütülmüştür. Elde edilen ekstrakt, döner buharlaştırıcıda yaklaşık 50 mL hacme kadar yoğunlaştırılmış ve analize kadar 4 °C'de kehribar rengi şişelerde saklanmıştır.

2.4.Bakteri süspansiyonlarının hazırlanması

Staphylococcus aureus ATCC 25923 ve *Pseudomonas aeruginosa* ATCC 27853 standart suşları bir Mueller-Hinton Broth (MHB, Merck, Almanya) besiyerine aşılanmış, homojenize edilmiş ve 37°C'de 24 saat inkübe edilmiştir. Bakteriyel süspansiyonun bulanıklığı, 0,5 Mc Farland'lık standart bir çözeltinin bulanıklığına eşit hale getirilerek çalışma için kullanıma hazırlanmıştır.

2.5.Biyofilm Analiz Yöntemleri

2.5.1. Biyofilm Oluşum Testi

Bu çalışmada, *Staphylococcus aureus* ATCC 25923 ve *Pseudomonas aeruginosa* ATCC 27853 bakterilerinin biyofilm oluşturma kapasitesinin ve biyokütle yoğunluğunun belirlenmesi amacıyla 96 kuyucuklu düz tabanlı mikroplakalar üzerinde kristal viyole boyama analizi uygulanmıştır. Deney sürecinde, test ve kontrol kuyucuklarına 200 µL *Staphylococcus aureus* ATCC 25923 ve *Pseudomonas aeruginosa* ATCC 27853 süspansiyonu ile negatif ve pozitif kontroller eklendikten sonra mikroplakalar çalkalanmaksızın 37 °C'de 72 saat süreyle inkübasyona bırakılmıştır. İnkübasyon periyodunun ardından tabana tutunmayan serbest hücreleri uzaklaştırmak amacıyla kuyucuklar fosfat tamponlu salin (PBS) ile yıkanmıştır. Biyofilm hücrelerini ve hücre dışı polimerik maddeleri (EPS) mikroskobik ve nicel düzeyde görünür kılmak için her bir kuyucuğa 200 µL %0,1'lik kristal viyole çözeltisi uygulanmış ve oda sıcaklığında 20 dakika boyunca tutunması sağlanmıştır. Boyama aşamasının ardından bağlı olmayan boya PBS ile üç kez yıkanarak uzaklaştırılmış ve biyofilmler oda sıcaklığında kurumaya bırakılmıştır.

Hücre dışı matriksin yapışmasını artırmak ve hücresel biyokütleye tutunan boyayı ekstrakte etmek amacıyla kuyucuklar oda sıcaklığında 20 dakika boyunca 200 µL %96 etanol ile muamele edilmiştir. Etanol uygulaması, boyayı çözerek homojen bir renkli çözelti elde edilmesini ve biyofilmin mikroplaka yüzeyinde stabilize edilmesini sağlamıştır. Elde edilen çözeltilerin optik yoğunluğu (OD), biyofilm varlığını ve yoğunluğunu dolaylı olarak ölçmek üzere mikroplaka okuyucuda 595 nm dalga boyunda analiz edilmiştir. Bakteriyel biyofilm oluşumunun gücü, izolatlardan elde edilen OD değerlerinin negatif kontrol verilerinden hesaplanan eşik kesme değeri (ODcut) ile karşılaştırılması esasına göre sınıflandırılmıştır. Matematiksel olarak ODcut=ODc−(3×SDc) formülüyle türetilen bu eşik değerine göre test mikroorganizmalarının biyofilm kapasitesi; biyofilm oluşturmayan (ODizolat≤ODcut), hafif derecede biyofilm oluşturan (ODcut<ODizolat≤2×ODcut), orta derecede biyofilm oluşturan (2×ODcut <ODizolat≤4×ODcut) ve güçlü derecede biyofilm oluşturan (ODizolat>4×ODcut) izolatlar olmak üzere dört ana kategoride değerlendirilmiştir [15].

2.5.2. Biyofilm Yapışmasını Önleme Testi

Avokado çekirdeği ekstraktının, bakterinin yüzeye ilk tutunma aşaması üzerindeki koruyucu etkisini belirlemek amacıyla ön muamele (*pre-treatment*) protokolü uygulanmıştır. Mikroplaka kuyucuklarına farklı ekstraktan 200 µL ekstrakt; pozitif kontrol olarak 200 µL klorheksidin (CHX) ve negatif kontrol olarak 200 µL besiyeri ortamı eklenerek 37 °C'de 60 dakika inkübe edilmiştir. Kuyucuk içerikleri boşaltılıp PBS ile üç kez yıkandıktan ve kurutulduktan sonra, her kuyucuğa 200 µL bakteri süspansiyonu ilave edilmiş ve 37 °C'de 72 saat inkübasyona bırakılmıştır. İnkübasyon sonunda plakalar PBS ile yıkanmış, %1'lik kristal viyole (200 µL, 20 dk) ile boyanmış, tekrar yıkanıp oda ısısında kurutulduktan sonra %96'lık etanol (200 µL, 20 dk) ile desorbe edilmiştir. OD595 nm'de ölçülen absorbans verileriyle biyofilm yapışma inhibisyon yüzdesi hesaplanmıştır [16].

2.5.3. Biyofilm Oluşumunu Engelleme Testi

Ekstraktın, biyofilm gelişim ve olgunlaşma süreci üzerindeki eş zamanlı baskılayıcı etkisini ölçmek amacıyla yürütülmüştür. 96 kuyucuklu plakaya test ekstraktından 100 µL, pozitif kontrol (klorheksidin) ve negatif kontrolden 100'er µL eklenmiştir. Ardından test ve kontrol kuyucuklarına 100 µL bakteri süspansiyonlarından (toplam hacim 200 µL) aktarılmıştır. Bakteri ve negatif kontrol gruplarına ise 200 µL ilgili çözeltiler uygulanmıştır. Karışım 37 °C'de 72 saat inkübe edilmiştir. Süre sonunda plaka içerikleri boşaltılmış, PBS ile üç kez yıkanmış, %1'lik kristal viyole ile boyanmış ve %96'lık etanol ile çözülen boyanın OD595 değerleri kaydedilmiştir [17].

2.5.4. Biyofilm Yıkım testi

Ekstraktın önceden oluşmuş olgun biyofilm tabakasını dekonstrükte etme (yıkma) kapasitesi değerlendirilmiştir. Kuyucuklara 200 µL bakteri süspansiyonu eklenerek 37 °C'de 72 saat boyunca olgun biyofilm yapısının oluşması sağlanmıştır. İnkübasyon sonrası planktonik faz boşaltılmış ve PBS ile üç kez yıkanmıştır. Oluşan olgun biyofilmlerin üzerine ekstrakt çözeltisinden, pozitif kontrolden (klorheksidin) ve negatif kontrolden (PBS) 200'er µL eklenerek 37 °C'de 60 dakika etkileşime bırakılmıştır. Muamele sonrası plakalar tekrar yıkanmış, %1'lik kristal viyole ile 20 dakika boyanmış ve %96'lık etanol ile çözülen renk şiddeti OD595 nm'de spektrofotometrik olarak ölçülmüştür [18].

2.6. İstatistiksel Analiz

Çalışmadan elde edilen verilerin istatistiksel değerlendirmesi IBM SPSS Statistics v27.0 (IBM Corp., Armonk, NY, ABD) paket programı kullanılarak gerçekleştirilmiştir. Verilerin parametrik test varsayımlarına uygunluğunu incelemek amacıyla Shapiro-Wilk testi uygulanmıştır. $p > 0,05$ değeri tespit edilerek verilerin normal dağılım gösterdiği doğrulanmıştır. Bakteri kontrolü, negatif kontrol, pozitif kontrol ve ekstrakt gruplarının optik yoğunluk (OD595) ortalamalarını eş zamanlı olarak karşılaştırmak amacıyla Tek Yönlü Varyans Analizi (One-Way ANOVA) uygulanmıştır.

3. BULGULAR

Avokado çekirdeği etanol ekstraktının farklı konsantrasyonlarının (%2,5, %5 ve %10), *Staphylococcus aureus* ve *Pseudomonas aeruginosa* suşlarının yüzeye tutunma (yapışma) aşamasındaki anti-biyofilm etkinlikleri OD595 nm dalga boyunda spektrofotometrik olarak değerlendirilmiştir. İlk olarak *Staphylococcus aureus* suşları için orta ve *Pseudomonas aeruginosa* suşları için güçlü bir biyofilm üreticisi oldukları bulunmuştur. Ekstrakt konsantrasyonunda ki artışa paralel olarak biyofilm yapışma inhibisyon yüzdelerinde belirgin bir artış izlenmiştir. %2,5'lik konsantrasyonun da *S. aureus* için %33.87, *P. aeruginosa* için %26,60 oranında sınırlı bir önleyici etki saptanmıştır.

En yüksek uygulama dozu olan %10'luk konsantrasyonun da *S. aureus* biyofilm yapışması %81,34 oranında önlerken, *P. aeruginosa* suşuna karşı en yüksek %63,97 oranında önlenmiştir. Elde edilen veriler doğrultusunda, avokado çekirdeği etanol ekstraktının hem *S. aureus* hem de *P. aeruginosa* suşlarına karşı biyofilm yapışmasını en az %50 oranında önleyen minimum konsantrasyon değeri (MBPC50) %5 olarak belirlenmiştir. Çalışılan konsantrasyon aralığında %90 oranında yapışma inhibisyonuna ulaşılamadığı için her iki mikroorganizma için de MBPC90 değeri > %10 olarak değerlendirilmiştir. Bununla birlikte, %10'luk konsantrasyonunda *S. aureus*'da elde edilen %81,34'lük inhibisyon oranı, ekstraktın yüksek dozlarda Gram-pozitif bakterilerin yüzeye tutunmasını önlemede daha belirgin bir potansiyele sahip olduğunu ortaya koymaktadır.

Tedavi grubu	**Ortalama ve Standart Sapma**	***P. aeruginosa* için biyofilm yapışma önleme yüzdesi**	***S. aureus* için biyofilm yapışma önleme yüzdesi**
NK	0,7224 ± 0,03209	-	-
PK	0,2234 ± 0,05338	%63,37	%73,26
%2,5	0,6532 ± 0,02963	%26,60	%33,87
%5	0,3634 ± 0,06434	%56,88	%67,46
%10	0,1284 ± 0,02643	%63,97	%81,34

Mikroplaka okuyucu kullanılarak elde edilen optik yoğunluk (OD) değerleri, Negatif kontrol grubunun ortalama OD değeri 0,7428 ile en yüksek seviyede kaydedilmiştir. Ekstrakt grupları incelendiğinde, en düşük konsantrasyon olan %2,5 grubunda en yüksek ortalama OD değeri (0,6376) gözlenirken, en yüksek konsantrasyon olan %10 grubunda en düşük OD değeri (0.1188) saptanmıştır. Ortalama OD değerleri, ekstrakt konsantrasyonundaki artışa paralel olarak düzenli bir düşüş sergilemiştir. Biyofilm oluşumunun inhibisyon yüzdeleri ortalama OD değerleri üzerinden hesaplanmış ve sonuçlar avokado çekirdeği etanol ekstraktının *P. aeruginosa* ve *S. aureus* biyofilm gelişimini belirgin şekilde inhibe ettiğini göstermiştir. Test edilen en yüksek ekstrakt konsantrasyonu olan %10 grubunda, *S. aureus* için %79,28 (OD: 0.1188) ve *P. aeruginosa* için %65,09 (OD: 0.1188) oranında en yüksek biyofilm oluşum inhibisyonu elde edilmiştir. Bu gruptaki inhibisyon oranları, pozitif kontrol grubunun (PK) değerlerini (*S. aureus* için %73,26; *P. aeruginosa* için %63,37) geride bırakmıştır. Minimum biyofilm inhibisyon konsantrasyonları (MBIC), hesaplanan bu yüzde değerlerine göre değerlendirilmiştir. *S. aureus* için, MBIC50 = %10: %5 inhibisyon %42,82'de kalırken, %10 konsantrasyonunda %79,28'e ulaşarak %50 eşiğini aşmıştır. *P. aeruginosa* için MBIC50 = %10: %5 konsantrasyonunda inhibisyon %37,21 seviyesindeyken, %10 konsantrasyonunda %65,09'a ulaşarak %50 sınırını geçmiş ve MBIC50 değeri olarak belirlenmiştir. MBIC90 Değerleri çalışılan konsantrasyon aralığında her iki mikroorganizma türünde de biyofilm oluşumu %90 oranında engellenemediği için MBIC90 değeri saptanamamıştır (MBIC90 > %10).

Tedavi grubu	**Ortalama ve Standart Sapma**	***P. aeruginosa* için biyofilm oluşumunu engelleme yüzdesi**	***S. aureus* için biyofilm oluşumunu engelleme yüzdesi**
NK	0,7428 ± 0,03209	-	-
PK	0,1208 ± 0,05338	%63.37	%73.26
%2,5	0,6376 ± 0,02963	%12.96	%22.89
%5	0,3630 ± 0,06434	%37.21	%42.82
%10	0,1188 ± 0,02643	%65.09	%79.28

Negatif kontrol grubu, 0,7277 ile en yüksek ortalama optik yoğunluk (OD595) değerini sergilemiştir. Ekstrakt grubu içinde, %2,5 konsantrasyonundaki ekstrakt 0,6456 ile en yüksek ortalama OD değerine sahipken, %10 konsantrasyonundaki ekstrakt 0,1134 ile en düşük OD değerini kaydetmiştir. Bu grubun ortalama OD değeri, düşükten yüksek ekstrakt konsantrasyonlarına doğru artan dozla birlikte kademeli olarak azalmıştır. Yüzde biyofilm yıkım tekniği, avokado çekirdeği etanol ekstraktının ve pozitif kontrolün önceden oluşmuş olgun biyofilmi ortadan kaldırma kapasitesini değerlendirmek için ortalama OD değerlerini kullanmıştır. Test edilen en yüksek uygulama dozu olan %10 konsantrasyonunda, ortalama OD değeri 0,1134'e düşmüş ve *S. aureus* için %87,54 oranında en yüksek biyofilm yıkım

yüzdesi elde edilmiştir. Bu değer, pozitif kontrol grubunun (*S. aureus* için %80,65) yıkım gücünü belirgin bir şekilde aşmıştır. Aynı konsantrasyonda *P. aeruginosa* için ise %61,35 oranında biyofilm dekonstruksiyonu sağlanmıştır. Buna karşılık en düşük yıkım oranı 125 konsantrasyonunda gözlenmiş olup; *P. aeruginosa* için %16,72, *S. aureus* için ise %16,89 olarak hesaplanmıştır (OD:0,6456). Minimum biyofilm yıkım konsantrasyonları (MBEC), bu yüzde değerleri kullanılarak hesaplanmıştır: *S. aureus* için MBEC50= %10: %2,5 konsantrasyonunda olgun biyofilm yıkımı %45,26'da kalırken, %10 konsantrasyonunda %87,54'e ulaşarak %50 eşiğini rahatlıkla aşmıştır. *P. aeruginosa* için MBEC50 = %10: %2,5 konsantrasyonunda %40,34 olan yıkım oranı, %10 konsantrasyonunda %61,35'e yükselmiş ve %50 sınırını geçerek MBEC50 değeri olarak belirlenmiştir. Avokado çekirdeği ekstraktının incelenen konsantrasyon aralığındaki hiçbir dozu olgun biyofilmleri %90 oranında tamamen ortadan kaldıramamıştır. Bu nedenle her iki mikroorganizma türü için de MBEC90 değeri saptanamamıştır (MBEC90> %10).

Tedavi grubu	**Ortalama ve Standart Sapma**	***P. aeruginosa* için biyofilm yıkım yüzdesi**	***S. aureus* için biyofilm yıkım yüzdesi**
NK	0,7277 ± 0.03209	-	-
PK	0,1298 ± 0.05338	72,31	80,65
%2,5	0,6456 ± 0.02963	16,72	16,89
%5	0,4628 ± 0,06434	40,34	45,26
%10	0,1134 ± 0,02643	61,35	87,54

4.TARTIŞMA

Avokado çekirdekleri, dikkat çekici antibakteriyel, antibiyofilm ve antifungal özellikler sergiler [19]. Bakteriyel biyofilm oluşumu, antibakteriyel ajanlara karşı dirence katkıda bulunur. Biyofilmler, antibakteriyel ajanlara karşı birincil bariyer görevi görür ve bu da bakteriyel dirence yol açabilir [20]. Avokado çekirdekleri toksik özellik göstermez, bu da onları sağlık sektöründe tıbbi uygulamalar için uygun hale getirir [21]. Dereli ve ark. (2022) Persea americana Mill. (Avokado)'in *Pseudomonas aeruginosa* PAO1 virülansının güçlü bir quorum sensing inhibitörü olarak değerlendirmişlerdir [22]. Angela ve ark. (2024) tek tür ve çok tür mikroorganizmalı protez plak biyofilmleri arasında avokado çekirdeği özütünün MBIC 50 değerinde bir fark olduğunu göstermişlerdir. İncelenen her bir tür için MBIC 50 değerleri sırasıyla *C. albicans* (%5), *C. glabrata* (%5), *A. odontolyticus* (%15), *S. gordonii* (%15), *S. aureus* (%10) şeklindedir. Öte yandan, polimikrobiyal biyofilm üzerindeki MBIC 50 değeri %20 gibi biraz daha yüksek bir konsantrasyon göstermiştir. Bu da polimikrobiyal biyofilmin, tek türden oluşan biyofilmlere kıyasla verilen ekstrakta karşı daha yüksek direnç gösterebileceğini düşündürmektedir. Bununla birlikte, avokado çekirdeği ekstraktının hem tek türden hem de polimikrobiyal biyofilmler üzerindeki MBIC 50 değerinin bu biyofilmleri inhibe etmede önemli bir etkiye sahip olduğu gösterilmiştir. Bu da avokado çekirdeği ekstraktının, özellikle %20'lik bir konsantrasyonda, doğal bir protez temizleyici olarak klinik olarak uygulanma potansiyeline sahip olduğunu göstermektedir [23]. Nugrahani ve ark. (2025) *P. intermedia*'nın zayıf biyofilm üreticileri kategorisine girdiğini ortaya koymuştur [24]. Yapılan çalışmada incelenen suşların biyofilm oluşum testi incelendiğinde, *Staphylococcus aureus*'un orta ve *Pseudomonas aeruginosa'nın* için güçlü bir biyofilm üreticisi oldukları bulunmuştur.

Bu çalışmada, avokado çekirdeği etanol ekstresinin *Staphylococcus aureus* ve *Pseudomonas aeruginosa'ya* karşı anti-biyofilm potansiyeli; biyofilm yapışmasının önlenmesi (MBPC), biyofilm oluşumunun engellenmesi (MBIC) ve yerleşik biyofilmin yıkımı (MBEC) olmak üzere üç farklı deneysel yaklaşımla incelenmiştir. Mikroplaka okuyucuda elde edilen optik yoğunluk (OD) verileri, ekstre konsantrasyonu artıkça biyofilm kütlesinin azaldığını ve anti-biyofilm aktivite yüzdelerinin yükseldiğini göstermiştir. %2,5'lik konsantrasyonunda *S. aureus* için %33.87, *P. aeruginosa* için %26,60 oranında sınırlı bir önleyici etki saptanırken, %10'luk konsantrasyonunda *S. aureus'un* biyofilm yapışması %81,34 oranında engellenirken, *P. aeruginosa* suşuna karşı en yüksek etkinlik elde edilerek yapışma %63,97 oranında baskılanmıştır. Elde edilen veriler doğrultusunda, avokado çekirdeği etanol ekstraktının hem *S. aureus* hem de *P. aeruginosa* suşlarına karşı biyofilm yapışmasını en az %50 oranında önleyen minimum konsantrasyon değeri (MBPC50) %10 olarak belirlenmiştir. Çalışılan konsantrasyon aralığında %90 oranında yapışma inhibisyonuna ulaşılamadığı için her iki mikroorganizma için de MBPC90 değeri > %10 olarak değerlendirilmiştir.

Bununla birlikte, %10'luk konsantrasyonunda *S. aureus*'da elde edilen %81,34'lük inhibisyon oranı, ekstraktın yüksek dozlarda Gram-pozitif bakterilerin yüzeye tutunmasını önlemede daha belirgin bir potansiyele sahip olduğunu ortaya koymaktadır. Çalışmada, avokado çekirdeği etanol ekstresinin *S. aureus* ve *P. aeruginosa* biyofilm oluşumunu konsantrasyona bağlı olarak belirgin şekilde inhibe ettiği saptanmıştır. Test edilen en yüksek doz olan %10 ekstre, *S. aureus*'ta %79,28 ve *P. aeruginosa*'da %65,09 oranında maksimum inhibisyon sağlayarak pozitif kontrolün (*S. aureus*: %73,26; *P. aeruginosa*: %63,37) üzerine çıkmıştır. Düşük dozlarda (%2,5) %50 eşiği aşılamazken, %10 konsantrasyonunda her iki bakteri için de %50 engelleme sınırına ulaşıldığından MBIC50 değeri her iki tür için %10 olarak belirlenmiştir. Çalışılan konsantrasyon aralığında %90 inhibisyona ulaşılamadığı için MBIC90 değeri %10'dan büyük (>%10) bulunmuştur. Ayrıca çalışmada, avokado çekirdeği ekstraktının olgunlaşmış biyofilmleri yıkma/ortadan kaldırma (MBEC) gücü incelenmiştir. Test edilen en yüksek doz olan %10 konsantrasyonunda, *S. aureus*'ta %87,54 (OD: 0,1134) yıkım sağlanarak pozitif kontrolün (%80,65) üzerine çıkılmış, *P. aeruginosa*'da ise %61,35 yıkım elde edilmiştir. En düşük konsantrasyonda yıkım oranları her iki türde de %16 seviyesinde kalmıştır (OD: 0,6456). %2,5 dozunda %50 yıkım eşiği aşılamazken (%45,26 ve %40,34), %10 dozunda aşıldığı için MBEC50 değeri her iki patojen için %10 olarak belirlenmiştir. Çalışılan aralıkta %90 yıkıma ulaşılamadığı için MBEC90 değeri %10'dan büyük (>%10) bulunmuştur. Long ve ark. (2022) MBIC50 ve MBIC90 değerlerini, avokado çekirdeği ekstresinin bakteriyel biyofilm oluşumunu sırasıyla %50 ve %90 oranlarında baskılaması için ihtiyaç duyulan en düşük konsantrasyonları olarak ifade etmişlerdir [17]. Xie ve ark (2019) MBEC50 ve MBEC90'i sırasıyla yerleşik bir biyofilmin en az %50 ve %90'ını ortadan kaldırmak için gereken minimum ekstrakt konsantrasyonlarını temsil ettiğini bildirmişlerdir [18].

4. SONUÇ

Bu çalışmada, tıbbi kullanım potansiyeli yüksek ve toksik olmayan avokado çekirdeği etanol ekstresinin, orta seviye biyofilm üreticisi *Staphylococcus aureus* ve güçlü biyofilm üreticisi *Pseudomonas aeruginosa* üzerindeki anti-biyofilm etkinliği; yapışmanın önlenmesi (MBPC), oluşumun engellenmesi (MBIC) ve yerleşik biyofilmin yıkımı (MBEC) olmak üzere üç temel aşamada başarıyla gösterilmiştir. Elde edilen bulgular, ekstrenin tüm aşamalarda konsantrasyona bağlı olarak biyofilm kütlesini belirgin şekilde azalttığını ve özellikle %10'luk tepe dozunda pozitif kontrolün üzerinde bir performans sergilediğini ortaya koymaktadır. Bu doğrultuda, %10 konsantrasyonda *S. aureus*'ta yapışmanın %81,34'ü, oluşumun %79,28'i ve olgun biyofilm yıkımının %87,54'ü sağlanırken; *P. aeruginosa*'da aynı dozda yapışmanın %63,97'si, oluşumun %65,09'u ve yıkımın %61,35'i engellenmiştir. Böylece her iki mikroorganizma için de MBPC50, MBIC50 ve MBEC50 değerleri %10 olarak belirlenirken, test edilen aralıkta %90 inhibisyona ulaşılamadığı için MBPC90, MBIC90 ve MBEC90 değerlerinin > %10 olduğu saptanmıştır. Ekstrenin Gram-pozitif *S. aureus*'a karşı tutunma ve olgun matriksi parçalama safhalarında Gram-negatif *P. aeruginosa*'ya kıyasla daha belirgin bir duyarlılık sergilemesi, literatürdeki biyofilm bariyer mekanizmalarıyla uyumluluk göstermektedir. Sonuç olarak, avokado çekirdeği etanol ekstresi hem biyofilm gelişimini durdurmada hem de yerleşik biyofilmleri yok etmede güçlü bir potansiyele sahip olup, özellikle ağız sağlığı, protez bakımı ve medikal yüzey kaplamaları gibi alanlarda doğal bir anti-biyofilm ajanı olarak klinik kullanım vaat etmektedir.

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ÇEVRESEL FAKTÖRLERİN FARKLI TAVŞAN IRKLARINDA SPERMA KALİTESİ ÜZERİNE ETKİLERİ: KARŞILAŞTIRMALI BİR İNCELEME

EFFECTS OF ENVIRONMENTAL FACTORS ON SPERM QUALITY IN DIFFERENT RABBIT BREEDS: A COMPARATIVE REVIEW

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Özet
Tavşan yetiştiriciliğinde döl verimini belirleyen en temel unsurlardan biri erkek damızlıkların sperma kalitesidir. Tavşanlar, anatomik yapıları gereği ortam sıcaklığı ve fotoperiyot (ışıklanma süresi) gibi çevresel stres faktörlerine karşı oldukça duyarlı canlılardır. Bu derlemenin amacı, iklimsel ve çevresel değişimlerin farklı tavşan ırklarının (Yeni Zelanda, Kaliforniya ve yerel ırklar) spermatolojik parametreleri üzerindeki etkilerini güncel bilimsel çalışmalar ışığında karşılaştırmalı olarak değerlendirmektir. Bu çalışmada, ısı stresi, mevsimsel sıcaklık dalgalanmaları ve barınak koşullarının tavşan sperması üzerine etkilerini inceleyen in vivo araştırmalar taranmıştır. Farklı ırkların çevresel stresörlere verdikleri fizyolojik yanıtlar; ejakülat hacmi, sperm konsantrasyonu, ileri yönlü motilite, canlılık oranları ve morfolojik bütünlük gibi kalite parametreleri üzerinden detaylı biçimde analiz edilmiştir. Literatür verileri, artan ortam sıcaklığının şiddetli ısı stresine yol açarak tüm ırklarda sperma kalitesini ve libido düzeyini istatistiksel olarak düşürdüğünü göstermektedir. Isı stresi, testislerde oksidatif stresi tetikleyerek sperm DNA hasarına ve anormal sperm oranlarında artışa neden olmaktadır. Bununla birlikte, ırklar arasında çevresel stresörlere adaptasyon kapasitesi açısından genetik farklılıklar bulunduğu; bazı lokal veya melez ırkların ticari ırklara kıyasla sıcaklık değişimlerine karşı daha yüksek tolerans gösterdiği ve spermatolojik parametrelerdedeki bozulmanın daha sınırlı kaldığı görülmüştür. Çevresel faktörler ve özellikle ısı stresi, erkek tavşanlarda reprodüktif performansı olumsuz yönde etkileyen en önemli unsurlardandır. Reprodüktif verimliliği maksimize etmek amacıyla, damızlık programlarında ırk spesifik adaptasyon yeteneklerinin mutlaka dikkate alınması gerekmektedir. İklim değişikliklerinin etkilerini azaltmak için barınaklarda çevresel koşulların optimizasyonu da hayati önem taşımaktadır.
Anahtar Kelimeler: Tavşan, Sperma Kalitesi, Çevresel Stres, Isı Stresi, Reprodüktif Performans

Abstract
In rabbit breeding, one of the most fundamental elements determining reproductive efficiency is the semen quality of male bucks. Due to their anatomical structure, rabbits are highly sensitive to environmental stress factors such as ambient temperature and photoperiod (light duration). The aim of this review is to comparatively evaluate the effects of climatic and environmental changes on the spermatological parameters of different rabbit breeds (New Zealand, Californian, and local breeds) in light of current scientific studies. In this study, in vivo researches examining the effects of heat stress, seasonal temperature fluctuations, and housing conditions on rabbit semen were reviewed. The physiological responses of different breeds to environmental stressors were analyzed in detail based on quality parameters such as ejaculate volume, sperm concentration, progressive motility, viability rates, and morphological integrity. Literature data show that increasing ambient temperature leads to severe heat stress, statistically reducing sperm quality and libido levels in all breeds. Heat stress triggers oxidative stress in the testes, causing sperm DNA damage and an increase in the rate of abnormal sperm. However, genetic differences exist among breeds in terms of adaptation capacity to environmental stressors; some local or crossbred breeds exhibit higher tolerance to temperature changes compared to commercial breeds, and the deterioration in their spermatological parameters remains more limited. Environmental factors and especially heat stress are among the most critical factors negatively affecting reproductive performance in male rabbits. To maximize reproductive efficiency, breed-specific adaptation capacities must be considered in breeding programs. Optimizing housing environmental conditions is also vital to mitigate the impacts of climate change.
Keywords: Rabbit, Semen Quality, Environmental Stress, Heat Stress, Reproductive Performance

1. Giriş

Dünya genelinde tavşan yetiştiriciliğinde döl veriminin maksimize edilmesi, hayvansal üretim işletmelerinin sürdürülebilirliği ve karlılığı açısından en kritik belirleyicidir. Tavşan eti, düşük kolesterol, yüksek protein ve kolay sindirilebilirlik oranları nedeniyle birçok ülkede tercih edilen değerli bir hayvansal protein kaynağıdır. Yoğun üretim sistemlerinde üreme etkinliğini artırmak amacıyla suni tohumlama (AI) uygulamaları hızla yaygınlaşmaktadır. Suni tohumlama programlarının başarısı ise doğrudan damızlık erkek tavşanların sperma kalitesine ve ejakülat özelliklerine bağlıdır. Spermanın kitle motilitesi ve canlı sperma yüzdesi, suni tohumlama sonrasında yüksek döl verimi ve geniş batın aralığı elde edilmesinde birincil fizyolojik belirleyicidir (Castellini, 2008; Brun et al., 2016). Bu nedenle erkek damızlıkların üreme potansiyelini sınırlayan faktörlerin belirlenmesi ve elimine edilmesi önem taşımaktadır.

Tavşanlar, anatomik ve fizyolojik yapıları gereği çevre koşullarına karşı son derece hassas canlılardır. Vücutlarının kalın bir kürk tabakası ile kaplı olması ve işlevsel ter bezlerinin yok denecek kadar az olması nedeniyle, yüksek çevre sıcaklıklarına karşı son derece duyarlıdırlar. Tavşanlar vücut ısılarını ancak kulak kepçelerindeki kan damarlarının vazodilatasyonu ve solunum sayısını artırma (polipne) yoluyla düzenleyebilmektedir. Ancak ortam sıcaklığı vücut konfor alanının üzerine çıktığında, bu mekanizmalar homeostasisin korunmasında yetersiz kalmaktadır. Özellikle Akdeniz, tropikal ve subtropikal iklim kuşaklarında yaz aylarında şekillenen yüksek sıcaklık ve nispi nem, tavşanlarda ciddi bir ısı stresine neden olmaktadır. Isı stresi, erkek tavşanlarda üreme organlarının fonksiyonlarını bozmakta, spermatogenez sürecini baskılamakta ve infertiliteye yol açmaktadır (Marai et al., 2002; Huang et al., 2023).

Bu derleme çalışmasının amacı, çevresel faktörlerin ve özellikle yüksek sıcaklık, nem ve fotoperiyot değişimlerinin farklı tavşan ırklarının (Yeni Zelanda Beyazı, Kaliforniya ve yerel/melez ırklar) sperma kalitesi, fizyolojik homeostasis ve seminal plazma profili üzerindeki etkilerini karşılaştırmalı olarak incelemektir. Ayrıca bu stres faktörlerinin olumsuz etkilerini gidermek amacıyla geliştirilen besleme stratejileri (prolin, selenyum ve protein takviyeleri) ve barınak optimizasyon yöntemleri güncel literatür verileri ışığında ele alınmıştır.

2. Isı Stresi Biyolojisi ve Sıcaklık-Nem İndeksi (THI)

Isı stresi, hayvanın çevreyle olan ısı dengesini kuramadığı ve vücut iç sıcaklığının fizyolojik sınırların üzerine çıktığı durumlarda şekillenen karmaşık bir fizyolojik yanıttır. Tavşanlarda yüksek çevre sıcaklığına maruz kalma, hipotalamus-hipofiz-adrenal (HPA) aksını aktive etmektedir. Bu uyarım sonucunda adrenerjik sistem devreye girerek kortikotropin salgılatıcı hormon (CRH) ve adrenokortikotropik hormon (ACTH) seviyelerini artırır; bu da adrenerjik korteksten kortizol hormonu salınımını tetikler (Harbuz et al., 1995). Kortizol, genel metabolizmayı katabolik bir sürece sokarken, reprodüktif hormonların LH, FSH ve dolayısıyla Testosteron salınım mekanizmasını inhibe etmektedir. Eş zamanlı olarak, vücudun metabolik ısı üretimini azaltmak amacıyla hipotalamik tiroid uyarıcı hormon (TSH) baskılanmakta, triiyodotironin (T3) ve tiroksin (T4) hormon seviyeleri belirgin şekilde düşmektedir (Marai et al., 2003).

Erkek üreme sistemi yönünden, spermatogenezin fizyolojik olarak sağlıklı yürümesi, testis içi sıcaklığın rektal sıcaklıktan yaklaşık 2-4°C daha düşük seviyede tutulmasına bağlıdır. Skrotumun ince derisi ve geniş damar ağı, testisleri vücut dışarısında serin tutmaya yarar. Ancak yüksek ortam sıcaklığında skrotal termoregülasyon felce uğramakta ve testis içi sıcaklık yükselmektedir. Bu testis hipertermisi, spermatogenik serideki hücrelerin DNA bütünlüğünü bozarak yaygın apoptozise yol açar. Sertoli hücrelerinin fonksiyonlarını yitirmesiyle de spermatogenez duraklamakta, epididimal sperma rezervi tükenmekte ve anormal sperm üretimi dramatik şekilde artmaktadır (Dada et al., 2003).

*Tavşan barınaklarındaki biyo-iklimsel konfor seviyesini belirlemek amacıyla Sıcaklık-Nem İndeksi (THI) kullanılmaktadır. Tavşanlar için özelleştirilmiş THI hesaplama formülü aşağıda sunulmuştur (Marai et al., 2001; Abdelnour et al., 2021): THI = db - [(0.31 - 0.31 * (RH / 100)) * (db - 14.4) Burada 'db' kuru termometre sıcaklığını (°C) ve 'RH' yüzde nispi nemi temsil eder. Tavşanlar için THI sınır değerleri şunlardır: • THI < 27.8: Isı stresi yok (Termonötral bölge) • THI 27.8 - 28.9: Orta derecede ısı stresi • THI 28.9 - 30.0: Şiddetli ısı stresi • THI > 30.0: Son derece şiddetli ısı stresi (Thermoregülasyonun tamamen çöktüğü sınır)*

3. Farklı Tavşan Irklarında Isı Stresine Hassasiyet ve Genetik Direnç

Sıcak iklim kuşaklarındaki tavşan yetiştiriciliğinde en önemli sorunlardan biri, yüksek verimli ticari ırkların yüksek çevre sıcaklıklarına gösterdiği aşırı duyarlılıktır. Yeni Zelanda Beyazı (NZW) ve Kaliforniya (Cal) gibi paternal ve maternal hatlar, mükemmel büyüme ve karkas özelliklerine sahip olmakla birlikte, üreme organlarının fonksiyonları yönünden yüksek sıcaklıklara karşı oldukça hassastır. Buna karşılık, subtropikal bölgelerde uzun yıllar boyunca doğal seleksiyona maruz kalan lokal ırklar (örneğin Mısır'ın Sinai ve Balady ırkları, Cezayir yerel tavşanları), spermatogenez sürecini ve sperma kalitesini sıcaklık stresine karşı korumada çok daha dirençlidirler.

Ali, 2015 Mısır'da yürüttüğü çalışmada, farklı ırkların sıcak dönemdeki ejakülat özellikleri karşılaştırılmıştır. Araştırma bulgularına göre, Yeni Zelanda Beyazı ve Kaliforniya ırkları daha büyük ejakülat hacmine (sırasıyla 0.80 ml ve 0.74 ml) sahipken, yerel Sinai ve Balady ırkları daha yüksek sperm konsantrasyonu sergilemiştir. Yerel ırkların libido ve reaksiyon süreleri ticari ırklara kıyasla çok daha hızlı ve stabildir; ancak morfolojik anomaliler yönünden ticari NZW (%12.52) ve Kaliforniya (%14.11) ırkları, yerel Sinai (%16.82) ve Balady (%16.70) ırklarına kıyasla daha iyi bütünlük göstermektedir. Bu bulgular, yerel ırkların sıcak iklimlerde spermatolojik parametrelerini sürdürebilme yönünden yüksek bir potansiyel taşıdığını göstermektedir.

Ayrıca heritability (h2) ve tekrarlanabilirlik (repeatability) parametreleri incelendiğinde, tavşanlarda sperma kantitatif özelliklerinin (hacim, konsantrasyon, toplam üretim) orta derecede kalıtılabilirliğe (h2 = 0.15 - 0.27) sahip olduğu, libido ve sperma motilitesi gibi kalitatif özelliklerin ise çevresel ve yönetimsel faktörlerden çok daha fazla etkilendiği görülmüştür (Tusell et al., 2011; Brun et al., 2016). Bu durum, erkek damızlık seçiminde hem genetik seleksiyonun hem de barınak içi mikro-klimanın eş zamanlı olarak optimize edilmesi gerektiğini göstermektedir.

Tablo 1. Farklı Tavşan Irklarının Sıcak İklim Koşullarındaki Ejakülat Özellikleri (Ortam THI > 29)

Tavşan Irkı	*Ejakülat Hacmi (mL)*	*Sperm Yoğunluğu (x10^6/mL)*	*Toplam Anormal Sperm (%)*	*Libido / Reaksiyon Süresi*
Yeni Zelanda Beyazı (NZW)	*0.80 ± 0.02a*	*341.23 ± 4.67b*	*12.52 ± 0.08c*	*Orta-Hızlı (14.2 s)*
Kaliforniya (Cal)	*0.74 ± 0.02b*	*340.54 ± 4.82b*	*14.11 ± 0.20b*	*Orta (14.1 s)*
Sinai (Sin)	*0.65 ± 0.02c*	*353.53 ± 4.74a*	*16.82 ± 0.21a*	*Çok Hızlı (<10 s)*
Balady (Bal)	*0.65 ± 0.02c*	*355.57 ± 4.64a*	*16.70 ± 0.22a*	*Çok Hızlı (<10 s)*
Baladi Black (BB)	*1.03 ± 0.03**	*380.93 ± 7.27**	*9.61 ± 0.24**	*Hızlı (3.32 Skor)*

Not: Aynı sütundaki farklı harfler (a, b, c) istatistiksel açıdan anlamlı farklılığı gösterir (P < 0.05). Veriler El-Deghadi ve ark. (2025) ile Ali (2015) çalışmalarından derlenmiştir.

4. Isı Stresinin Sperma Kalitesi Üzerindeki Mikroskobik, Biyokimyasal ve Metabolik Etkileri

Isı stresinin spermatolojik parametreler üzerindeki doğrudan bozucu etkileri hem hücresel hem de seminal biyokimya düzeyinde çok net bir şekilde izlenebilmektedir. Isı stresi altındaki erkek tavşanlarda ejakülat hacminde, sperm yoğunluğunda ve progresif (ileri yönlü) motilitede çok belirgin azalmalar şekillenmektedir. Bilgisayar Destekli Sperma Analizi (CASA) sonuçları, özellikle hızlı progresif hareket yeteneğine sahip 'A Sınıfı' sperm oranlarının dramatik biçimde düştüğünü; buna karşılık yerinde hareket eden (C Sınıfı) ve tamamen hareketsiz (D Sınıfı) spermatozoa oranlarının arttığını göstermektedir (Huang et al., 2023; Chrenek et al., 2011). Spermatogenesisin baskılanmasıyla toplam sperma üretimi (TSO) ve toplam fonksiyonel sperm fraksiyonu (TFSF) çok ciddi seviyelerde gerilemektedir.

Seminal plazmanın biyokimyasal bileşimi de ısı stresi altında altüst olmaktadır. En hassas hücresel stres indikatörü olan Isı Şok Proteini 70 (HSP70), seminal sıvıda anlamlı düzeyde yükselir (1255.38 pg/mL'den 1523.25 pg/mL'ye). Buna karşın, testis ve epididimis hasarının bir sonucu olarak seminal plazma testosteron seviyeleri ve sperm hücrelerinin metabolik enerji kaynağı olan fruktoz konsantrasyonu düşmektedir. Sperma membran stabilitesini koruyan Mg2+, Na+ ve K+ iyon seviyelerinde meydana gelen azalmalar, spermanın canlılığını ve motilitesini sekteye uğratmaktadır. Karaciğer ve testis doku hasarının birer yansıması olarak da seminal plazmada GPT ve GOT enzim aktivitelerinde belirgin artışlar saptanmıştır (Marai et al., 2003; Huang et al., 2023).

Tablo 2. Yeni Zelanda Beyazı Tavşanlarda Ilıman ve Şiddetli Isı Stresi Koşullarının Ejakülat Parametrelerine Etkisi

İncelenen Parametre	*Ilıman Koşullar (THI ~ 20.5)*	*Şiddetli Isı Stresi (THI > 29)*	*İstatistiksel Önem (P)*
Ejakülat Hacmi (mL)	*0.66 ± 0.02*	*0.53 ± 0.02*	*P < 0.01*
Sperm Konsantrasyonu (x10^6/mL)	*312.30 ± 10.10*	*187.30 ± 7.10*	*P < 0.01*
Toplam Sperm Üretimi (x10^6/ejakülat)	*204.60 ± 10.20*	*102.10 ± 6.70*	*P < 0.01*
Ölü Sperm Oranı (%)	*25.20 ± 0.90*	*25.10 ± 1.10*	*Önemsiz (NS)*
Sperm Morfolojik Anomalisi (%)	*17.90 ± 0.70*	*19.70 ± 0.90*	*Önemsiz (NS)*
Seminal Plazma HSP70 (pg/mL)	*1255.38 ± 245.28*	*1523.25 ± 108.99*	*P < 0.001*
Seminal Plazma Testosteron (pg/mL)	*341.49 ± 40.60*	*266.71 ± 40.97*	*P < 0.001*
Seminal Plazma Fruktoz (mg/mL)	*1.46 ± 0.10*	*1.30 ± 0.06*	*P < 0.001*
Seminal Plazma Asit Fosfataz (ACP, ng/mL)	*56.02 ± 4.19*	*72.36 ± 6.26*	*P < 0.001*
Seminal Plazma α-glukozidaz (α-Glu, mg/mL)	*25.94 ± 4.46*	*22.33 ± 4.21*	*P < 0.001*
Seminal Plazma Potasyum İyonu (K+, mmol/L)	*8.30 ± 0.24*	*7.89 ± 0.43*	*P < 0.001*

Not: Veriler New Zealand White erkek tavşanlarında yürütülen in vivo çalışmaların (Marai et al., 2003 ve Huang et al., 2023) sonuçlarından derlenerek entegre edilmiştir.

Bunun yanı sıra, UPLC-MS/MS tabanlı metabolomik araştırmalar, ısı stresinin seminal plazmada stearik asit, betain, araşidonik asit, L-malik asit ve indol gibi toplam 71 adet kritik metabolit seviyesini bozduğunu ortaya koymuştur. KEGG yolak analizleri, sperm metabolizmasında hayati öneme sahip olan keton cisimlerinin sentezi/yıkımı, serin/treonin metabolizması, triptofan metabolizması ve sitrik asit (TCA) döngüsü gibi toplam 51 farklı metabolik yolağın ısı stresi altında kesintiye uğradığını kanıtlamaktadır (Huang et al., 2023). Bu metabolik tıkanıklık, sperm hücrelerinin enerji (ATP) üretim mekanizmalarını sekteye uğratarak ileri yönlü motilite kaybının temel biyokimyasal nedenini oluşturmaktadır.

5. Fotoperiyot ve Işıklanma Süresinin Etkileri

Yoğun tavşan yetiştiriciliğinde barınak aydınlatma programları, özellikle dişi tavşanlarda üreme ritmini düzenlemek, östrus senkronizasyonunu uyarmak ve döl verimini optimize etmek amacıyla sıklıkla kullanılmaktadır (Gerencsér et al., 2012). Erkek damızlık tavşanlarda ise sperma miktarını ve kalitesini artırabilmek için yapay uzun gün ışığı programları (16 saat ışık / 8 saat karanlık) önerilmiştir.

Akdeniz iklim kuşağındaki ticari suni tohumlama merkezlerinde yapılan uzun süreli in vivo araştırmalar, sabit uzun gün ışığı (16 saat) uygulamalarının doğal gün ışığı alan kontrol grupları ile karşılaştırıldığında sperma üretimi ve spermatolojik kalite üzerinde belirgin bir üstünlük sağlamadığını belirlemişlerdir (Sánchez et al., 2006). Araştırmacılar, ılık ve sıcak iklimlerde gözlenen mevsimsel sperma kalitesi dalgalanmalarının birincil sürücüsünün gün uzunluğundaki (fotoperiyot) değişimlerden ziyade Sıcaklık-Nem İndeksi (THI) olduğunu saptamışlardır. Yüksek sıcaklık ve nemin tetiklediği ısı stresi, uygulanan aydınlatma programından bağımsız olarak sperma kalitesinde gerilemeye yol açmaktadır. Bu nedenle, erkek tavşanların reprodüktif sağlığını ve sperma kalitesini korumada gün uzunluğunu manipüle etmekten ziyade, barınak içi sıcaklık ve nem seviyelerini kontrol altında tutmanın ve ısı stresini engellemenin çok daha öncelikli ve etkili bir yönetimsel strateji olduğu belirtilmiştir (Sánchez et al., 2006).

6. İyileştirme Stratejileri ve Barınak Koşullarının Optimizasyonu

Küresel ısınma ve iklim değişikliklerinin tavşan yetiştiriciliğinde yarattığı üreme problemlerini aşmak amacıyla farklı koruyucu ve iyileştirici stratejiler geliştirilmiştir. Bu stratejiler temelde rasyonun besin madde içeriğinin optimize edilmesi, antioksidan/ozmoprotektif takviyelerin yapılması ve barınak çevre koşullarının iyileştirilmesini kapsamaktadır.

Rasyonel takviyeler arasında en dikkat çeken gelişmelerden biri, fonksiyonel bir amino asit olan prolinin kullanımıdır. Prolin, hücreleri dehidrasyona karşı koruyan güçlü bir ozmoprotektan ve hücresel oksidatif hasarı engelleyen önemli bir antioksidandır. Abdelnour ve ark. (Abdelnour et al., 2021) tarafından yürütülen çalışmada, şiddetli ısı stresi (ortalama THI = 31.99) altında tutulan erkek tavşanların rasyonuna 50-100 mg/kg DM düzeyinde prolin ilave edilmesinin çok yönlü olumlu etkileri gözlenmiştir. Prolin takviyesi, hayvanların solunum hızını (135.67'den 98.39 soluk/dk'ya) ve rektal sıcaklıklarını (38.91'den 38.38°C'ye) kuadratik olarak düşürmüştür. Plazma toplam antioksidan kapasitesini (TAC) ve süperoksit dismutaz (SOD) enzim aktivitesini belirgin seviyede artıran prolin, lipid peroksidasyonunu (MDA seviyelerini) azaltmış, hemoglobin (Hb) seviyesini ve kırmızı kan hücresi (RBC) sayısını yükseltmiştir. Bu fizyolojik iyileşmeler sperma kalitesine de yansımış; sperm motilitesi, canlılığı ve testosteron seviyeleri artarken anormal sperm oranlarında önemli azalmalar sağlanmıştır.

Tablo 3. Isı Stresi Altındaki Erkek Tavşanlarda Rasyona Prolin İlavesinin Hematolojik ve Antioksidan Göstergelere Etkisi

Fizyolojik Parametre	*Kontrol Grubu (P0)*	*Prolin (50 mg/kg - P50)*	*Prolin (100 mg/kg - P100)*	*İstatistiksel Eğilim (P)*
Rektal Sıcaklık (°C)	*38.91 ± 0.03a*	*38.43 ± 0.03b*	*38.38 ± 0.03b*	*P < 0.001 (Kuadratik)*
Solunum Hızı (soluk/dakika)	*135.67 ± 2.38a*	*105.94 ± 2.38b*	*98.39 ± 2.38c*	*P < 0.001 (Kuadratik)*
Kırmızı Kan Hücresi (RBC, 10^6/mL)	*3.89 ± 0.17b*	*4.44 ± 0.17ab*	*4.73 ± 0.17a*	*P < 0.05 (Lineer)*
Hemoglobin (Hb, g/dL)	*10.69 ± 0.45b*	*13.75 ± 0.45a*	*12.98 ± 0.45a*	*P < 0.01 (Lineer)*
Toplam Antioksidan Kapasite (TAC, mM/L)	*1.63 ± 0.10b*	*2.26 ± 0.10a*	*2.06 ± 0.10a*	*P < 0.01 (Kuadratik)*
Süperoksit Dismutaz (SOD, U/mL)	*0.152 ± 0.01b*	*0.237 ± 0.01a*	*0.222 ± 0.01a*	*P < 0.05 (Kuadratik)*

Not: Aynı satırdaki farklı harfler (a, b, c) istatistiksel açıdan anlamlı farklılığı ifade eder (P < 0.05). Veriler Abdelnour ve ark. (2021) çalışmasından alınmıştır.

Ayrıca sıcak tropikal iklim koşullarında (Zaria, Nijerya gibi) rasyonun protein seviyesinin ve antioksidan mineral Selenyumun (Se) optimize edilmesi de damızlık erkeklerin üreme performansını korumada etkili bulunmuştur. Rasyonda %18 ham protein (CP) ve 0.4 mg/kg Se seviyesinin, sıcak çevre koşullarında testis büyüklüğünü (uzunluk, genişlik, ağırlık ve hacim) desteklediği, sperm konsantrasyonu ve motilitesini dengede tuttuğu saptanmıştır (Abdulrashid & Juniper, 2016). Bununla birlikte, rasyonel iyileştirmelerin barınak koşullarının kontrolüyle entegre edilmesi gerekmektedir. Barınaklarda havalandırma fanları, evaporatif pedli soğutma sistemleri (cooling pads) ve iyi bir çatı yalıtımının uygulanması, çevre sıcaklığının tavşanlar için konfor eşiği olan 18-20°C (veya en azından kritik tolerans sınırı olan 25°C'nin altında) tutulmasında vazgeçilmez altyapı adımlarıdır.

7. Sonuç

Çevresel faktörler ve özellikle Sıcaklık-Nem İndeksi (THI) artışına bağlı olarak şekillenen ısı stresi, erkek tavşanların reprodüktif sağlığını baltalayan ve yetiştiricilikte verimliliği sınırlayan en kritik unsurdur. Isı stresi, hipotalamus-hipofiz-adrenal aksını uyararak genel homeostasis mekanizmalarını bozmakta, testis hipertermisine yol açmakta, seminal plazma mineral ve metabolite dengesini altüst etmekte ve sperm hücrelerinin enerji metabolizmasını felç etmektedir. Bu durum kitle motilitesinde ve sperm yoğunluğunda dramatik düşüşlere, anormal sperm üretiminde ve DNA hasarında ise belirgin artışlara neden olmaktadır. Mevsimsel ve iklimsel değişimlerden kaynaklanan bu olumsuz etkilerin en aza indirilmesi amacıyla şu adımların atılması önerilmektedir: 1. Damızlık programlarında, sıcaklık değişimlerine ve zorlu çevre koşullarına genetik olarak dirençli olan lokal gen kaynaklarının (örneğin Sinai ve Balady ırkları ile bunlardan geliştirilmiş sentetik melez hatların) erkek teke damızlığı olarak kullanımı yaygınlaştırılmalıdır. 2. Ticari işletmelerde barınak içi mikro-klima (sıcaklık, nem ve havalandırma) optimizasyonuna büyük öncelik verilmeli ve THI değerlerinin konfor sınırlarında (THI < 27.8) tutulabilmesi için evaporatif soğutma sistemleri ve fan altyapıları etkinleştirilmelidir. 3. Sıcak yaz aylarında damızlık rasyonlarına antioksidan ve ozmoprotektif etkileri bilimsel olarak kanıtlanmış Prolin (50-100 mg/kg DM), Selenyum (0.4 mg/kg Se) ve dengeli protein (%18 CP) takviyeleri yapılarak testisler ve sperm hücreleri oksidatif hasara karşı hücresel düzeyde korunmalıdır. Bu entegre yaklaşımların hayata geçirilmesi, küresel ısınma koşullarında tavşan yetiştiriciliğinde üreme performansının ve sunif tohumlama başarısının sürdürülebilir kılınmasında anahtar rol oynayacaktır.

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YAYGIN KULLANILAN BİR ANTİPARAZİTER OLAN İVERMEKTİNİN ERKEK ÜREME SİSTEMİ VE SPERMA KALİTESİ ÜZERİNE TOKSİKOLOJİK ETKİLERİ

TOXICOLOGICAL EFFECTS OF IVERMECTIN, A COMMONLY USED ANTIPARASITIC, ON THE MALE REPRODUCTIVE SYSTEM AND SPERM QUALITY

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ÖZET

İvermektin, veteriner hekimlikte paraziter enfeksiyonların kontrolünde yaygın olarak kullanılan geniş spektrumlu makrosiklik lakton türevi bir antiparaziter ilaçtır. Terapötik dozlarda güvenli kabul edilmesine rağmen, özellikle damızlık değeri olan erkek hayvanlarda üreme sistemi ve spermatolojik parametreler üzerindeki potansiyel toksikolojik etkileri endişe yaratmaktadır. Bu derlemenin amacı, ivermektin uygulamasının testis histolojisi, sperma kalitesi ve reprodüktif hormon profilleri üzerindeki etkilerini güncel bilimsel literatür ışığında kapsamlı bir şekilde değerlendirmektir. Bu derleme kapsamında, ivermektinin farklı doz ve sürelerde uygulandığı in vivo deney hayvanı (kemirgen ve tavşan) modellerini inceleyen araştırmalar taranmıştır. Literatür araştırmasında; sperm motilitesi, yoğunluğu, morfolojik anormallik oranları ve DNA hasarını değerlendiren çalışmalar merkeze alınmıştır. Ayrıca, hücresel düzeyde meydana gelen oksidatif stres belirteçleri (lipid peroksidasyonu) ve testis dokusundaki histopatolojik değişimleri (seminifer tübül dejenerasyonu, apoptoz) analiz eden araştırmalar karşılaştırmalı olarak incelenmiştir. İncelenen literatür verileri, ivermektinin özellikle yüksek dozlarda ve uzun süreli kullanımlarında sperma canlılığını, motilitesini ve yoğunluğunu istatistiksel olarak anlamlı düzeyde düşürdüğünü göstermektedir. Biyokimyasal analizler, ilacın antioksidan enzim kapasitesini zayıflatarak reaktif oksijen türlerinin (ROS) artışına ve sperma membranında şiddetli lipid peroksidasyonuna yol açtığını ortaya koymaktadır. Histolojik bulgular ise seminifer tübül epitelinde dejeneratif değişiklikler ve germ hücrelerinde apoptotik indeksin arttığını doğrulamaktadır. Leydig hücrelerindeki disfonksiyona bağlı olarak serum testosteron seviyelerinde düşüşler rapor edilmiştir. Sonuç olarak, ivermektinin erkek üreme sistemi üzerinde doza ve süreye bağlı reprodüktif toksisite potansiyeli taşıdığı, bu toksisitenin temelinde yatan ana mekanizmanın oksidatif stres olduğu anlaşılmaktadır. Damızlık erkek hayvanlarda ivermektin kullanımında doz optimizasyonuna titizlikle dikkat edilmeli ve olası fertilite kayıpları mutlaka göz önünde bulundurulmalıdır. Reprodüktif hasarı önlemeye yönelik antioksidan stratejilerin araştırılması büyük önem taşımaktadır.

Anahtar Kelimeler: İvermektin, Sperma Kalitesi, Reprodüktif Toksisite, Oksidatif Stres, Veteriner Farmakoloji.

ABSTRACT

Ivermectin is a broad-spectrum macrocyclic lactone derivative antiparasitic drug widely used in veterinary medicine for the control of parasitic infections. Although considered safe at therapeutic doses, its potential toxicological effects on the reproductive system and spermatological parameters, especially in breeding male animals, raise concerns. The aim of this review is to comprehensively evaluate the effects of ivermectin administration on testicular histology, sperm quality, and reproductive hormone profiles in the light of current scientific literature. Within the scope of this review, studies examining in vivo experimental animal (rodent and rabbit) models in which ivermectin was administered at various doses (therapeutic and toxic) and durations were screened. In the literature search, studies evaluating sperm motility, density, morphological abnormality rates, and DNA damage were centered upon. Furthermore, researches analyzing oxidative stress markers (lipid peroxidation) occurring at the cellular level and histopathological changes (seminiferous tubule degeneration, apoptosis) in testicular tissue were examined comparatively. Examined literature data indicate that ivermectin, especially in high doses and during long-term use, statistically significantly decreases sperm viability, motility, and concentration. Biochemical analyses reveal that the drug weakens the antioxidant enzyme capacity, leading to an increase in reactive oxygen species (ROS) and severe lipid peroxidation in the sperm membrane. Histological findings confirm degenerative changes in the seminiferous tubule epithelium and an increased apoptotic index in germ cells. Decreases in serum testosterone levels have been

reported due to dysfunction in Leydig cells. In conclusion, it is understood that ivermectin carries a potential for dose- and duration-dependent reproductive toxicity on the male reproductive system, and the main mechanism underlying this toxicity is oxidative stress. Strict attention must be paid to dose optimization in the use of ivermectin in breeding male animals, and possible fertility losses must absolutely be taken into consideration. Investigating antioxidant strategies to prevent reproductive damage is of great importance.
Keywords: Ivermectin, Sperm Quality, Reproductive Toxicity, Oxidative Stress, Veterinary Pharmacology.

1. GİRİŞ

İvermektin, Streptomyces avermitilis adlı toprak aktinomisetinden elde edilen avermektinlerin (özellikle 22,23-dihidroavermectin B1a ve B1b homologlarının karışımı) yarı sentetik bir makrosiklik lakton türevidir. İlk olarak 1970'lerde Satoshi Ōmura ve William C. Campbell tarafından keşfedilmiş ve 1981 yılında ticari olarak piyasaya sürülmüştür. Hem veteriner hekimlikte hem de insan tıbbında geniş spektrumlu endektosit aktivitesi ile nematodlar ve eklembacaklı ektoparazitlere karşı yaygın şekilde kullanılmaktadır. Parazitlerin nöromüsküler kavşaklarında bulunan glutamat kapılı klor kanallarına bağlanarak klor geçirgenliğini artırır, hiperpolarizasyona ve sonuç olarak parazitin paralizine yol açar.
Memelilerde glutamat kapılı klor kanalları bulunmadığından ve ivermektinin etki ettiği GABAerjik reseptörler kan-beyin bariyeri (P-glikoprotein) sayesinde korunduğundan, ilacın terapötik dozlarda memeli konakçılar için oldukça geniş bir güvenlik marjına sahip olduğu kabul edilmektedir. Ancak ivermektin yüksek oranda lipofilik bir moleküldür ve yağ dokularında birikerek organizmada uzun süre kalıcı olabilmektedir. Bu durum, özellikle paraziter enfeksiyonların mücadelesinde tekrarlanan doz şemalarının uygulanmasıyla birleştiğinde, hepatik, renal, nöral ve reprodüktif sistemler üzerinde belirgin toksik yan etkilerin ortaya çıkmasına zemin hazırlayabilmektedir.
Son yıllarda yapılan epidemiyolojik ve deneysel çalışmalar, ivermektin tedavisinin damızlık erkek hayvanlar ve insan hastalar üzerindeki olumsuz reprodüktif etkilerine dikkat çekmektedir. İlacın testis parankim dokusunda hücresel harabiyete yol açtığı, sperma kalitesini dramatik şekilde düşürdüğü ve androjenik hormon dengesini bozduğu yönündeki veriler literatürde giderek artış göstermektedir. Bu bağlamda, hazırlanan bu çalışma, ivermektin kullanımının erkek reprodüktif sistemine olan çok yönlü toksikolojik etkilerini güncel in vivo, in vitro, klinik ve moleküler düzeydeki bilimsel kanıtlar ışığında bir araya getirmeyi, toksisitenin moleküler ve hücresel mekanizmalarını (özellikle oksidatif stres ve programlanmış hücre ölümü - apoptoz ekseninde) açıklamayı ve reprodüktif fonksiyonları korumaya yönelik potansiyel terapötik ve antioksidan koruma stratejilerini derlemeyi amaçlamaktadır.

2. MATERYAL VE YÖNTEM

Bu derleme çalışmasında, ivermektinin erkek üreme sistemi üzerindeki toksik etkilerini değerlendiren bilimsel literatür sistematik bir şekilde taranmış ve elde edilen bulgular sentezlenmiştir. Literatür taraması kapsamında PubMed, ScienceDirect, Web of Science ve TÜBİTAK Ulakbim gibi veri tabanları üzerinden 'ivermectin', 'male fertility', 'reprotoxicity', 'sperm quality', 'testis histopathology', 'oxidative stress' ve 'apoptosis' anahtar kelimeleri kullanılarak in vivo ve in vitro çalışmalar incelenmiştir. Derleme kapsamına dahil edilen araştırmalarda şu kriterler dikkate alınmıştır:

In vivo deneysel modeler: Wistar ve Sprague-Dawley sıçanları, New Zealand tavşanları, Akkaraman ve Awassi koyun ırkları, Friesian boğaları ve Freiberger damızlık aygırlarında terapötik (0.2 mg/kg) ve yüksek/tekrarlanan doz ivermektin uygulamalarının spermatolojik etkileri.

Klinik insan verileri: Nigerian onchocerciasis (nehir körlüğü) hastalarında ivermektin tedavisinin (150 µg/kg) sperma fonksiyonları üzerindeki 11 aylık uzun dönemli etkilerini inceleyen klinik araştırmalar.

In vitro hücresel çalışmalar:Sıçan birincil testis hücre kültürleri, fare type B GC-1 spermatogoni hücre hatları ve domuz granüloza hücrelerinde ivermektine bağlı sitotoksisite ve apoptotik süreçler.
İncelenen temel parametreler: Sperma parametreleri (yoğunluk, motilite, canlılık, anormal morfoloji oranı, membran bütünlüğü), serum hormon seviyeleri (testosteron, LH, FSH), testis/epididimis histopatolojisi, hücresel oksidatif stres belirteçleri (malondialdehit-MDA, reaktif oksijen türleri-ROS,

antioksidan enzim aktiviteleri), DNA fragmentasyonu ve apoptoz belirteçleri (Caspase-3, PCNA, Annexin-V).
Derlenen veriler, farklı memeli türleri arasındaki duyarlılık farklarını ortaya koymak, toksisite gelişim mekanizmasını hücresel ve moleküler düzeyde analiz etmek ve toksisiteyi hafifletmek amacıyla uygulanan koruyucu antioksidan maddelerin (Vitamin E/Selenyum, Vitamin A, Vitamin C, Alfa Lipoik Asit, Çinko Nanopartikülleri ve Melatonin) etkinliğini değerlendirmek üzere sistematik bir yapı içinde sunulmuştur.

3. BULGULAR VE TARTIŞMA

Bilimsel literatürün analizi, ivermektinin erkek üreme sistemi üzerinde ciddi ve çok yönlü toksik etkilere yol açtığını doğrulamaktadır. Toksisite doza, uygulama süresine ve konakçı türüne bağlı olarak değişkenlik göstermektedir. Bu olumsuz süreçlerin temelinde spermatolojik bozulmalar, oksidatif stresin tetiklenmesi, germ hücrelerinde apoptoz eğiliminin artması ve hormonal baskılanma yatmaktadır.

3.1. Sperma Parametreleri ve Fertilizasyon Yeteneği Üzerine Etkileri

Farklı dozlardaki ivermektin uygulamalarının, sperm kalitesini belirleyen en kritik parametreler olan sperma sayısı, yoğunluğu, prograsif motilite, canlılık oranı ve morfolojik anormallik yüzdesi üzerinde belirgin negatif etkileri rapor edilmiştir. Wistar sıçanlarında terapötik dozda (0.2 mg/kg) ivermektin enjeksiyonunun, sperm canlılık ve motilite yüzdelerinde anlamlı düşüşlere yol açtığı ve dev başlı sperm ya da bükük kuyruklu sperm gibi birincil ve ikincil morfolojik anormallik oranlarını artırdığı tespit edilmiştir (Ahmed ve ark., 2020; El-Nahas ve El-Ashmawy, 2008). Benzer şekilde, 0.56 mg/kg dozda ivermektin uygulanan sıçanlarda epididimal sperm yoğunluğu ve motilitesinin ciddi oranda azaldığı ve canlı sperma yüzdesinin düştüğü belirlenmiştir (El-Maddawy ve Abd El Naby, 2017).
Klinik düzeyde en çarpıcı kanıtlar, onchocerciasis (nehir körlüğü) teşhisi konulmuş ve ivermektin (150 µg/kg) tedavisi almış erkek hastalarda yapılan 11 aylık uzun dönemli takiple elde edilmiştir. Idonije ve arkadaşları (2011) tarafından gerçekleştirilen araştırmada, tedavi sonrasında hastaların sperm konsantrasyonu ve motilitesinde dramatik düşüşler gözlenmiştir. Daha da önemlisi, spermlerin morfolojik analizinde çift baş, çift kuyruk, aşırı büyük baş ve pigment kaybı (albino sperm) gibi şiddetli morfolojik kusurların oranında çok belirgin bir artış kaydedilmiştir. Bu bulgular, ivermektinin insan fertilitesi üzerinde de ciddi bir risk faktörü taşıdığını göstermektedir.
Koyun ve koçlar üzerinde yapılan çalışmalarda da benzer toksisite bulguları mevcuttur. Akkaraman koçlarına 0.2 mg/kg s.c. dozunda uygulanan ivermektin, enjeksiyondan sonraki 1. saatten başlayarak 120. saate kadar sperm motilitesini ve yoğunluğunu istatistiksel açıdan anlamlı derecede düşürmüştür (Tanyıldızı ve Bozkurt, 2002). Bu düşüşe paralel olarak, sperm hücresinin ovuma penetrasyonunda ve akrozomal aktivitede kritik rol oynayan seminal ve serum hyaluronidaz enzim aktivitelerinde ise belirgin bir artış gözlenmiştir. Hücre dışı enzim sızıntısının, sperm membran bütünlüğünün ve hücresel bütünlüğün bozulmasının doğrudan bir sonucu olduğu düşünülmektedir. Irak Awassi koçlarında yapılan çalışmalarda ise, ivermektin enjeksiyonunun 3. gününde ejakülat hacmi, sperm konsantrasyonu ve testosteron seviyelerinde keskin bir düşüş olmuş, enjeksiyon acısına ve ilaç yarilanma ömrüne bağlı gelişen bu akut tablonun 7. günden itibaren kademeli olarak toparlandığı ve spermatogenezin geri döndürülebilir bir karakter sergilediği bildirilmiştir (Ali, 2014; Naoman, 2012).
Damızlık boğalarda (Friesian), ilginç bir şekilde ivermektin uygulamalarının olumsuz bir spermatolojik tablo yaratmadığı, aksine post-thaw (çözünme sonrası) sperm motilitesini, bütünlüğünü ve akrozomal kalitesini, diğer yaygın kullanılan antiparaziterlerden (albendazol, levamizol) çok daha iyi koruduğu gözlenmiştir (Tabl ve ark., 2012). Bu durum, ivermektinin üreme sistemindeki toksisitesinin türler arası farmakokinetik ve biyoyararlanım dinamiklerine, kan-testis bariyeri geçirgenlik farklılıklarına bağlı olabileceğini düşündürmektedir.

Tablo 1: Farklı Türlerde İvermektin Uygulamasının Spermatolojik ve Biyokimyasal Parametreler Üzerindeki Etkileri

Tür (Model)	Doz / Uygulama	Temel Spermatolojik ve Hormonal Bulgular	Hücresel ve Histopatolojik Etkiler	Referanslar
Sıçan (Wistar/SD)	0.2 - 1.0 mg/kg s.c. / Tek veya Tekrarlı Doz	Sperma sayısında, motilitesinde ve canlılığında şiddetli düşüş; serum testosteron, LH ve FSH hormon seviyelerinde baskılanma.	Germinal epitel disorganizasyonu, epitel içi vakuolizasyon, seminifer tübüllerde atrofi, apoptotik Caspase-3 artışı, DNA fragmentasyonu, yüksek lipid peroksidasyonu.	Ahmed ve ark., 2020; Cordeiro ve ark., 2018; El-Maddawy ve ark., 2017
Tavşan (New Zealand)	0.4 - 0.8 mg/kg s.c. / Haftalık 4-8 hafta	Sperma yoğunluğunda ve prograsif motilitesinde istatistiksel olarak anlamlı düşüş; testosteron düzeylerinde azalma.	Seminifer tübül dejenerasyonu, spermatogenik seride nekroz ve lümene dökülme; böbrek, karaciğer ve beyin dokusunda yaygın hücresel hasar.	GabAllh ve ark., 2017; El-Shobokshy ve ark., 2023
Koyun / Koç (Awassi/Akkaraman)	0.2 mg/kg s.c. / Tek doz	Sperm motilitesinde ve yoğunluğunda hızlı düşüş; ejakülat hacminde ve testosteronda 3. günde geçici baskılanma (7. gün iyileşme).	Seminal ve serum hyaluronidaz enzim aktivitelerinde belirgin artış (membran sızıntısı); spermatogenez hasarında kısmi reversibilite.	Tanyıldızı ve Bozkurt, 2002; Ali, 2014; Naoman, 2012
Boğa (Friesian)	200 µg/kg s.c. / Tekrarlı doz (8 hf ara)	Sperma ejakülat hacmi, motilitesi ve canlılığında stabilite veya artış; çözünme sonrası akrozom bütünlüğünde koruma.	Seminal plazmada toplam protein ve globulin düzeylerinde artış; seminifer tübül histolojisinde belirgin bir negatif etki yok.	Tabl ve ark., 2012
İnsan (Hasta Grubu)	150 µg/kg p.o. / Klinik tedavi	Sperma sayısında ve motilitesinde dramatik azalma; sperma viskozite ve hacminde belirgin değişiklik yok.	Anormal morfolojili spermada (çift baş, çift kuyruk, ekstra büyük baş, albino spermler) anlamlı ve fertiliteyi bozacak düzeyde artış.	Idonije ve ark., 2011

3.2. Oksidatif Stres ve Biyokimyasal Mekanizmalar

İvermektinin memeli üreme hücrelerinde yol açtığı toksisitenin temelinde yatan ana mekanizmanın, hücresel düzeyde gelişen reaktif oksijen türleri (ROS) artışı ve buna bağlı olarak ortaya çıkan oksidatif stres olduğu anlaşılmaktadır. İvermektin lipofilik doğası gereği hücre membranlarına, özellikle de mitokondri membranına nüfuz ederek hücresel solunum zincirini etkilemekte ve mitokondriyal membran potansiyelinin kollapsına neden olmaktadır. Bu durum, aşırı miktarda süperoksit anyonu ve nitrik oksit (NO) salınımını tetiklerken, enzim kökenli antioksidan savunma sistemlerini baskılamaktadır (Basini ve ark., 2026; Chavez Varias ve ark., 2026).

Erkek sıçanların testis dokularında yapılan biyokimyasal analizlerde, ivermektinin lipid peroksidasyonunun en önemli son ürünü ve hücresel hasarın temel belirteci olan malondialdehit (MDA / TBARS) ile hidrojen peroksit (H_2O_2) düzeylerini istatistiksel düzeyde çok anlamlı derecede yükselttiği saptanmıştır (Ahmed ve ark., 2020; El-Maddawy ve Abd El Naby, 2017). Eş zamanlı olarak, hücreleri oksidatif hasara karşı koruyan enzimatik antioksidanlar olan süperoksit dismutaz (SOD), katalaz (CAT), glutatyon peroksidaz (GPx) ve enzimatik olmayan azaltılmış glutatyon (GSH) seviyelerinin dramatik şekilde azaldığı tespit edilmiştir.

Sperma hücrelerinin membran yapısı çok yüksek oranda çoklu doymamış yağ asitleri (PUFA) içerdiğinden, bu hücreler ivermektin kaynaklı lipid peroksidasyonuna karşı son derece duyarlıdır. Sperm membranında meydana gelen lipid peroksidasyonu, aksonemal proteinlerin hasar görmesine, sperm motilitesinin kalıcı kaybına ve DNA'nın bütünlüğünün bozulmasına yol açmaktadır.

3.3. Testis Histopatolojisi ve Germ Hücre Apoptozu (Caspase-3 ve PCNA)

Histolojik incelemeler, ivermektin uygulamasının testis parankim dokusunun mimari yapısını bozduğunu açıkça ortaya koymaktadır. Kontrol gruplarında seminifer tübüller normal çap ve epitel yüksekliğinde, germ hücre katmanları ise düzenli bir mimari sergilerken, ivermektin alan hayvanlarda (sıçan ve tavşan modelleri) tübül çaplarında daralma, germinal epitel yüksekliğinde azalma ve belirgin epitel içi vakuolizasyon saptanmıştır (Cordeiro ve ark., 2018; El-Shobokshy ve ark., 2023). Şiddetli olgularda, spermatogenik hücrelerin seminifer tübül epitelinden koparak lümene döküldüğü (deskuamasyon), tübül lümeninin hücresel döküntüler ve nekrotik spermatid kalıntılarıyla dolduğu gözlenmiştir. Sertoli hücrelerinin oklüzif bağlantılarının (kan-testis bariyeri) hasar görmesi, germ hücrelerinin epitelden koparak lümene dökülmesinin en önemli patolojik tetikleyicisi olarak kabul edilmektedir.

Moleküler ve immünohistokimyasal analizler, bu dejeneratif süreçlerin arkasındaki mekanizmanın kontrolsüz ve aşırı apoptoz (programlanmış hücre ölümü) aktivasyonu olduğunu göstermektedir. Apoptozun en önemli yürütücü enzimi olan Caspase-3 immünohistokimyasal olarak incelendiğinde, ivermektin uygulanan sıçanların ve tavşanların testis dokularındaki seminifer tübüllerde ve lümendeki dökülmüş hücrelerde Caspase-3 ekspresyonunun (özellikle kuvvetli işaretlenmiş tübül oranının) anlamlı derecede arttığı doğrulanmıştır (Cordeiro ve ark., 2023; El-Shobokshy ve ark., 2023). Slobodticov ve arkadaşları (2026) tarafından yürütülen güncel bir çalışma, ivermektine bağlı germinal hücre apoptozunun üreme yaşından bağımsız olduğunu; genç, peripubertal ve yetişkin sıçanlarda aynı apoptotik Caspase-3 aktivasyonunu ve histopatolojik disorganizasyonu tetiklediğini kanıtlamıştır. Ayrıca, genomik DNA analizi, ivermektine maruz kalan testis dokularında apoptotik hücre ölümlerinin moleküler kanıtı olan DNA merdivenleşmesini (laddering) ve fragmentasyonunu ortaya koymuştur (Ahmed ve ark., 2020).

Apoptozdaki bu artışa paralel olarak, hücre siklusunun S-fazında DNA sentezi ve replikasyonunda anahtar rol oynayan ve hücre çoğalmasının göstergesi olan Proliferating Cell Nuclear Antigen (PCNA - Proliferatif Hücre Nükleer Antijeni) ekspresyonunun ivermektin uygulamasıyla sıçan ve tavşan testislerinde çok ciddi düzeyde baskılandığı tespit edilmiştir (Ahmed ve ark., 2020; El-Shobokshy ve ark., 2023). PCNA ekspresyonunun azalması, germ hücrelerinin replikasyon yeteneğini bloke etmekte, hücre siklusunu durdurmakta ve sonuçta spermatogenik hücre sayısında ve sperm üretim kapasitesinde kalıcı bir azalmaya yol açmaktadır.

3.4. Hormonal Profil ve Leydig Hücre Fonksiyonları

Erkek reprodüktif fonksiyonlarının ve spermatogenezin sürdürülebilmesi, testis içi ve sistemik testosteron hormonunun kararlı düzeylerde bulunmasına bağlıdır. Yapılan araştırmalarda, ivermektin uygulanan erkek sıçanlarda ve tavşanlarda serum testosteron seviyelerinde istatistiksel düzeyde çok ciddi düşüşler gözlenmiştir (Ahmed ve ark., 2020; El-Maddawy ve Abd El Naby, 2017). Testosterondaki bu azalmaya, hipofiz kaynaklı gonadotropik hormonlar olan luteinizan hormon (LH) ve folikül uyarıcı hormon (FSH) seviyelerindeki düşüşler eşlik etmektedir. Bu hormonal tablo, ivermektinin hipotalamus-hipofiz-testis (HPG) aksını baskıladığını göstermektedir.

Histolojik çalışmalarda testosteron üreten Leydig hücrelerinin sayısal sıklığında veya morfolojisinde belirgin bir değişiklik saptanmamıştır (Cordeiro ve ark., 2018). Bu durum, Leydig hücrelerinin doğrudan yok edilmediğini, ancak fonksiyonel düzeyde baskılandığını göstermektedir. İvermektinin konakçı dokularındaki en önemli etki mekanizmalarından biri GABA-mimetik etkisidir. Üreme organlarında, sperm hücresinde ve Leydig hücrelerinde fonksiyonel GABA reseptörleri (GABAA, GABAB, GABAC) bulunmaktadır. İvermektinin lokal Leydig hücrelerindeki GABAA reseptörlerini aşırı uyararak steroidogenezi (testosteron sentezi) baskıladığı, hipofiz reseptör hassasiyetini etkilediği ve HPG aksında negatif geribildirim mekanizmalarını tetiklediği hipotezi üzerinde durulmaktadır (Cordeiro ve ark., 2023).

3.5. Toksisiteyi Önleyici ve Koruyucu Yaklaşımlar (Antioksidan Stratejiler)

İvermektinin erkek fertilitesi üzerinde yarattığı olumsuz etkilerin temelinde oksidatif stres ve buna bağlı gelişen hücre hasarının bulunması, araştırmacıları eş zamanlı antioksidan tedavilerin etkinliğini

araştırmaya yöneltmiştir. Güncel çalışmalar, belirli antioksidan moleküllerin ivermektin toksisitesini çok yönlü olarak hafiflettiğini ve fertiliteyi koruduğunu doğrulamaktadır:

Vitamin E ve Selenyum Kombinasyonu (Vit E + Se): Wistar sıçanlarında ivermektine bağlı gelişen karaciğer ve testis hasarını sinerjik bir etkiyle hafifletmiştir. Antioksidan enzimleri uyararak lipid peroksidasyonunu (MDA) düşürmüş, sperm sayı ve kalitesini normalize etmiş, testis dokusundaki DNA fragmentasyonunu azaltmış ve hücre canlılığını (PCNA) korumuştur (Ahmed ve ark., 2020).

Alfa Lipoik Asit (ALA): Güçlü bir hücresel antioksidan olan ALA, ivermektin uygulanan sıçanlarda testis dokusunun antioksidan kapasitesini artırmıştır. Testis dokusundaki apoptotik stres genleri olan IGFBP-3 ve HSPA1 (Hsp70.1) ekspresyon seviyelerindeki anormal artışı baskılayarak germ hücresi apoptozunu engellemiş, semen kalitesini ve testosteron düzeylerini korumuştur (El-Maddawy ve Abd El Naby, 2017).

Çinko Nanopartikülleri (ZnNPs): Tavşanlarda ivermektin maruziyetine bağlı gelişen büyüme geriliğini ve yem tüketimi azalmasını düzeltmiştir. Sperma parametrelerini, sperm membran bütünlüğünü ve testosteron düzeylerini iyileştirmiş; testis histopatolojik hasar skorunu, Caspase-3 ekspresyonunu azaltırken PCNA düzeylerini korumuştur (El-Shobokshy ve ark., 2023).

Vitamin A ve Vitamin C Kombinasyonu: Ratlarda ivermektin maruziyetinde gelişen serolojik, biyokimyasal ve hematolojik bozulmaları hafifletmiş; sperm sayısı, motilitesi ve histolojik tübül bütünlüğünü korumada tek başlarına kullanımlarına kıyasla daha üstün bir etki sergilemiştir (Omshi ve ark., 2018).

Melatonin ve Agomelatin: In vitro fare GC-1 spermatogoni hücresel modelinde ivermektinin tetiklediği aşırı ROS birikimini ve sitozolik Ca2+ aşırı yüklenmesini engellemiştir. Mitokondriyal membran potansiyelini ve oksidatif fosforilasyonu koruyarak hücresel enerji metabolizmasını sürdürmüş, kaspaz aktivasyonunu, BAX/BCL-2 oranını ve sitokrom c salınımını azaltarak spermatogonial apoptozu önlemiştir (Chavez Varias ve ark., 2026).

4. SONUÇ

Bu derleme çalışması sonucunda, ivermektinin veteriner hekimlikte ve insan tıbbında son derece başarılı bir antiparaziter ilaç olmasına rağmen, damızlık değeri olan erkek hayvanlarda ve üreme çağındaki insanlarda doza ve kullanım süresine bağlı olarak ciddi reprodüktif toksisite riskleri taşıdığı gösterilmiştir. Toksisitenin temel hücresel mekanizmasının, testis dokusunda ve mitokondriyal seviyede tetiklenen reaktif oksijen türleri (ROS) artışı ve antioksidan kapasitenin yetersiz kalmasıyla gelişen oksidatif stres olduğu; bunun da germ hücrelerinde DNA hasarına, PCNA baskılanmasına ve Caspase-3 bağımlı kontrolsüz apoptoza yol açtığı düşünülmektedir.

Klinik veteriner hekimliği, hayvan ıslahı ve damızlık yönetimi açısından şu öneriler önem arz etmektedir:

1. ***Doz Optimizasyonu:*** Damızlık değeri olan erkek hayvanlarda (koç, teke, boğa vb.) ivermektin ve diğer avermektin grubu ilaçların kullanımında üretici firma tarafından önerilen standart terapötik doz sınırlarına titizlikle uyulmalı, toksisite riskini artıran tekrarlı yüksek doz şemalarından kaçınılmalıdır.
2. ***Zamanlama Planlaması:*** Fertilite parametrelerini geçici veya kalıcı olarak olumsuz etkileme potansiyeli bulunduğundan, ivermektin uygulamalarının koç katımı / çiftleşme sezonu öncesinde veya damızlık hayvanların aktif aşım dönemlerinde yapılması tavsiye edilmemektedir. Tedaviler üreme sezonu dışı dönemlerde planlanmalıdır.
3. ***Antioksidan Destek Stratejileri:*** Paraziter enfeksiyon nedeniyle ivermektin uygulanmasının zorunlu olduğu damızlık erkek hayvanlarda, olası fertilite hasarını ve testis doku yıkımını önlemek amacıyla tedaviye sinerjik antioksidan takviyelerin (Vitamin E/Selenyum, Alfa Lipoik Asit veya organik Çinko formları) eklenmesi farmakolojik bir koruma stratejisi olarak uygulanmalıdır.

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PSİKİYATRİ HEMŞİRELİĞİNDE YAPAY ZEKA UYGULAMALARI: KULLANIM ALANLARI VE SINIRLILIKLAR

ARTIFICIAL INTELLIGENCE APPLICATIONS IN PSYCHIATRIC NURSING: AREAS OF USE AND LIMITATIONS

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Amaç: Yapay zeka, ruh sağlığı hizmetlerinde semptom değerlendirme, risk tahmini, klinik karar desteği, psikoeğitim ve bireyselleştirilmiş bakıma ek olarak akıllı telefon uygulamaları, sanal gerçeklik ve yapay zekâ destekli sohbet robotları gibi dijital terapötik müdahalelerin geliştirilmesi ve uygulanmasında giderek daha fazla kullanılmaktadır (Lu ve diğerleri, 2026; Reyes ve diğerleri, 2026; Can Öz ve Duran, 2026). Bu derlemenin amacı, psikiyatri hemşireliği uygulamalarında yapay zekânın kullanım alanlarını ve bu teknolojilerin hemşirelik bakımı üzerindeki etkilerini güncel literatür doğrultusunda değerlendirmektir.
Yöntem: Bu çalışma, literatür taramasına dayalı bir derleme niteliği taşımaktadır. Psikiyatri hemşireliğinde yapay zekâ kullanımına ilişkin son beş yılda yayımlanan çalışmalar, PubMed ve Google Scholar gibi veri tabanlarında "artificial intelligence", "psychiatric nursing", "mental health" ve "generative artificial intelligence" anahtar kelimeleri kullanılarak taranmıştır.
Bulgular: İncelenen çalışmalarda, yapay zekânın ruh sağlığı hizmetlerinde farklı kullanım alanları ile sağladığı yararlar ve sınırlılıkları ele alınmıştır. Auf ve ark. (2025), yapay zekânın ruh sağlığı hizmetlerinde klinik karar desteği, erken tanılama ve öz yönetimi desteklese de klinik uygulamaya entegrasyon açısından sınırlılıklar bulunduğunu bildirmiştir. Benzer şekilde, Reyes ve diğerleri (2026) yaptıkları çalışmada, yapay zekâ destekli araçların psikoeğitim, duygusal destek ve stres yönetimini desteklediğini vurgulamıştır. Yapılan bir sistematik derlemede, yapay zekâ destekli bilişsel davranışçı terapi uygulamalarının depresyon, anksiyete ve stres belirtilerini azaltmada etkili olduğu, ancak veri gizliliği ve etik sorunların sürdüğü belirtilmiştir (Ravikrishnan, 2026). Li ve Song (2026), yapay zekâ destekli sanal gerçeklik uygulamalarının ruh sağlığı eğitimini destekleyerek stres yönetimine katkı sağladığını bildirmiştir. Albikawi ve diğerleri (2025)'nin çalışması, hemşirelik öğrencilerinin yapay zekâ destekli ruh sağlığı uygulamalarına yönelik algılarının genel olarak olumlu olduğunu göstermiştir. Ayrıca, Tuncer ve Çetinkaya Duman (2025) ise psikiyatri hemşirelerinin yapay zekâyı bakım süreçlerini destekleyen yararlı bir araç olarak değerlendirmekle birlikte empati, terapötik ilişki ve klinik yargının yerini alamayacağını vurgulamıştır.
Sonuç: Yapay zekâ, psikiyatri hemşireliği bakım süreçlerini desteklemede önemli bir potansiyele sahip olabilir. Ancak klinik uygulamalara güvenli ve etkili biçimde entegre edilebilmesi için etik ve veri güvenliği ilkeleri göz önünde bulundurulmalı, psikiyatri hemşireleri ve farklı örneklemlerde yürütülecek uzun dönemli ve yüksek kaliteli araştırmalarla mevcut kanıtların güçlendirilmesi önerilmektedir.

ABSTRACT

Aim: Artificial intelligence is increasingly being used in mental health services for symptom assessment, risk prediction, clinical decision support, psychoeducation, and personalized care, as well as in the development and implementation of digital therapeutic interventions such as smartphone apps, virtual reality, and AI-powered chatbots (Lu et al., 2026; Reyes et al., 2026; Can Öz and Duran, 2026). The purpose of this review is to evaluate the areas of application of artificial intelligence in psychiatric nursing practice and the effects of these technologies on nursing care in light of the current literature.

Method: This study is a literature-based review. Studies published in the last five years regarding the use of artificial intelligence in psychiatric nursing were searched in databases such as PubMed and Google Scholar using the keywords "artificial intelligence," "psychiatric nursing," "mental health," and "generative artificial intelligence."

Results: The reviewed studies addressed the benefits and limitations of artificial intelligence in mental health services across various application areas. Auf et al. (2025) reported that while artificial intelligence supports clinical decision-making, early diagnosis, and self-management in mental health services, there are limitations regarding its integration into clinical practice. Similarly, in their study, Reyes et al. (2026) emphasized that AI-supported tools facilitate psychoeducation, emotional support, and stress management. A systematic review indicated that AI-supported cognitive-behavioral therapy applications are effective in reducing symptoms of depression, anxiety, and stress, though data privacy and ethical concerns persist (Ravikrishnan, 2026). Li and Song (2026) reported that AI-supported virtual reality applications contribute to stress management by supporting mental health education. A study by Albikawi et al. (2025) showed that nursing students' perceptions of AI-supported mental health applications were generally positive. Furthermore, Tuncer and Çetinkaya Duman (2025) noted that while psychiatric nurses view AI as a useful tool to support care processes, they emphasized that it cannot replace empathy, the therapeutic relationship, or clinical judgment.
Conclusion: Artificial intelligence may hold significant potential for supporting psychiatric nursing care processes. However, to ensure its safe and effective integration into clinical practice, ethical and data security principles must be taken into account; it is recommended that psychiatric nurses and long-term, high-quality research conducted across diverse samples be used to strengthen the existing evidence.

1. GİRİŞ

Ruh sağlığı, Dünya Sağlık Örgütü (2026)'ne göre bireyin yaşamın olağan stresleriyle başa çıkabilmesini, kendi yeteneklerini fark edebilmesini, öğrenebilmesini, çalışabilmesini ve içinde yaşadığı topluma katkıda bulunabilmesini sağlayan bir iyilik hâli olarak tanımlanmaktadır. Ruh sağlığı yalnızca ruhsal bir bozukluğun bulunmaması ile sınırlı olmayıp bireyin işlevselliği ve genel iyilik hâli açısından önemli olabilir (WHO, 2026). Bireysel özelliklerin yanı sıra yoksulluk, şiddet, eşitsizlik ve diğer olumsuz yaşam koşulları da ruh sağlığını etkileyebilmektedir. 2023 yılında, dünya genelinde her 7 kişiden yaklaşık 1'i (1,2 milyar) bir ruhsal bozuklukla yaşıyordu ve en yaygın olanları anksiyete ve depresyon bozukluklarıdır (WHO, 2025). Ancak, bu verilere göre, etkili tedavi ve yaklaşımlar mevcut olsa da hala ruh sağlığı hizmetlerine erişim oldukça sınırlı olabilmektedir. Teknolojik gelişmeler bu hizmetlere erişim gereksiniminin karşılanmasında ve ruh sağlığı hizmetlerinin gelişmesinde önemli olabilir (Yıldız, 2025). Dijital sağlık uygulamaları, telepsikiyatri, mobil sağlık uygulamaları, giyilebilir teknolojiler, sanal gerçeklik ve yapay zeka destekli sistemler aracılığıyla ruh sağlığı hizmetlerinin kapsamlı ve daha erişilebilir olmasını destekleyebilir (Yıldız, 2025; Han, 2025).

Yapay zeka, makine öğrenmesi, doğal dil işleme ve derin öğrenme gibi yöntemleri kullanarak büyük miktardaki verilerin analiz edilmesini ve bu verilerden örüntülerin belirlenmesini sağlayan teknolojileri kapsamaktadır. Ayrıca sağlık hizmetlerinde klinik karar desteği, hasta izlemi, risk tahmini, dokümantasyon ve kişiselleştirilmiş bakım gibi farklı amaçlarla kullanılabilmektedir (Mahmoudi & Moradi, 2024). Nitekim, Dünya Sağlık Örgütü, sağlıkta yapay zekanın güvenli, etik ve eşitlikçi bir biçimde kullanılmasını ve uygun yönetişim ile düzenleme mekanizmalarıyla desteklenmesini önermektedir (WHO, 2024). Ruh sağlığı alanında yapay zeka, tarama, tanı, tedavi planlaması, semptom izlemi ve terapötik destek gibi bakımın farklı aşamalarında kullanılmaktadır (Odame ve diğerleri, 2026). Makine öğrenmesi risk örüntülerinin ve ruhsal sağlık sonuçlarının tahmin edilmesinde kullanılabilirken, doğal dil işleme yazılı ve sözlü ifadeler üzerinden duygusal ve bilişsel semptomların belirlenmesini destekleyebilmektedir. Giyilebilir ve mobil yapay zeka sistemleri ise özellikle stres ve davranış gibi değişkenlerin sürekli izlenmesine olanak sağlayabilir (Odame ve diğerleri, 2026).

Psikiyatri hemşireliği, bu teknolojik dönüşümden doğrudan etkilenen alanlardan biridir (Li ve diğerleri, 2024). Psikiyatri hemşirelerinin bakım süreçlerinde ruhsal durum değerlendirmesi, risk değerlendirmesi, semptom izlemi, psikoeğitim, terapötik iletişim, kriz yönetimi, ilaç yönetimi ve bakımın sürekliliğinin sağlanması gibi sorumlulukları yer almaktadır (Nashwan ve diğerleri, 2023). Yapay zeka bu süreçlerde hemşirenin veri analizi ve karar verme kapasitesini destekleyebilirken, psikiyatri hemşireliğinin ilişki temelli yapısı nedeniyle teknolojinin insan bakımının yerine geçmemesi gerekmektedir (Yıldız, 2025). Li ve diğerleri, (2024), psikiyatri hemşireliğinde yapay zekanın kişiselleştirilmiş bakım, semptom izleme, risk değerlendirmesi, hasta sonuçlarının geliştirilmesi, hemşirelik eğitimi, klinik yönetim, duygusal destek ve nüks yönetimi gibi çeşitli alanlarda kullanıldığını bildirmiştir. Bu durum, yapay zekanın psikiyatri hemşireliği açısından tek bir uygulama alanıyla sınırlı olmadığını ve bakım sürecinin farklı aşamalarında değerlendirilebileceğini gösterebilir.

Ancak ruh sağlığı alanında yapay zeka kullanımının kendine özgü sınırlılıkları bulunmaktadır (Dong ve diğerleri, 2026). Ruhsal bozuklukların psikolojik, sosyal ve bağlamsal boyutlarının yüksek düzeyde öznel olması, bu alanın yapay zeka açısından fiziksel sağlık alanlarına kıyasla daha karmaşık olmasına neden olmaktadır (Dong ve diğerleri, 2026). Veri gizliliği, algoritmik yanlılık, şeffaflık, yanlış bilgi, klinik sorumluluk ve insan merkezli bakımın korunması da önemli sorun alanlarını oluşturmaktadır (Han, 2025; Olla, 2025; Solaiman ve diğerleri, 2023). Bu doğrultuda, bu derlemenin amacı psikiyatri hemşireliği uygulamalarında yapay zekanın kullanım alanlarını, hemşirelik bakımına sağlayabileceği katkıları ve yapay zeka kullanımının klinik, etik, hukuki ve mesleki sınırlılıklarını güncel literatür doğrultusunda değerlendirmektir.

2.TARTIŞMA

2.1 Psikiyatri Hemşireliğinde Yapay Zekanın Kullanım Alanları

2.1.1 Klinik Değerlendirme ve Klinik Karar Desteği

Psikiyatri hemşireliğinde klinik değerlendirme, bireyin görünümü, davranışı, konuşması, duygudurum ve duygulanımı, düşünce süreçleri, algı, bilişsel işlevleri, içgörüsü ve yargılama kapasitesinin birlikte değerlendirilmesini gerektirmektedir (Tuncer ve diğerleri, 2026). Yapay zekâ farklı kaynaklardan elde edilen klinik verileri analiz ederek hemşirenin değerlendirme ve karar verme sürecine destek olabilmektedir (Mahmoudi & Moradi, 2024). Yapay zekâ destekli karar sistemleri elektronik sağlık kayıtları, klinik belirtiler ve davranışsal veriler gibi farklı veri kaynaklarını bir araya getirerek klinik kararların desteklenmesini sağlayabilmektedir (Dong ve diğerleri,). Psikiyatri hemşirelerinin görüşlerini inceleyen Dong ve diğerleri, (2026), hemşirelerin yapay zekânın büyük veri analizi aracılığıyla karmaşık vakalarda karar desteği sunabileceğini ve bakım planlarının daha bireyselleştirilmesine katkıda bulunabileceğini düşündüklerini göstermiştir. Auf ve diğerleri, (2025) tarafından gerçekleştirilen kapsamlandırma çalışmasında yapay zekânın ruh sağlığı hizmetlerinde karar destek amacıyla kullanılmasına ilişkin çalışmalar incelenmiş ve yapay zekânın erken tanılama, tanı, tedavi ve öz bakım alanlarında karar destek potansiyeline sahip olduğu gösterilmiştir. Auf ve diğerleri, (2025) tarafından genç yetişkin ruh sağlığı alanındaki sağlık profesyonellerinin görüşlerini inceleyen başka bir çalışmada ise yapay zekânın kişiselleştirilmiş bakım ve karar desteğinde fırsatlar sunduğu, ancak güven, kapsayıcılık ve klinik iş akışına entegrasyon gibi sorunların devam ettiği belirtilmiştir. Klinik karar desteğinin önemli bir kullanım alanı hemşirelik bakım planlarının oluşturulmasıdır (Li ve diğerleri, 2024). Bununla birlikte Woodnutt ve diğerleri, (2024), ChatGPT tarafından oluşturulan ruh sağlığı hemşireliği bakım planının ilk bakışta uygun görünmesine karşın klinik açıdan önemli hatalar ve etik sorunlar içerdiğini göstermiştir. Bu nedenle yapay zeka tarafından oluşturulan bakım önerilerinin doğrudan uygulanmadan önce sağlık profesyonelleri tarafından doğrulanması gerekmektedir (Woodnutt ve diğerleri, 2024).

2.1.2 Erken tanılama ve risk değerlendirmesi

Erken tanılama ve risk değerlendirmesinde yapay zeka, depresyon, anksiyete, stres, travma sonrası stres bozukluğu ve intihar düşüncesi gibi durumların erken belirlenmesi ve risk sınıflandırılmasında kullanılabilmekte, makine öğrenmesi modelleri klinik verilerdeki örüntülerden yararlanarak ruhsal sonuçların ortaya çıkma olasılığını tahmin edebilmektedir (Odame ve diğerleri, 2026). Doğal dil işleme ise hastaların yazılı veya sözlü ifadelerindeki dilsel ve duygusal değişikliklerin analiz edilmesini sağlayabilmektedir (Han, 2025). Psikiyatri servislerinde şiddet riskinin öngörülmesi de psikiyatride önemli alanlardan biri olabilir (Li ve diğerleri, 2024). Nitekim, Hu ve diğerleri, (2023) tarafından elektronik hemşirelik kayıtları kullanılarak gerçekleştirilen çalışmada, metin madenciliği ve makine öğrenmesi yöntemleri ile psikiyatri hastalarında şiddet davranışının tahmin edilmesine yönelik bir model geliştirilmiştir. Şiddetin yanı sıra psikiyatri tanılı bireylerde önemli konulardan biri olan intihar riski de yapay zekanın önemli ancak yüksek riskli kullanım alanlarından biridir (Odame ve diğerleri, 2026). Nitekim, Kim ve diğerleri (2023) kırsal bölgelerde yaşayan yaşlı bireylerde gerçekleştirilen çalışmada makine öğrenmesi yöntemleriyle intihar düşüncesi açısından yüksek riskli grubun belirlenmesine yönelik tahmin modeli geliştirilmiştir. Bu tür sistemlerin psikiyatri hemşiresine temel katkısı, olası risk durumlarına ilişkin erken uyarı sağlayabilmesidir (Kim ve diğerleri, 2023;Dong ve diğerleri, 2026). Ancak özellikle, intihar ve ciddi şiddet riski gibi durumlarda sürekli insan gözetimi ve profesyonel klinik değerlendirme gerekebilir (Odame ve diğerleri, 2026).

2.1.3 Semptom izleme ve uzaktan hasta izlemi

Ruhsal bozuklukların çoğu zaman değişken bir seyir göstermesi nedeniyle semptomların zaman içindeki değişimlerinin izlenmesi psikiyatri hemşireliği bakımının önemli bileşenlerinden biridir (Li ve diğerleri, 2024). Yapay zekâ destekli mobil uygulamalar, giyilebilir cihazlar ve dijital platformlar bu izlemin sürekliliğini artırabilmektedir (Han, 2025). Giyilebilir cihazlar kalp hızı, uyku, fiziksel aktivite ve diğer fizyolojik göstergeler hakkında sürekli veri sağlayabilmektedir (Mahmoudi & Moradi, 2024). Bu veriler makine öğrenmesi yöntemleriyle analiz edilerek stres veya ruhsal durumdaki değişikliklere ilişkin tahminler oluşturulabilmektedir (Odame ve diğerleri, 2026). Akut psikiyatri servislerinde ise yapay zeka destekli uzaktan izlem, hastaların gece boyunca sensörlerle izlenmesini ve hemşirelik gözlemlerinin hastanın uykusunu daha az bölerek gerçekleştirilmesini sağlayabilmektedir (Barrera ve diğerleri, 2020). Uzaktan izlem ayrıca sağlık hizmetlerine erişimin sınırlı olduğu bölgelerde bakımın sürekliliğini destekleyebilmektedir (Nashwan ve diğerleri, 2023).

2.1.4 Kişiselleştirilmiş bakım ve tedavi

Yapay zekanın psikiyatri hemşireliğindeki temel kullanım alanlarından biri bireyselleştirilmiş bakımın desteklenmesidir (Li ve diğerleri, 2024). Yapay zeka hasta öyküsü, semptomlar, davranışsal veriler ve diğer klinik göstergeleri bir arada değerlendirerek bakım gereksinimlerine ilişkin öneriler oluşturabilmektedir (Dong ve diğerleri, 2026). Nashwan ve diğerleri (2023), yapay zekanın çeşitli veri kaynaklarını analiz ederek belirli bireyler için daha uygun tedavi ve bakım seçeneklerinin belirlenmesini destekleyebileceğini ifade etmektedir. Bununla birlikte bireyselleştirilmiş bakımın yalnızca dijital verilere dayandırılması önemli bir risk oluşturabilir. Yıldız (2026), dijital fenotiplemenin kişinin yaşam öyküsü ve kendi anlatısının önüne geçmesi durumunda "kişiselleştirme"nin bireyin gerçek bakım gereksinimlerini azaltarak yalnızca ölçülebilir göstergelere indirgenebileceğini savunmaktadır. Bu nedenle yapay zeka tarafından kişi için üretilen veriler, hastanın kendi deneyimi, tercihleri ve yaşam öyküsü birlikte değerlendirilmelidir (Yıldız, 2026).

2.1.5 Sohbet robotları, psikoeğitim ve yapay zeka destekli psikososyal müdahaleler

Sohbet robotları ruh sağlığı hizmetlerinde bilgi sağlama, psikoeğitim, stres yönetimi, semptom izlemi ve öz yönetim desteği gibi amaçlarla kullanılabilmektedir (Han, 2025). Reyes ve ark. (2026), yapay zeka destekli uygulamaların stres yönetimi, psikoeğitim ve duygusal desteği destekleyebileceğini bildirmiştir. Yapay zeka destekli bilişsel davranışçı terapi uygulamaları da depresyon, anksiyete ve stres belirtilerinin azaltılmasında umut verici bulunmuştur (Ravikrishnan, 2026). Sohbet robotlarında görülen dilsel akıcılık ve duygusal ifadeler ise gerçek terapötik varlık ile eşdeğer değildir (Yıldız, 2026). Durmuş ve Okanlı (2024), ChatGPT'nin gerçek zamanlı bilgi ve etkileşim sağlayabilmesine karşın insanlara özgü empati, kişilerarası beceri ve insani rehberlik kapasitesine sahip olmadığını vurgulamıştır. Bu nedenle sohbet robotlarının psikoeğitim ve destekleyici uygulamalarda tamamlayıcı araç olarak kullanılması, ancak yüksek riskli klinik durumlarda insan değerlendirmesinin temel unsur olarak korunması gerekmektedir (Han, 2025).

2.1.6. Sanal gerçeklik ve yapay zeka destekli sanal hasta uygulamaları

Sanal gerçeklik ve yapay zeka destekli sanal hasta uygulamaları, özellikle psikiyatri hemşireliği eğitiminde giderek daha fazla kullanılmaktadır. Psikiyatri hemşireliği eğitiminde yapay zeka kullanımına ilişkin yapılan nitel meta-sentezde, öğrencilerin yapay zekanın eğitim süreçlerindeki kullanımına yönelik görüşleri incelenmiştir (Son & Park, 2025). Bu doğrultuda yapay zekâ destekli uygulamaların öğrenme süreçlerini destekleyebileceği, ancak teknolojinin sunduğu olanakların yanı sıra sınırlılıklarının ve etik boyutlarının da dikkate alınması gerektiği vurgulanmıştır (Son & Park, 2025). Psikiyatri hemşireliği öğrencileri açısından sanal hasta uygulamaları, gerçek hastaya zarar verme riski olmadan farklı klinik senaryolarda tekrar tekrar uygulama yapma olanağı sağladığı ve iletişim becerilerini desteklediği bildirilmiştir (Tuncer ve diğerleri, 2026). Li ve Song (2026) tarafından gerçekleştirilen çalışmada yapay zeka ile sanal gerçekliğin psikolojik eğitim ve ruh sağlığı desteğinde bütünleştirilmesi incelenmiş ve yapay zeka destekli sanal gerçeklik grubunun geleneksel öğrenmeye kıyasla bilgi, stres ve katılım gibi sonuçlarda daha olumlu gelişmeler sağlayabildiği bildirilmiştir. Bununla birlikte literatürde sanal ortamlar gerçek hastanın yüz ifadesi, ses tonu, beden dili, spontane tepkileri ve terapötik ilişki dinamiklerini tamamen yansıtamadığı belitrilmektedir (Son & Park, 2025).

Tuncer ve diğerleri (2026) çalışmasında öğrenciler gerçek hastayla yüz yüze görüşmenin farklı olduğunu ve kişinin görünümü ile konuşmasındaki ayrıntıların klinik değerlendirmede önemli ipuçları sağladığını ifade etmiştir. Bu nedenle sanal hasta uygulamaları gerçek klinik deneyimin alternatifi değil, klinik eğitimi destekleyen tamamlayıcı bir araç olarak değerlendirilebilir.

2.1.7. Hemşirelik eğitimi ve yapay zeka okuryazarlığı

Yapay zekânın psikiyatri hemşireliği eğitimindeki kullanım alanları yalnızca öğrenci eğitiminden oluşmamaktadır. Psikiyatri hemşirelerinin yapay zeka konusunda bilgi ve becerilerini geliştirmeleri, teknolojinin güvenli ve etkili biçimde kullanılmasının temel koşullarından biridir (Khalil ve diğerleri, 2025). Bilkay ve diğerleri (2026) tarafından yapılan çalışmada psikiyatri hemşirelerinin bilgi gereksinimleri incelenmiş ve bu gereksinimlerin farmakolojik uygulamalar, psikiyatri bakım süreçleri, psikiyatrik bozukluklar, tedavi ve bakım yaklaşımları, hemşirenin rol ve sorumlulukları ile tıbbi terminoloji olmak üzere altı ana başlıkta toplandığı belirlenmiştir. Aynı çalışmada ChatGPT'nin farmakolojik bilgi ve tıbbi terminoloji alanında daha başarılı olduğu, duygusal etkileşimi yüksek bakım süreçlerinde ise daha sınırlı kaldığı bildirilmiştir (Bilkay ve diğerleri,2026). Khalil ve diğerleri(2025), psikiyatri hastanesinde çalışan hemşirelere yönelik yapılandırılmış yapay zeka eğitiminin hemşirelerin bilgi ve tutumları üzerinde olumlu etkisi olduğunu bildirmiştir. Eğitim programında yapay zekanın temel özelliklerinin yanı sıra chatbotlar, tahmine dayalı analiz, psikiyatrik değerlendirme, bakım planlaması ve etik hukuki sorunlara yer verilmiştir (Khalil ve diğerleri, 2025). Albikawi ve diğerleri (2025), hemşirelik öğrencilerinin yapay zeka destekli ruh sağlığı desteğine ilişkin algılarını incelemiş ve yapay zekanın öğrenciler tarafından ruh sağlığı desteği açısından dikkate değer bir kaynak olarak değerlendirildiğini göstermiştir. Aynı çalışmada öğrencilerin yapay zeka destekli ruh sağlığı araçlarına ilişkin algıları ile profesyonel psikolojik yardım arama tutumları arasındaki ilişkiler değerlendirilmiştir (Albikawi ve diğerleri,2025). Buna göre, psikiyatri hemşireliği eğitiminde yapay zeka okuryazarlığının yalnızca teknik becerileri değil, teknolojinin sınırlarını değerlendirme becerisini de içermesi gerektiği düşünülebilir.

2.1.8 Yapay Zekanın Psikiyatri Hemşireliği Bakımına Katkıları

Yapay zeka, büyük miktardaki veriyi hızlı analiz ederek psikiyatri hemşirelerinin klinik değerlendirme ve erken risk belirleme süreçlerini destekleyebilir (Mahmoudi & Moradi, 2024). Sürekli hasta izlemini destekleyen yapay zeka uygulamaları, semptom, uyku ve davranış değişikliklerine ilişkin veri sağlayabilir (Han, 2025).Yapay zeka destekli sistemler, rutin dokümantasyon ve idari görevleri kolaylaştırarak hemşirelerin iş yükünü azaltabilir (Dong ve diğerleri, 2026). Nitekim yapay zekanın hemşireye zaman kazandırarak hastaların duygusal gereksinimlerine daha fazla odaklanmayı ve bakımın erişilebilirliğini artırmayı sağlayabileceği belirtilmektedir (Nashwan ve diğerleri, 2023). Ayrıca yapay zeka, klinik kararları destekleyen bir araç olarak kullanıldığında hemşirelik bakımının niteliğine katkıda bulunabilir (Yıldız, 2025). Literatürde yapay zekanın klinik karar verme ve erken risk belirlemede hemşirenin kapasitesini destekleyebileceği vurgulanmaktadır (Odame ve diğerleri, 2026).

2.1.9 Yapay Zekanın Sınırlılıkları ve Etik Boyutu

Yapay zekanın psikiyatri hemşireliğinde kullanımı birçok imkanı sunmakla birlikte etik, hukuki, klinik ve mesleki sınırlılıklar içermektedir (Li ve diğerleri, 2024). Özellikle hassas ruh sağlığı verilerinin güvenliği, algoritmik yanlılık, bilgi doğruluğu ve karar süreçlerinin açıklanabilirliği temel sorunlar arasında yer almaktadır (Solaiman ve diğerleri, 2023; Olla, 2025; Odame ve diğerleri, 2026). Yapay zeka tarafından oluşturulan klinik öneri ve bakım planlarının hata içerebilmesi nedeniyle profesyonel bir denetleme gerekmektedir (Bilkay ve diğerleri, 2026; Woodnutt ve diğerleri, 2024). Ayrıca yapay zekanın terapötik ilişki ve insan merkezli bakımın yerini alamayacağı, özellikle kriz ve intihar riski gibi durumlarda hemşirenin klinik yargısının korunması gerektiği vurgulanmaktadır (Durmuş & Okanlı, 2024; Han, 2025; Yıldız, 2026). Bu nedenle yapay zeka, hemşirenin yerini alan değil, klinik karar verme, veri analizi ve dokümantasyon süreçlerini destekleyen bir araç olarak kullanılabilir (Dong ve diğerleri, 2026).

3. SONUÇ VE ÖNERİLER

Yapay zeka, psikiyatri hemşireliğinde erken risk belirleme, klinik değerlendirme, semptom izleme, kişiselleştirilmiş bakım, psikoeğitim, uzaktan hasta izlemi ve hemşirelik eğitimine birçok katkı sunabilir (Li ve diğerleri, 2024; Odame ve diğerleri, 2026).

Özellikle sohbet robotları, dijital uygulamalar, sanal hastalar ve sanal gerçeklik teknolojileri, psikoeğitim, öz yönetim ve klinik eğitim süreçlerini destekleme açısından umut verici sonuçlar ortaya koymaktadır (Reyes ve diğerleri, 2026; Son & Park, 2025; Tuncer ve diğerleri, 2026). Bununla birlikte, yapay zeka çıktılarının doğruluğunun her durumda geçerli ve kesin olamaması, veri gizliliği, algoritmik yanlılık, açıklanabilirlik ve klinik sorumluluk gibi konular güvenli kullanım açısından önemli sınırlılıklar oluşturmaktadır (Solaiman ve diğerleri, 2023; Bilkay ve diğerleri, 2026; Odame ve diğerleri, 2026). Yapay zekanın psikiyatri hemşireliğine entegrasyonunda temel ilke, teknolojinin terapötik ilişkinin ve insan merkezli bakımın yerine geçmemesi olabilir (Yıldız, 2025; Yıldız, 2026). Bireyin öznel deneyimleri, yaşam öyküsü ve tercihleri klinik değerlendirmede korunmalı; özellikle intihar, kendine zarar verme ve şiddet riski gibi yüksek riskli durumlarda yapay zekâ çıktıları bağımsız bir karar mekanizması olarak kullanılmamalıdır (Odame ve diğerleri, 2026). Bu doğrultuda psikiyatri hemşirelerinin yapay zekâ okuryazarlığının geliştirilmesi ve algoritmik yanlılık, veri güvenliği, etik ilkeler ve çıktıların klinik doğrulanmasına yönelik yetkinliklerin eğitim programlarına dâhil edilmesi önerilmektedir (Khalil ve diğerleri, 2025; Son & Park, 2025). Gelecek araştırmalarda yapay zeka uygulamalarının farklı kültürel ve klinik gruplardaki etkinliği, güvenilirliği ve eşitlik üzerindeki etkileri gerçek klinik ortamlarda incelenmesi önerilebilir (Li ve diğerleri, 2024; Odame ve diğerleri, 2026). Ayrıca hasta güveni, özerklik ve terapötik ilişki gibi hasta merkezli sonuçların değerlendirilmesi önemli olabilir (Yıldız, 2026).

Sonuç olarak yapay zekanın psikiyatri hemşireliğinde kullanımı, hemşirenin klinik yargısı ve etik sorumluluğu ile bütünleştirilmelidir. İnsan denetimini temel alan bakım modelleri, teknolojik olanaklardan yararlanırken insan merkezli bakımın korunması açısından uygun bir yaklaşım sunabileceği düşünülmektedir.

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ERGENLİK DÖNEMİNDE SIK GÖRÜLEN RUHSAL BOZUKLUKLARDA HEMŞİRELİK YAKLAŞIMLARINA GÜNCEL KANITLAR DOĞRULTUSUNDA İNCELENMESİ

EXAMINATION OF NURSING APPROACHES TO COMMON MENTAL DISORDERS IN ADOLESCENCE IN LIGHT OF CURRENT EVIDENCE

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Amaç
Ergenlik dönemi, biyopsikososyal değişimlerin yoğun olarak yaşandığı ve ruhsal bozuklukların sıklıkla ilk kez ortaya çıktığı kritik bir gelişim dönemidir. Dünya Sağlık Örgütü (DSÖ), dünya genelinde her yedi ergenden birinin ruhsal bozukluk yaşadığını; depresyon, anksiyete ve davranış bozukluklarının ergenlerde hastalık yükünün başlıca nedenleri arasında yer aldığını bildirmektedir. Ayrıca intihar, 15–29 yaş grubunda önde gelen ölüm nedenlerinden biridir (WHO, 2024). Ergenlik döneminde en sık görülen ruhsal bozukluklar arasında depresyon, anksiyete bozuklukları, dikkat eksikliği ve hiperaktivite bozukluğu, yeme bozuklukları ve madde kullanım bozuklukları yer almakta olup, erken tanı ve uygun hemşirelik girişimleri uzun dönem ruh sağlığı sonuçlarının iyileştirilmesinde kritik öneme sahiptir. (National Institute for Health and Care Excellence, 2022). Bu bildirinin amacı, ergenlik döneminde sık görülen ruhsal bozukluklarda güncel hemşirelik yaklaşımlarını kanıta dayalı literatür doğrultusunda değerlendirmektir.

Yöntem
Bu derleme çalışmasında PubMed, Scopus, Web of Science, CINAHL ve Google Scholar veri tabanlarında 2020–2026 yılları arasında yayımlanan ulusal ve uluslararası çalışmalar incelenmiştir. İnceleme kapsamında ergen ruh sağlığı, psikiyatri hemşireliği, depresyon, anksiyete, dikkat eksikliği ve hiperaktivite bozukluğu, yeme bozuklukları ve hemşirelik girişimlerine ilişkin sistematik derlemeler, meta-analizler, randomize kontrollü çalışmalar ve güncel klinik rehberler değerlendirilmiştir.

Bulgular
Güncel kanıtlar, psikiyatri hemşirelerinin ergen ruh sağlığının korunması ve geliştirilmesinde önemli rol üstlendiğini göstermektedir. Hemşire liderliğinde yürütülen ruh sağlığı taramaları, psikoeğitim, bilişsel davranışçı terapi temelli girişimler, aile merkezli bakım, okul temelli ruh sağlığı programları, stres yönetimi ve duygu düzenleme becerilerinin geliştirilmesine yönelik uygulamalar depresyon ve anksiyete belirtilerini azaltmakta, psikolojik iyi oluşu ve tedaviye uyumu artırmaktadır. Ayrıca intihar riskinin erken değerlendirilmesi ile okul temelli tele-ruh sağlığı uygulamalarının bakımın sürekliliğini desteklediği ve ruh sağlığı hizmetlerine erişimi kolaylaştırdığı bildirilmektedir (Gray et al., 2024; Wang et al., 2024; García-Fernández et al., 2024).

Sonuç
Ergenlik döneminde görülen ruhsal bozuklukların erken dönemde belirlenmesi ve kanıta dayalı hemşirelik girişimleriyle yönetilmesi, ruh sağlığının korunması ve geliştirilmesinde önemli rol oynamaktadır. Hemşire liderliğinde yürütülen tarama programları, psikoeğitim uygulamaları, aile katılımının desteklenmesi ve okul temelli ruh sağlığı hizmetlerinin yaygınlaştırılması; ergenlerin psikolojik iyilik hâlinin artırılması, riskli davranışların azaltılması ve yaşam kalitesinin geliştirilmesine katkı sağlayacaktır. Bu doğrultuda çocuk ve ergen ruh sağlığı hizmetlerinde multidisipliner ekip yaklaşımının güçlendirilmesi ve kanıta dayalı hemşirelik uygulamalarının yaygınlaştırılması önerilmektedir.
Anahtar Kelimeler: Ergenlik, Ruhsal Bozukluklar, Psikiyatri Hemşireliği, Ruh Sağlığı, Hemşirelik Girişimleri.

Abstract

Aim: Adolescence is a critical developmental period characterized by intense biopsychosocial changes, during which mental disorders frequently emerge for the first time. The World Health Organization (WHO) reports that one in every seven adolescents worldwide experiences a mental disorder; depression, anxiety, and behavioral disorders are among the leading causes of disease burden in adolescents. In addition, suicide is one of the leading causes of death among individuals aged 15–29 years (WHO, 2024). The most common mental disorders during adolescence include depression, anxiety disorders, attention-deficit/hyperactivity disorder, eating disorders, and substance use disorders, and early diagnosis and appropriate nursing interventions are of critical importance in improving long-term mental health outcomes (National Institute for Health and Care Excellence, 2022). The aim of this paper is to evaluate current nursing approaches to common mental disorders during adolescence in line with evidence-based literature.

Method

In this review study, national and international studies published between 2020 and 2026 were examined in the PubMed, Scopus, Web of Science, CINAHL, and Google Scholar databases. Within the scope of the review, systematic reviews, meta-analyses, randomized controlled trials, and current clinical guidelines related to adolescent mental health, psychiatric nursing, depression, anxiety, attention-deficit/hyperactivity disorder, eating disorders, and nursing interventions were evaluated.**Results:** Current evidence indicates that psychiatric nurses play an important role in protecting and promoting adolescent mental health. Nurse-led mental health screenings, psychoeducation, cognitive behavioral therapy-based interventions, family-centered care, school-based mental health programs, and interventions aimed at improving stress management and emotion regulation skills reduce symptoms of depression and anxiety while improving psychological well-being and treatment adherence. In addition, early assessment of suicide risk and school-based tele-mental health practices have been reported to support continuity of care and facilitate access to mental health services (Gray et al., 2024; Wang et al., 2024; García-Fernández et al., 2024).

Conclusion

Early identification of mental disorders occurring during adolescence and their management through evidence-based nursing interventions play an important role in protecting and promoting mental health. Expanding nurse-led screening programs, psychoeducation practices, support for family involvement, and school-based mental health services will contribute to improving adolescents' psychological well-being, reducing risky behaviors, and enhancing quality of life. Accordingly, strengthening the multidisciplinary team approach in child and adolescent mental health services and expanding evidence-based nursing practices are recommended.

Keywords: Adolescence, Mental Disorders, Psychiatric Nursing, Mental Health, Nursing Interventions.

1.GİRİŞ

Ergenlik, bireyin fiziksel gelişiminin yanı sıra bilişsel, duygusal ve sosyal açıdan da önemli dönüşümler geçirdiği bir gelişim evresidir. Dünya Sağlık Örgütü (DSÖ)'nün tanımına göre adölesan dönem 10-19 yaş aralığı olarak tanımlanmaktadır. Küresel veriler, ergenlerin yaklaşık %15–20'sinde ruhsal bozukluk görüldüğünü ve ruhsal bozuklukların yaklaşık %34,6'sının 14 yaşından önce, %48,4'ünün ise 18 yaşından önce başladığını göstermektedir (Grgić, 2023; Solmi ve diğerleri, 2022). Kimlik oluşumu ve benlik algısının şekillenmesi bu dönemin temel özellikleri arasında yer alırken, ruhsal bozuklukların ilk belirtileri de sıklıkla bu süreçte ortaya çıkmaktadır (Uygun, 2025). Tanı konulan bu bozuklukların %40'ını depresyon ve anksiyete oluşturmakta, bunu dikkat eksikliği ve hiperaktivite bozukluğu (DEHB), davranış bozuklukları, yeme bozuklukları, psikotik bozukluklar ve madde kullanım bozuklukları izlemektedir (Ruiz-Ranz ve Asín-Izquierdo, 2025). Çocuk ve ergenlerde psikiyatrik sorunların yaygın görülmesi ve birden fazla bozukluğun aynı bireyde eş zamanlı bulunabilmesi, değerlendirme ve tedavi süreçlerini daha karmaşık hâle getirmektedir. Bu nedenle ergenlik, ruhsal sorunların erken fark edilmesi, risklerin belirlenmesi ve uygun müdahalelerin planlanması bakımından önemli bir dönem olarak kabul edilmektedir (Uygun, 2025; Aydın & Karabekiroğlu,2018.). Ergenlerde görülen ruhsal sorunların değerlendirilmesinde gelişimsel özelliklerin dikkate alınması gerekmektedir.

Depresyon ve anksiyete gibi bozuklukların belirtileri ergenlerde erişkinlerden farklı biçimlerde görülebilmekte; duygu durum değişikliklerinin yanında sosyal geri çekilme, okul işlevselliğinde bozulma ve davranış değişiklikleri de ortaya çıkabilmektedir (NICE, 2019). Bu nedenle ergenin yalnızca belirti düzeyinin değil, belirtilerin günlük yaşam üzerindeki etkisinin de değerlendirilmesi önemli olabilir (NICE, 2019).

Özellikle ruhsal belirtilere eşlik edebilen intihar düşüncesi ve kendine zarar verme davranışları, ergen ruh sağlığı açısından öncelikli değerlendirme alanları arasında yer almaktadır. Richardson ve diğerleri (2024) tarafından gerçekleştirilen kapsamlı derleme ve meta-analizde, ergenlerde kendine zarar verme ve intihar davranışlarıyla ilişkili çok sayıda bireysel, ilişkisel ve çevresel risk faktörü belirlenmiştir. Çalışmada özellikle zorbalığa maruz kalma, uyku sorunları ve okul devamsızlığı gibi faktörlerin yanı sıra önceki kendine zarar verme ve ruhsal bozukluk öyküsünün önemli risk göstergeleri arasında olduğu bildirilmiştir (Richardson ve diğerleri, 2024). Bu bulgular, ergen ruh sağlığı değerlendirmesinde bireyin yalnızca mevcut ruhsal belirtilerinin değil, içinde bulunduğu sosyal ve çevresel koşulların da ele alınması gerektiğini gösterebilir (Richardson ve diğerleri, 2024). Bu nedenle ergen ruh sağlığı hizmetlerinde hemşirelik yaklaşımının yalnızca hastalık belirtilerinin izlenmesiyle sınırlandırılmaması gerekebilir. Bu kapsamlı değerlendirme, ruhsal risklerin erken fark edilmesine ve uygun hemşirelik girişimlerinin planlanmasına katkı sağlayabilir. Ergenin bireysel özellikleri, aile ilişkileri, okul yaşantısı, akran ilişkileri ve psikososyal çevresi birlikte değerlendirilmelidir (Richardson ve diğerleri, 2024). Özellikle okul ortamında yürütülen koruyucu ve önleyici uygulamalar, ruhsal risklerin erken fark edilmesi açısından önemli olabilir. Hemşirelik bakımı, ergenin ruhsal durumunun değerlendirilmesi, risklerin erken belirlenmesi, birey ve ailenin desteklenmesi ile uygun sağlık hizmetlerine yönlendirilmesini kapsamaktadır. Hemşireler okul ve sağlık hizmetlerinde ruhsal belirtilerin fark edilmesi, psikoeğitim ve koruyucu önleyici uygulamalarda önemli rol üstlenmektedir (Putkuri ve diğerleri, 2022). Ergen ruh sağlığında erken tanılama ve tarama, ruhsal sorunların zamanında belirlenmesi ve uygun müdahalelerin başlatılması açısından önemlidir. Değerlendirmede ergenin gelişimsel özellikleri ve günlük yaşam işlevselliği dikkate alınmalıdır (NICE, 2019). Psikoeğitim ve okul temelli ruh sağlığı uygulamalarının ise ruh sağlığının geliştirilmesine katkı sağladığı bildirilmektedir (Putkuri ve diğerleri, 2022; Wang ve diğerleri, 2024). Ergenlerde sık görülen ruh sağlığı sorunlarından depresyon ve anksiyete belirtilerinin yönetiminde bilişsel davranışçı terapi temelli uygulamalar olumlu sonuçlar gösterebilmekte ve hemşirelerin multidisipliner ekip içerisinde psikososyal girişimlere katkı sunması önem taşımaktadır (Gray ve diğerleri, 2024). Aile katılımının desteklenmesi de bakımın sürekliliği açısından önemli olabilir (NICE, 2019). İntihar ve kendine zarar verme davranışlarında önceki kendine zarar verme öyküsü, ruhsal bozukluk, zorbalık, okul devamsızlığı ve uyku sorunları gibi risk faktörlerinin birlikte değerlendirilmesi gerekmektedir (Richardson ve diğerleri, 2024). Bu doğrultuda ergen ruh sağlığı hizmetlerinde birey, aile, okul ve sağlık profesyonellerini kapsayan multidisipliner yaklaşımın benimsenmesi önemli olabilir (NICE, 2019; Putkuri ve diğerleri, 2022). Bu derlemede, ergenlik döneminde sık görülen ruhsal bozukluklarda güncel kanıtlar doğrultusunda hemşirelik yaklaşımlarının incelenmesi amaçlanmıştır.

2.TARTIŞMA

2.1. Ergen Ruh Sağlığında Hemşirelik Yaklaşımı

Ergen ruh sağlığı hizmetlerinde hemşirelik yaklaşımının değerlendirme, erken fark etme, psikoeğitim, danışmanlık ve uygun hizmetlere yönlendirme gibi farklı uygulamaları içerebildiği görülmektedir. Okul hemşirelerinin ergenlerle güvene dayalı iletişim kurması ve gerektiğinde diğer profesyonellerle iş birliği yapması, ruhsal sorunların erken fark edilmesini destekleyebilmektedir (Moen ve Jacobsen, 2022; Hoskote ve diğerleri, 2023). Bununla birlikte hemşirelerin ruh sağlığı alanındaki uygulamalarını etkileyebilecek eğitim ve kaynak gereksinimlerinin bulunduğu bildirilmektedir (Hoskote ve diğerleri, 2023). Bu nedenle hemşirelerin ergen ruh sağlığına yönelik bilgi ve uygulama yeterliliklerinin desteklenmesi önemli olabilir.

Ruh sağlığı okuryazarlığının geliştirilmesi de hemşirelik bakımının önemli bir bileşeni olarak değerlendirilebilir. Carvalho ve diğerleri (2022), pozitif ruh sağlığı okuryazarlığının yalnızca ruhsal sorunlara ilişkin bilgiyle sınırlı olmadığını, özdenetim, problem çözme, özerklik ve kişilerarası ilişkiler gibi becerileri de kapsadığını belirtmiştir. Bu doğrultuda psikoeğitim uygulamalarının ergenlerin ruh sağlığı konusunda farkındalıklarını ve baş etme becerilerini destekleyecek şekilde yapılandırılması düşünülebilir.

Bununla birlikte ergenlerin yardım arama davranışları yalnızca ruh sağlığı bilgisiyle açıklanamayabilir. Damgalanma, mahremiyetle ilgili kaygılar ve sorunları bireysel olarak çözme eğilimi, profesyonel destek alma konusunda engel oluşturabilir. Bu nedenle hemşirelik uygulamalarında ergenin kendini güvende ve anlaşılmış hissedebileceği, mahremiyetin gözetildiği iletişim ortamlarının oluşturulması önem taşıyabilir (Helland Lindborg ve diğerleri, 2024).

2.2. Okul Temelli ve Psikososyal Müdahaleler

Okul ortamı, ergenlere ulaşılabilir olması nedeniyle ruh sağlığını geliştirmeye yönelik müdahaleler açısından önemli bir uygulama alanı olarak değerlendirilmektedir. Okul temelli hemşirelik uygulamalarında eğitim, danışmanlık, akran desteği, fiziksel aktivite ve çeşitli psikososyal etkinliklerden yararlanılabildiği bildirilmektedir (Yosep ve diğerleri, 2023). Wang ve diğerleri (2024) tarafından yapılan sistematik derleme de okul temelli transdiagnostik müdahalelerin ruh sağlığı ve duygusal iyi oluşun desteklenmesinde kullanılabileceğini göstermektedir. Duygu düzenleme becerilerinin geliştirilmesi de bu müdahalelerin önemli bir bileşeni olabilir. Helland ve diğerleri (2022), duygu düzenlemeye yönelik müdahalelerde psikoeğitim ve beceri geliştirme içeriklerinin kullanılmasının yararlı olabileceğini bildirmiştir. Bilişsel davranışçı terapi temelli uygulamalar da özellikle okul ortamında kullanılabilecek psikososyal yaklaşımlar arasında yer almaktadır. Gray ve diğerleri (2024), okul ortamında yürütülen bilişsel davranışçı terapi temelli müdahalenin ergenlerin ruhsal belirtilerinin azaltılmasına katkı sağlayabileceğini bildirmiştir. Bu tür uygulamalarda hemşirenin rolü, kendi mesleki yetkinliği ve eğitim sınırları içerisinde psikososyal desteğin sağlanması ve gerektiğinde psikolog veya psikiyatrist gibi diğer profesyonellere yönlendirme yapılması şeklinde ele alınabilir. Okul temelli müdahalelerin bir diğer yönü, ruh sağlığı hizmetlerinin ergenlerin günlük yaşam ortamına taşınmasına imkan sağlaması olabilir. Bununla birlikte müdahalenin süresi, içeriği, uygulayıcının özellikleri ve öğrencilerin bireysel gereksinimleri sonuçları etkileyebileceğinden, bu uygulamaların her ergen için aynı düzeyde sonuç vereceği düşünülmemelidir (Wang ve diğerleri, 2024).

2.3. Zorbalık, İntihar Riski ve Koruyucu Yaklaşımlar

Ergen ruh sağlığının değerlendirilmesinde zorbalık, okul devamsızlığı, uyku sorunları ve önceki kendine zarar verme öyküsü gibi faktörlerin dikkate alınması önem taşımaktadır. Richardson ve diğerleri (2024), zorbalık ve uyku sorunlarının yanı sıra önceki kendine zarar verme ve ruhsal sorun öyküsünün intihar ve kendine zarar verme davranışlarıyla ilişkili olabileceğini bildirmiştir. Bu doğrultuda hemşirelik değerlendirmesinin yalnızca mevcut belirtilere odaklanmaması, ergenin okul yaşantısı, akran ilişkileri, uyku düzeni ve psikososyal çevresini de kapsaması uygun olabilir. Zorbalığın önlenmesine yönelik eğitim ve danışmanlık uygulamalarında hemşirelerin öğretmenler ve ailelerle iş birliği içinde çalışması da önemli olabilir (Yosep, Hikmat ve Mardhiyah, 2023). Siber zorbalığa yönelik hemşire eğitimlerinin ise hemşirelerin farkındalığını artırabildiği bildirilmiştir (Yosep ve diğerleri, 2023). İntihar ve kendine zarar verme riski açısından yalnızca risk faktörlerinin belirlenmesi yeterli olmayabilir, koruyucu faktörlerin de bakım sürecine dahil edilmesi gerekebilir. Richardson ve diğerleri (2024), okul temelli müdahaleler ve yeterli uyku süresini koruyucu faktörler arasında değerlendirmiştir. Bu durum, hemşirelik bakımında risklerin azaltılmasının yanı sıra ergenin okul ile bağının ve sağlıklı yaşam alışkanlıklarının desteklenmesinin de ele alınabileceğini düşündürmektedir.

2.4. Bireyselleştirilmiş ve Multidisipliner Bakım

Ergenlerin ruhsal gereksinimleri farklılık gösterebildiğinden, bakımın bireysel özellikler ve yaşam koşulları dikkate alınarak planlanması gerekebilir. Özellikle travmatik yaşantıları bulunan ergenlerde ruhsal sorunların daha karmaşık ve süreklilik gösterebildiği bildirilmektedir (Bürgin ve diğerleri, 2023). Bu nedenle güvenli iletişim, süreklilik ve uygun profesyonellere yönlendirme önem kazanabilir. İncelenen mevcut çalışmalar, ergen ruh sağlığında hemşirelik bakımının bireysel değerlendirme, psikoeğitim, duygu düzenleme, okul temelli müdahaleler, risk değerlendirmesi ve multidisipliner iş birliğinin birlikte ele alındığı bir yaklaşım içerisinde yürütülebileceğini göstermektedir. Bununla birlikte bazı müdahalelere ilişkin kanıtların sınırlı veya yöntemsel açıdan heterojen olması nedeniyle, elde edilen sonuçların farklı ergen gruplarına genellenmesinde dikkatli olunması gerekmektedir (Pawils ve diğerleri, 2023; Balasooriya Lekamge ve diğerleri, 2025).

3. Sonuç ve Öneriler

İncelenen mevcut kanıtlar, ergen ruh sağlığına yönelik hemşirelik uygulamalarında psikososyal müdahalelerin, okul temelli çalışmaların ve bireyselleştirilmiş izlemin yararlı olabileceğini düşündürmektedir. Bu doğrultuda psikiyatri hemşirelerinin okul temelli ruh sağlığı hizmetlerindeki rolünün güçlendirilmesi, aile katılımının desteklenmesi ve riskli durumlarda düzenli izlemin sürdürülmesi önerilebilir (NICE, 2019; WHO, 2024). Psikoeğitim, duygu düzenleme becerilerinin desteklenmesi ve gerektiğinde multidisipliner ekip ile iş birliği yapılması da hemşirelik bakımının sürekliliğine katkı sağlayabilir. Ayrıca ergenlerin bireysel özellikleri ve içinde bulundukları sosyal çevre dikkate alınarak bakım planlarının kişiselleştirilmesi uygun olabilir. Özellikle intihar düşüncesi, kendine zarar verme ve zorbalık gibi risk durumlarında erken değerlendirme ve uygun yönlendirme süreçlerinin güçlendirilmesi önem taşımaktadır. Okul, aile ve sağlık hizmetleri arasındaki iletişimin geliştirilmesi, ergenlerin ruh sağlığı hizmetlerine erişimini ve bakımın sürekliliğini destekleyebilir (Richardson ve diğerleri, 2024; WHO, 2024).Gelecekte farklı kültürel ve klinik özelliklere sahip ergenlerle yürütülecek uzunlamasına çalışmaların, hemşirelik uygulamalarının etkinliği ve sürdürülebilirliğine ilişkin kanıtların geliştirilmesine katkı sağlayabileceği düşünülmektedir (García-Fernández ve diğerleri, 2024; Wang ve diğerleri, 2024). Ayrıca farklı hemşirelik müdahalelerinin uzun dönem sonuçlarını ve farklı ortamlardaki uygulanabilirliğini değerlendiren çalışmaların yapılması, ergen ruh sağlığı hizmetlerinde kanıta dayalı uygulamaların güçlendirilmesine katkı sağlayabilir.

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HİDRASYON VE VÜCUT BİLEŞİMİ

HYDRATION AND BODY COMPOSITION

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ÖZET

Bireylerin hidrasyon durumu, susuzluk mekanizması, içeceklerin hidrasyon indeksi, bireysel (yaş, cinsiyet, vücut kompozisyonu, sağlık durumu, fiziksel aktivite düzeyi, meslek) ve çevresel faktörlerden (iklim, çalışılan ortam vb) etkilenmektedir ve saptanması oldukça zordur. Literatürde hidrasyon düzeyinin saptanmasında altın standart bir yöntem bulunmayıp, mevcut yöntemlerden en az 2 tanesinin (bazı kan parametreleri, bazı idrar parametleri, dilisyon yöntemi, vücut kütlesi farkı) birlikte kullanımı önerilmektedir. Bireylerde görülen dehidrasyon ve hiperhidrasyon yorgunluk, gerginlik, baş ağrısı, solunum güçlüğü, elektrolit dengesinde bozulma gibi pek çok sağlık sorununa sebep olabilmektedir. Bunun yanında hem dehidrasyon hem de hiperhidrasyon bireylerde tek frekanslı ve çok frekanslı biyoelektrik empedans analizi (BIA), dual-enerji X-ray absorbsiyometri (DXA) vb. ile tahmin edilen vücut kompozisyonu ölçümlerini de etkilemekte yanlış sonuç alınmasına sebep olabilmektedir. Çalışmalar, 500 mL ve daha fazla besin ve içecek tüketiminin ve dehidrasyonun tek ve çok frekanslı BIA, DXA, deri kıvrım kalınlıkları ile saptanan vücut kompozisyonu ölçümlerini etkilediğini, ancak ultrason, hava yer değiştirme pletismografisi, sualtı ağırlık ölçümü yöntemlerini etkilemediğini göstermiştir. Bu etkilerin dirençteki değişikliklerden, ozmotik dengenin bozulmasından, değişen plazma sodyum ve elektrolit konsantrasyonundan, cihaz yazılımında kullanılan tahmin denklemlerinden, bireysel gastrik boşalma hızı farklılıklardan kaynaklanabileceği düşünülmektedir. Hidrasyonun antropometrik ölçümler üzerine karıştırıcı etkilerini engellemek için ölçümlerden önce bireylerin hidrasyon durumlarının saptanması ve cihaz ölçüm kılavuzlarındaki kurallara mutlak uyulmasına dikkat edilmesi doğru sonuçlar alınması için oldukça önemlidir.

Anahtar Kelimeler: Hidrasyon, Vücut Bileşimi, Dehidrasyon

ABSTRACT

The hydration status of individuals is affected by the thirst mechanism, beverages hydration index, individual (age, gender, body composition, health condition, physical activity level, occupation), and environmental factors, so it is difficult to determine. In the literature, there is no gold standard method for determining the level of hydration. Therefore, it is recommended to use at least 2 of the existing methods (blood, urine variables, stable isotope dilution, body mass changes, BIA, and BIVA). Dehydration and hyperhydration may cause many health problems (fatigue, headache, respiratory difficulties, electrolyte imbalance, etc.), as well as it affects predicted body composition measurements from bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). Studies have shown that food and beverage consumption of 500 mL or more and dehydration affect body composition measurements determined by single and multi-frequency BIA, DXA, and skinfold thicknesses, but not ultrasound, air displacement plethysmography, and underwater weighing methods. It is thought that these effects may be caused by changes in resistance, osmotic imbalance, changing plasma sodium and electrolyte concentration, estimation equations used in the device software, and individual gastric emptying rate differences. In order to prevent the confounding effects of hydration on anthropometric measurements, it is recommended to determine the hydration status of individuals before measurements and to comply with the rules in the device measurement guides.

Keywords: Hydration, Body Composition, Dehydration

GİRİŞ

Su, tüm vücut dokularının temel ve en büyük bileşeni olup (yağ hücreleri hariç) vücutta pek çok biyokimyasal reaksiyonun başlaması, sürdürülmesi ve tamamlanması için elzemdir (Je´quier ve Constant, 2010). Bireylerin hidrasyon durumu, susuzluk mekanizması, içeceklerin hidrasyon indeksi, bireysel (yaş, cinsiyet, sağlık durumu, fiziksel aktivite düzeyi, meslek, vücut kompozisyonu vb.) ve çevresel faktörlere (iklim vb.) bağlı olarak değişiklik göstermektedir (Maughan ve ark.,2016). Bireylerin hidrasyon durumunda meydana gelen değişiklikler, sahada ve araştırmalarda mevcut sağlık ve beslenme durumunun saptanmasında, büyüme gelişmenin takibinde ve hastalıkların tayininde belirteç olarak

sıklıkla kullanılan, tek frekanslı ve çok frekanslı biyoelektrik empedans analizi (BIA), dual-enerji X-ray absorbsiyometri (DXA) ile tahmin edilen vücut kompozisyonu ölçümlerini de etkilemektedir (Tinsley ve ark., 2022; Wagner, 2022). Hidrasyon düzeyinin vücut kompozisyonu ölçümleri üzerine karıştırıcı etkisini engellemek, bir başka ifade ile standardizasyonu sağlamak için ölçümden 8 saat önce içecek ve besin alımından, 24 saat önce orta dereceli ve/veya şiddetli fiziksel aktiviteden kaçınılması gerektiği bildirilmiş olsa da pratikte ve çalışmalarda bu prosedüre bağlı kalmak her zaman mümkün değildir (Tinsley ve ark., 2022). Bu doğrultuda araştırmalarda ve sahada ölçümlerden önce bireylerin mevcut hidrasyon durumlarının saptanması, hidrasyon durumunu etkileyen faktörlerin ve bu durumdan kaynaklı ölçümlerde ortaya çıkabilecek hataların bilinmesi sonuçların doğru değerlendirilmesi ve yorumlanması açısından oldukça önemli ve kritiktir (Tinsley ve ark., 2022; Wagner, 2022). Bu derlemede, hidrasyon durumunu etkileyen faktörler (susuzluk mekanizması, yaş, cinsiyet, sağlık durumu, fiziksel aktivite düzeyi, meslek, vücut kompozisyonu) ve hidrasyon durumunun vücut kompozisyonu ölçümleri üzerine etkisi tartışılmıştır.

GELİŞME

Hidrasyon durumunu etkileyen faktörler

Susuzluk mekanizması

Vücut su dengesi, merkezi ve çevresel sinir sistemi aracılığıyla geri besleme mekanizmasıyla düzenlenmektedir (Baron, 2014). Vücut kütlesinin yaklaşık %2 azalması veya plazma osmolalitesinin yaklaşık %2 artması, hipotalamik osmoreseptörleri uyararak hipofizden antidiüretik hormonun (ADH) salınmasına neden olur (Faraco ve ark., 2014). Hiperosmolarite ve ADH birlikte susama hissini artırırken, ADH böbreklerde akuaporin-2 kanallarını aktive ederek suyun geri emilimini artırır ve su kaybını azaltır. Aynı zamanda renin-anjiyotensin-aldosteron sistemi aktive olur; oluşan anjiyotensin II aldosteron salınımını uyararak böbreklerde sodyum ve dolaylı olarak su geri emilimini artırır (Je´quier ve Constant 2010). Böylece plazma ozmotik basıncı normal düzeylerine döner, ADH salınımı baskılanır ve vücut su dengesi korunur. Bu nöroendokrin süreç "susuzluk mekanizması" olarak adlandırılmaktadır (Millard-Stafford ve ark., 2012).

Bireysel faktörler

Yaş, cinsiyet ve vücut kompozisyonu

Vücutta farklı hücre tipleri, farklı miktarda su içermekte olup (bir hepatosit %70 su, bir adiposit %30 oranında su), dokuların su içeriği ve dağılımına bağlı olarak, bireyler arasında vücut su yüzdesi farklılık göstermektedir (Karapanagos, 2014). Kadınlarda vücut yağ kütlesinin erkeklere kıyasla daha fazla olması sebebiyle su miktarı daha az, yaşlı bireylerde ise kas dokusundaki azalma nedeniyle su miktarı yetişkin ve çocuklara kıyasla daha düşüktür (Arnaoutis ve ark., 2017). Yetişkin bir erkek, kadın, yaşlı ve yenidoğanın sırasıyla vücut ağırlığının yaklaşık %63'ü, %50-55'i, %50'si ve %75'i sudur. Vücut su yüzdesi, yağsız kütledeki su miktarının azalması, protein ve mineral içeriğindeki artışa bağlı olarak yaşamın ilk yılından sonra hızlı bir şekilde azalmaya başlar ve ilerleyen yaşla birlikte, intrasellüler ve plazma sıvı miktarı sabit kalırken, ekstrasellüler sıvı miktarı azalır (Karapanagos, 2014).

Fiziksel aktivite düzeyi

Vardiyalı çalışan bireyler, sporcular, madenciler, ağır işçiler ve askeri personel sıvıya erişimlerinin kısıtlı olması, yoğun güç gerektiren ve fiziksel olarak çok aktif oldukları işlerde çalışmaları sebebiyle sıvı alımları daha az ve terle kaybettikleri sıvı miktarları çok daha fazladır (terleme oranlarına ilişkin gözlemler, aktivitenin türüne ve yoğunluğuna bağlı olarak 0,29-2,37 L/s arasında değişmektedir), bu sebeple diğer bireylere kıyasla dehidrasyon açısından daha yüksek risk altındadırlar (Carretero-Krug ve ark., 2021).

Sağlık durumu

Bireylerin sağlık durumları ve kullandıkları ilaçlar da hidrasyon durumlarını etkilemektedir (Taylor ve Jones, 2022). Addison hastalığı, hipoaldosteronizm, hiperglisemi, enfeksiyonlar, yanıklar, pankreatit, astım, kronik obstrüktif akciğer hastalığı, diyabetes mellitus, hipertansiyon, böbrek hastalıkları ve kalp yetmezliği durumlarında deri, böbrekler ve gastrointestinal kanaldan istenmeyen su ve elektrolit kayıpları olmakta, emilim azalmakta ve sonucunda vücutta sıvı dengesi bozulmaktadır (Taylor ve Jones, 2022). Ayrıca hastalıklara bağlı diüretik, sedatif, antipsikotik, trankilizan ve steroid yapıda olmayan antienflamatuar ilaçların kullanımıda dehidrasyon riskini artırmaktadır (Maughan ve ark., 2016).

Ek olarak soğuk algınlığı, grip, boğaz ağrısı ve ateş gibi sağlık sorunlarında dahi susuzluk hissinde azalma, daha az su içme ve daha fazla terle su kaybı nedeniyle dehidrasyon riski artmaktadır (CDC, 2010).

Çevresel faktörler

Bireylerin yaşadığı veya çeşitli nedenlerle bulunduğu çevre de (sıcaklık, nem, yüksek rakım vb.) hidrasyon durumlarını etkileyebilmektedir (Taylor ve Jones, 2022). Deniz seviyesinde ve yüksek sıcaklıklarda yaşayan bireylerde, solunum yoluyla vücuttan su kaybı 500-600 mL/gün'e kadar çıkarken, sıcaklık ve nemin düşük olduğu bölgelerde 200 mL/gün'e kadar düşebilmektedir (EFSA, 2010). Benzer şekilde normal şartlar altında sedanter bir yetişkin terleme ile 0,3 L/sa, su kaybederken yüksek sıcaklık ve fiziksel aktivite durumunda 2,0 L/sa kadar su kaybı görülebilmektedir (Popkin ve ark., 2010). Ek olarak soğuk hava susuzluk hissini baskıladığından bireyler genellikle kış mevsiminde daha az su tüketmektedir (Malisova ve ark., 2013).

Hidrasyon durumunun vücut kompozisyonu ölçümleri üzerine etkisi

Hidrasyon düzeyinde meydana gelen değişikliklerin antropometrik ve laboratuvar yöntemleri kullanılarak tahmin edilen vücut kompozisyonu ölçümlerine etkisi tek ve çok frekanslı BIA, DXA, deri kıvrım kalınlığı ölçümleri için araştırılmıştır (Tinsley ve ark., 2022; Wagner, 2022).

Tek frekanslı biyoelektrik empedans analizi

Kontrollü ve düzenli şekilde akut su (500 mL - 2 L), izotonik salin solüsyonu (1500 mg sodyum içeren, 466 mL), elektrolit içecekleri (Gatorade 591 mL) ve çeşitli besinlerin (sandviç, salata, wrap, cips, çubuk kraker: 3847±900 kJ) tüketimlerinin sağlıklı yetişkinlerde tek frekanslı BIA ile tahmin edilen vücut kompozisyonuna etkilerinin değerlendirildiği çalışmalarda (alım sonrası ölçümlerde; idrar çıkışı olmadan), vücut kütlesi, yağ kütlesi, ekstrasellüler sıvı ve yağ yüzdesi anlamlı şekilde daha yüksek, toplam vücut suyu, intrasellüler sıvı ise olduğundan anlamlı şekilde daha az tahmin edilmiştir (Androutsos ve ark., 2015; Matthews ve Hosick, 2019; Kim ve ark., 2019; Ugras, 2020). Diğer taraftan, tek frekanslı BIA ile gerçekleştirilen bazı çalışmalarda tersi sonuçlarda gözlenmiştir; bir çalışmada 350 mL spor içeceği (Gatorade 350 mL), ve müsli (süt ve mısır gevreği 350 mL) tüketiminin vücut yağ yüzdesi, yağsız vücut kütlesi ve yağ kütlesi ölçümleri üzerinde anlamlı bir etkisi olmadığı (Heiss ve ark., 2008) ve son yıllarda yapılmış bir çalışmada <1500 mL su tüketiminin toplam vücut suyu ve yağsız vücut kütlesi tahminlerinde anlamlı değişiklik yaratmadığını bildirmiştir (Algül ve Özçelik, 2022).

Çok frekanslı biyoelektrik empedans analizi

Hiperhidrasyon ve dehidrasyonun çok frekanslı BIA ölçümlerini nasıl etkilendiğini araştıran çalışmaların sonuçları değişkenlik göstermektedir (Kim ve ark., 2019; Tinsley ve ark., 2022). Bazı çalışmalarda, akut su (531-1360 mL) ve çeşitli besinlerin (sandviç, salata, wrap, cips, çubuk kraker: 3847±900 kJ) tüketimi sonucu görülen hiperhidrasyonun, vücut kütlesi, yağ kütlesi ve yüzdesinin olduğundan fazla, total vücut suyu ve intrasellüler sıvının ise daha az tahmin edilmesine neden olduğu bildirilmiştir (Dixon ve ark., 2013; Tinsley ve ark., 2022). Aynı amaçla yürütülmüş bir başka çalışmada, akut su tüketiminin (500 mL) çok-frekanslı BIA ile saptanan total vücut suyu, ekstrasellüler ve intrasellüler sıvı ölçümlerini değiştirmediği belirlenmiştir (Kim ve ark., 2019). Dehidrasyon durumunun (%2 ve %3 vücut kütlesi kaybı) çok frekanslı-BIA'dan elde edilen vücut kompozisyonu ölçümlerine etkisini inceleyen çalışmalarda toplam vücut suyu, intrasellüler su ve yağsız vücut kütlesi ölçümlerinin dehidrasyondan etkilenmediği (Utter ve ark., 2012; Wagner, 2022) ancak vücut kütlesi ve yağ yüzdesinin önemli ölçüde azaldığı bildirilmiştir (Wagner, 2022).

Dual-Enerji X-ray absorbsiyometri (DXA)

Dual-enerji x-ray absorbsiyometri ölçümü çalışmalarda kemik mineral yoğunluğunun, yağsız yumuşak dokunun ve yağ kütlesinin saptanmasında sıklıkla kullanılmaktadır (Ong ve ark., 2022). Mevcut çalışmalar 500 mL'den daha az akut sıvı ve besin alımının (spor içeceği; Gatorade 350 mL ve müsli; süt ve mısır gevreği 350 mL) DXA'ile saptanan vücut yağ yüzdesi, yağsız vücut kütlesi ve yağ kütlesi ölçümlerini etkilemediğini göstermiştir (Kerr ve ark., 2017; Ong ve ark., 2022). Diğer taraftan, 500 mL ve daha fazla besin ve içecek (800-2400 mL karışık bir öğün, 500 mL müsli; yulaf ve süt ve içecek; 500 mL su) tüketiminin DXA ile belirlenen kemik mineral yoğunluğunu ve vücut yağ kütlesi ölçümlerini etkilemediği, ancak yağsız vücut kütlesinin daha fazla, yağ yüzdesinin ise daha az tahmin edilmesine

neden olduğu belirlenmiştir (Barreira ve Tseh, 2020; Ong ve ark., 2022). Dehidrasyonun (egzersiz ve ısı stresi kaynaklı %2 vücut kütlesi kaybı) DXA'dan tahmin edilen vücut kompozisyonu üzerine etkisini inceleyen bir çalışmada, toplam doku kütlesinde ve yağsız doku kütlesinde anlamlı bir azalma, gövde yağ yüzdesinde ise artış saptanmıştır (Rodriguez-Sanchez N ve Galloway, 2015). Başka çalışmalarda ise, dehidrasyon nedeniyle (sıvı kısıtlaması 1 günde 600–700 mL sıvı ve (ısı stresi ve egzersizle vücut kütlesinde %2,5 azalma) toplam ve gövde yağsız kütlesinde azalma görülürken, toplam ve bölgesel yağ kütlesi, kemik mineral yoğunluğu müdahalelerden etkilenmemiştir (Toomey ve ark., 2017; Ong ve ark., 2022).

Deri kıvrım kalınlığı ölçümleri

Mevcut çalışmalarda yalnızca dehidrasyonun deri kıvrım kalınlığı ölçümlerine etkisi incelenmiştir (Rodriguez-Sanchez ve Galloway, 2015; Liang ve ark., 2022). Önceki yıllarda yapılmış bir çalışmada, dehidrasyonun (egzersiz ve ısı stresi kaynaklı %2'lik vücut kütlesi kaybı) dokuların elastikiyetini ve sıkıştırılabilirliğini etkileyerek deri kıvrım kalınlıkları toplamını azalttığı (triceps, subscapular, biceps, iliac crest, supraspinale, abdominal, front thigh and medial calf) saptanmıştır (Rodriguez-Sanchez ve Galloway, 2015). Son yıllarda yapılan bir çalışmada ise dehidrasyonun (egzersizle %1.5 vücut kütlesi kaybı) deri kıvrım kalınlığı ölçümleri üzerine (triceps, subscapular, pektoral, midaxiller, suprailiac oblik, abdominal ve ön uyluk) bir etkisinin olmadığı belirlenmiştir (Liang ve ark., 2022).

Sonuç

Bireylerin hidrasyon durumu, susuzluk mekanizması, bireysel faktörler (yaş, cinsiyet, sağlık durumu, fiziksel aktivite düzeyi, meslek, vücut kompozisyonu vb.), çevresel faktörler (iklim, sıcaklık vb.) gibi pek çok karıştırıcı faktöre bağlı olarak değişiklik göstermektedir. Bu sebeple saptanması da oldukça zordur. Hidrasyon durumunda meydana gelen değişiklikler antropometrik ölçümler ve laboratuvar yöntemleriyle tahmin edilen vücut kompozisyonu ölçümlerini etkilemektedir. Çalışmalar 500 mL ve daha fazla besin ve içecek tüketiminin ve dehidrasyonun tek ve çok frekanslı BIA, DXA, deri kıvrım kalınlıkları ile saptanan vücut kompozisyonu ölçümlerini etkilediğini göstermiştir. Akut besin, içecek alımı ve dehidrasyona bağlı vücut kompozisyonu analizlerindeki yanlışlıkların, dirençteki değişikliklerden, ozmotik dengenin bozulmasından, değişen plazma sodyum ve elektrolit konsantrasyonundan, cihaz yazılımında kullanılan tahmin denklemlerinden, bireysel gastrik boşalma hızı, idrara çıkma ve gözlem süresindeki farklılıklardan kaynaklandığı düşünülmektedir. Bu doğrultuda dehidrate ve hiperhidrate bireyler için cihazlarda kullanılacak özel denklemlerin geliştirilmesi fayda sağlayacaktır. Ek olarak yürütülen çalışmalarda hidrasyonun antropometrik ölçümler üzerine karıştırıcı etkilerini engellemek için ölçümlerden önce bireylerin hidrasyon durumlarının saptanması ve kılavuzlarda önerilen (ölçümü öncesi 8 saat açlık ve 24 saat fiziksel aktivite yapmama vb) kurallara uyulması ölçüm yanlışlıklarını önleyecektir.

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THE ROLE OF FORENSIC MEDICINE AND PSYCHIATRY IN IDENTIFYING AND DOCUMENTING FORCED MARRIAGE

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ABSTRACT
Forced marriage, classified by the World Health Organisation in 2024 as a form of gender-based violence, requires specialized forensic and psychiatric assessment for accurate identification and legal documentation. Despite recent legislative developments, including Directive EU 2024/1385 which mandates criminalisation of forced marriage as a standalone offence, and Law No. 252/2025 in the Republic of Moldova, healthcare and judicial systems remain inadequately equipped with standardised protocols for evidence collection and trauma assessment. This article examines the clinical and forensic indicators of forced marriage, including physical markers of intimate partner violence, reproductive coercion, and psychological sequelae consistent with complex trauma and coercive control. The framework established by the Istanbul Convention Article 33 and reinforced by GREVIO's 2023 baseline evaluation of Moldova emphasises the necessity of trauma-informed approaches in forensic examination and psychiatric evaluation. The article identifies critical gaps in current practice: the absence of standardised forensic protocols for documenting coercive control mechanisms, insufficient psychiatric expertise in recognising complex trauma presentations specific to forced marriage, and poor coordination between medical and judicial institutions. Comparative analysis of forensic pathways in the United Kingdom, Sweden, and Germany demonstrates that effective identification depends upon multidisciplinary training, specialised victim assessment tools, and systematic integration of health findings into criminal proceedings. The article concludes that forensic medicine and psychiatry must assume a primary evidentiary role in establishing the non-consensual character of forced marriage, thereby strengthening both victim protection and prosecution outcomes under current European legislation.
Keywords: forced marriage, forensic medicine, psychiatric evaluation, coercive control, trauma-informed care, Directive EU 2024/1385, evidence documentation, gender-based violence.

SUMMARY
Forced marriage constitutes a complex manifestation of gender-based violence characterised by the entry into or continuation of matrimonial or cohabitative unions through the exercise of coercive control. The harm occasioned by forced marriage extends across physical, reproductive, and psychological domains, producing measurable health consequences that can be documented through appropriately trained forensic and psychiatric assessment. Despite the increasing criminalisation of forced marriage across European jurisdictions, the evidentiary framework for prosecution remains underdeveloped, particularly regarding the documentation of psychological coercion and the complex trauma responses that characterise forced marriage cases.
This article addresses the foundational role of forensic medicine and psychiatry in the identification, assessment, and documentation of forced marriage. It traces the clinical and medicolegal standards applicable to such assessment, examines current gaps in professional training and institutional capacity, and identifies the structural prerequisites for integrating forensic and psychiatric evidence into criminal justice responses. The analysis proceeds through six movements. The introduction establishes the foundational role of forensic assessment in forced marriage cases. The research and findings section examines, in turn, the physical health sequelae of forced marriage and their forensic documentation, the psychological and psychiatric consequences and assessment approaches, current protocols and their limitations, comparative institutional practice in jurisdictions with established forensic pathways, and recent legislative developments in the Republic of Moldova. The conclusion formulates evidence-based recommendations for strengthening forensic capacity in Moldovan institutions.
The central thesis advanced here is that the effective identification and prosecution of forced marriage depends fundamentally on the development of standardised, trauma-informed forensic and psychiatric protocols, on comprehensive professional training across medical and judicial sectors, and on systematic

integration of health system findings into criminal proceedings. Forensic evidence, when properly collected and documented, can establish the elements of coercion that distinguish forced marriage from consensual union and can corroborate victim testimony that is frequently constrained by trauma, fear, or ongoing dependence on perpetrators. The development of forensic capacity in forced marriage cases constitutes an essential component of the protective response required under international human rights law and current European legislation.

INTRODUCTION

The criminalisation of forced marriage, now advanced across the European Union and Council of Europe jurisdictions, raises a critical methodological question that has received insufficient attention: how can law enforcement, prosecutors, and courts establish with appropriate certainty that a marriage was forced rather than consensual or merely arranged? This question is not purely theoretical. The answer to it determines whether criminal legislation protects forced marriage victims or whether it remains inert, unenforced, or counterproductive because the evidence required to establish guilt beyond reasonable doubt cannot be readily gathered.

Forced marriage differs from many other criminal acts in that the coercive act itself may have occurred months or years prior to the moment when institutional intervention becomes possible. Unlike assault, which leaves contemporaneous injury, or trafficking, which involves movement across borders or into exploitative labour, forced marriage operates as an extended condition of control that is characteristically concealed behind narratives of cultural practice, family unity, or consensual choice. The absence of visible, temporal injury evidence means that forensic assessment must extend beyond immediate bodily examination to encompass the cumulative health sequelae of prolonged coercion, the psychological markers of complex trauma, and the patterns of control that persist within the marital relationship.

Forensic medicine and psychiatry are the disciplines equipped to undertake this assessment. Forensic medicine encompasses the application of medical knowledge to legal inquiry, including the documentation and interpretation of injury patterns consistent with particular forms of violence, the assessment of injury mechanisms, the collection of biological evidence for laboratory analysis, and the provision of expert opinion on causation and timing. Forensic psychiatry encompasses the application of psychiatric knowledge to legal questions, including the assessment of mental state, the documentation of psychological harm and its mechanisms, the assessment of decision-making capacity and the presence of coercion that negates consent, and the identification of trauma responses that may affect the demeanour or credibility of victims in investigative or judicial settings.

The present analysis examines the role these disciplines can and should assume in forced marriage cases. It is organised on the premise that current European legal responses to forced marriage are constrained not by inadequate criminal statutes but by the absence of developed forensic protocols, by insufficient training of health professionals in the identification of forced marriage indicators, and by poor integration of health system assessment into criminal justice proceedings. The development of such protocols and capacity constitutes an essential prerequisite for translating legislative prohibition into protective reality.

RESEARCH AND FINDINGS

I. Physical Health Sequelae of Forced Marriage and Their Forensic Documentation

Forced marriage produces documented and measurable health consequences across the physical domain. These consequences extend across multiple organ systems and arise through multiple pathways, including direct violence, reproductive coercion, malnutrition, lack of access to healthcare, and the physiological effects of chronic stress.

Intimate partner violence is a frequent concomitant of forced marriage, particularly once the marriage has been formalised and the victim is embedded within the household of the perpetrator or perpetrator's family. WHO prevalence research indicates that women in coercive unions experience intimate partner violence at rates substantially exceeding those in the general population. The physical manifestations of such violence include contusions, lacerations, abrasions, fractures, eye injuries, strangulation injuries, and traumatic brain injury. These injuries, when properly documented at the time of occurrence or through forensic assessment of healed injury patterns, provide objective evidence corroborating victim accounts of violence. Forensic assessment employs body mapping, photographic documentation, and structured injury assessment protocols to record injury location, morphology, and consistency with

stated mechanisms of causation. In forced marriage cases, the patterns of injury frequently reflect repeated episodes over extended periods, and forensic examination can document healed injury at various stages of healing, consistent with a pattern of recurrent violence.

Reproductive health consequences are particularly acute in forced marriage, especially where the marriage occurs at or before adolescence. Early entry into sexual relations produces gynaecological injury, including perineal trauma, vaginal and cervical lacerations, and sexually transmitted infections. Repeated pregnancy, often compelled through denial of contraceptive access, produces obstetric fistula, maternal anaemia, and increased risks of maternal mortality and neonatal death. These consequences are well-documented in reproductive health literature and in WHO clinical guidance. Forensic gynaecological examination can document evidence of reproductive trauma and sexually transmitted infection, providing objective corroboration of coercive sexual relations.

Malnutrition and micronutrient deficiency arise from restricted access to food, economic control, and the diversion of resources to other family members. Forensic anthropometric assessment documents weight loss, stunting, and other markers of nutritional deprivation. Nutritional status can be assessed through body mass index calculations, clinical examination, and where relevant, laboratory assessment of micronutrient levels.

The documentation of physical health sequelae requires forensic assessment undertaken by appropriately trained professionals. This assessment must be trauma-informed, conducted in settings that maximise victim safety and comfort, and integrated into comprehensive victim support that addresses both immediate health needs and longer-term rehabilitation. Current European protocols remain variable and underdeveloped in most jurisdictions, including the Republic of Moldova.

II. Psychological and Psychiatric Consequences and Assessment Approaches

Forced marriage produces profound and measurable psychological consequences. Research utilising standardised psychiatric assessment instruments demonstrates that women who have been subjected to forced marriage exhibit significantly elevated prevalence of post-traumatic stress disorder, complex trauma, major depressive disorder, generalised anxiety disorder, suicidal ideation, and dissociative symptoms compared with the general population. These findings are consistent across European epidemiological research conducted in clinical and community settings.

The mechanism of psychological harm operates primarily through what European standards term coercive control. This pattern of behaviour encompasses isolation from social and family support networks, economic deprivation and control of financial resources, systematic undermining of self-efficacy and decision-making capacity, surveillance including digital surveillance, threats directed at the victim or at family members, exploitation of cultural or religious authority, denial of reproductive autonomy, and the cultivation of emotional dependence. The Istanbul Convention explicitly recognises coercive control as a form of psychological violence under Article 33. The Council of Europe recognises that such control produces measurable and lasting psychiatric harm that can be assessed through structured clinical evaluation.

Forensic psychiatric assessment of forced marriage cases must employ validated assessment instruments designed to identify trauma and complex trauma presentations. These include the Posttraumatic Stress Disorder Checklist, the Complex Trauma Assessment Scale, structured clinical interview protocols addressing trauma history and current symptoms, and assessment of cognitive functioning, decision-making capacity, and the presence of coercive influence. Assessment must be trauma-informed, conducted by professionals with expertise in gender-based violence and complex trauma, and provided in settings that ensure confidentiality and safety. The assessment should document not only the presence of psychiatric symptoms but also the nexus between documented symptoms and the coercive circumstances that preceded or surrounded the forced marriage.

Critical to forensic psychiatric assessment is the evaluation of decision-making capacity at the time of marriage and the assessment of coercive influence that may have negated the capacity to refuse. This assessment addresses a specific forensic question: was the individual able, at the material time, to understand the nature and consequences of marriage, to retain that information, to weigh and evaluate options, and to communicate a choice free from external coercion? Forensic psychiatric expertise is essential to addressing this question, as it requires assessment of cognitive function, understanding of volition and coercive influence, and the ability to distinguish between legitimate persuasion and coercive control that negates authentic choice.

A fourth element of forensic psychiatric assessment concerns the assessment of trauma responses that may affect a victim's presentation during investigation or trial. Trauma can produce effects including hypervigilance, difficulty with recall of chronological detail, emotional dysregulation, and patterns of behaviour that, to uninformed observation, may appear inconsistent with victimhood. Forensic psychiatric expertise enables investigators and prosecutors to contextualise victim presentation within the framework of recognised trauma responses, reducing the risk that investigative or judicial processes will misinterpret trauma responses as indicators of false allegation or malingering.

III. Current Forensic Protocols and Their Limitations in Forced Marriage Cases

Most European jurisdictions, including the Republic of Moldova, do not currently maintain dedicated forensic protocols for forced marriage cases. Instead, cases are typically managed through general protocols developed for intimate partner violence, sexual assault, or human trafficking. While these protocols contain valuable elements applicable to forced marriage, they do not adequately address the specific forensic and temporal characteristics of forced marriage as an extended coercive condition.

General intimate partner violence protocols focus on documentation of acute injury and immediate circumstances, with timescales typically measured in days to weeks from the incident. Forced marriage, by contrast, may extend across years or decades, producing cumulative physical and psychological consequences rather than discrete acute injury. Current protocols do not systematically address the documentation of cumulative harm or the assessment of long-standing patterns of control.

General sexual assault protocols focus on the collection of biological evidence to establish penetrative sexual contact and on the assessment of contemporaneous injury. Forced marriage often involves ongoing coercive sexual relations within the marriage where consent has been negated by the initial lack of free consent to marriage itself and through ongoing control within the union. Current protocols do not adequately address this scenario of coercive sexuality within a nominally consensual relationship.

Human trafficking protocols, employed in some jurisdictions to address forced marriage, are designed to identify movement across borders and entry into exploitative labour or sexual exploitation. While forced marriage may occasionally involve border movement or economic exploitation, it is not fundamentally a trafficking crime and deployment of trafficking protocols risks obscuring the centrality of marital coercion.

The limitations of current general-purpose protocols create several forensic challenges specific to forced marriage. First, they do not provide structured guidance for the assessment and documentation of coercive control mechanisms that are psychological and behavioural rather than physical. Second, they do not address the temporal challenges of forced marriage, where significant time may have elapsed between the forced marriage event and the moment of intervention. Third, they do not integrate psychiatric assessment within the forensic framework. Fourth, they do not provide guidance for assessment of ongoing harm within the marital relationship. The development of dedicated forced marriage protocols, informed by both international standards and by evidence from jurisdictions with substantial experience, constitutes an essential gap requiring urgent remediation.

IV. Comparative Analysis of Established Forensic Pathways: United Kingdom, Sweden, and Germany

The United Kingdom has developed the most advanced forensic pathway for forced marriage assessment among comparable European jurisdictions. This pathway operates through multiple entry points. Victims may present to general practice, emergency medicine, or specialist services. In each setting, health professionals trained in the recognition of forced marriage indicators undertake structured assessment including documentation of injury, assessment of coercive circumstances, and referral to specialist services. The pathway includes specialist multidisciplinary teams in major urban areas, composed of forensic physicians, psychiatrists, social workers, and police liaison officers. Evidence collection follows the Code of Practice for the Investigation of Offences against Women and Children, which includes provisions addressing forced marriage. Documentation is standardised, with contemporary evidence recorded in structured formats enabling later interpretation by prosecutors and courts. The pathway achieves integration between health assessment and criminal justice through dedicated liaison protocols.

Sweden's approach emphasises early identification and prevention rather than forensic documentation of completed forced marriage. Swedish health services, including general practice and youth health services, employ routine screening for gender-based violence and harmful practices. Municipal integration services for migrants include staff trained in the recognition of prospective forced marriage indicators. When forced marriage is identified, the response prioritises victim protection through civil

remedies rather than criminal investigation, though criminal investigation remains available when a victim wishes to pursue prosecution. Where forensic assessment is undertaken, it follows general trauma assessment protocols but includes explicit training for health professionals on the specific manifestations of forced marriage.

Germany has developed a structured approach following the criminalisation of forced marriage in 2011. Protocols address identification of both completed and prospective forced marriage. Child protective services (Jugendamt) are trained to identify prospective forced marriage of minors and to intervene through child protection mechanisms. For adults, forensic assessment follows general gender-based violence protocols but includes specific training on forced marriage indicators. German protocols explicitly address the assessment of consent and the presence of coercive influence. Documentation practices follow established forensic standards, with evidence collection undertaken by trained forensic physicians.

Common elements emerge across these three systems as essential features of effective forensic response. First, the existence of a dedicated forced marriage offence provides clear guidance to investigators and forensic professionals as to what evidence is legally relevant. Second, training of health professionals specifically on forced marriage indicators enables identification and appropriate referral. Third, protocols address assessment of both immediate and cumulative harm. Fourth, protocols explicitly address assessment of coercive circumstances and their effect on decision-making capacity and consent. Fifth, documentation employs standardised formats enabling later interpretation. Sixth, there is systematic liaison between forensic professionals and criminal justice actors. Seventh, victim protection is prioritised in parallel with investigation. These structural features provide a template for capacity development in jurisdictions where such frameworks do not yet exist.

V. Recent Legislative Developments and Forensic Implications in the Republic of Moldova

Law No. 252/2025, which entered into force on 3 February 2026, criminalised forced marriage in the Republic of Moldova for the first time. Article 173 of the Criminal Code establishes the offences of forced marriage and forced cohabitation, with penalties of 5 to 10 years' imprisonment. The provision defines these offences broadly enough to encompass the range of coercive mechanisms through which forced marriage is accomplished, including force, threats, psychological pressure, and exploitation of authority.

The enactment of this criminal provision creates both an opportunity and a responsibility for development of forensic capacity. The opportunity lies in the ability to develop capacity prospectively, informed by evidence of what works in other jurisdictions, rather than retrospectively through trial and error. The responsibility lies in ensuring that the criminal offence, while normatively important, is supported by the infrastructure of trained professionals and established protocols without which it will remain largely unenforced.

The GREVIO baseline evaluation of Moldova, published in November 2023, identified gaps in the capacity of Moldovan health and judicial systems to respond to gender-based violence more broadly. Those gaps extend to forced marriage specifically. The evaluation noted the absence of national clinical protocols for identification and assessment of gender-based violence, insufficient training of health professionals, inadequate data collection, and poor coordination across sectors. These institutional constraints, pre-existing the recent criminalisation of forced marriage, must be addressed if the criminal provision is to become operationally effective.

CONCLUSIONS AND RECOMMENDATIONS

Forced marriage produces measurable health consequences across physical, reproductive, and psychological domains. These consequences can be identified, assessed, and documented through appropriately trained forensic and psychiatric professionals operating within established protocols. The translation of criminal prohibition into protective outcomes depends on the development of such capacity.

For the Republic of Moldova, the following recommendations are offered for implementation priority:

First, develop a dedicated national protocol for forensic assessment of forced marriage cases. This protocol should address the identification of physical injury markers, the documentation of reproductive health consequences, the assessment of psychological and psychiatric sequelae, the evaluation of decision-making capacity and coercive influence, and the structured documentation of findings in formats enabling later interpretation by prosecutors and courts. The protocol should be developed

through a multidisciplinary working group including forensic physicians, psychiatrists, gynaecologists, representatives of the Prosecutor General's Office, law enforcement, and civil society organisations.

Second, establish mandatory training for forensic physicians, psychiatrists, and other medical professionals who may undertake assessment of forced marriage cases. Training should address the clinical and forensic indicators of forced marriage, trauma-informed assessment approaches, protocols for evidence collection, and the legal standards applicable to forced marriage cases. Training should be incorporated into postgraduate medical education and into continuing professional development requirements.

Third, establish mandatory training for law enforcement personnel, prosecutors, and judges addressing the specific features of forced marriage cases, the role of forensic and psychiatric evidence, and trauma-informed investigation and prosecution approaches. This training should be delivered by professionals with expertise in gender-based violence and forensic medicine.

Fourth, establish or designate within existing health institutions a multidisciplinary team capable of undertaking forensic assessment of forced marriage cases. This team should include forensic physicians, psychiatrists, and social workers. The team should maintain liaison with the Prosecutor General's Office and law enforcement.

Fifth, develop standardised data collection mechanisms enabling recording of all cases of suspected or confirmed forced marriage, including the type of assessment undertaken, the findings of forensic and psychiatric examination, and the outcomes of any criminal proceedings. This data, disaggregated by gender, age, and relationship between victim and perpetrator, should be regularly analysed and published, enabling evidence-based policy refinement.

Sixth, ensure that forensic and psychiatric assessment of forced marriage cases is provided at no cost to victims and that assessment is undertaken in settings that prioritise victim safety and comfort.

The development of forensic capacity in forced marriage cases constitutes an essential complement to criminal prohibition. Forensic medicine and psychiatry provide the methodological framework through which the non-consensual character of forced marriage can be established with appropriate certainty, through which the cumulative harm occasioned by coercive control can be documented, and through which victims can be supported in bringing their experience within the purview of criminal justice while minimising the trauma of investigative and judicial processes. The investment in such capacity, undertaken now, positions Moldova as a jurisdiction that has not merely enacted prohibition but has equipped itself to translate prohibition into protection.

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THE POTENTIAL ROLE OF VENTRAL LATERAL ANTERIOR (VLAN) AND VENTRAL LATERAL POSTERIOR (VLPN) THALAMIC NUCLEI IN MIGRAINE PATIENTS

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ABSTRACT

Aim: The purpose of this study is to examine the effects of Ventral Lateral Anterior (VLAN) and Ventral Lateral Posterior (VLPN) Thalamic Nuclei in Migraine Patients via Machine Learning-Based Analysis.

Introduction
The thalamus acts as the critical gating relay station for the trigeminovascular pain pathway, making its structural remodeling a prime target for computational biomarkers. Anatomically, the ventral lateral nucleus consists of the ventral lateral anterior (VLa/VLAN) and ventral lateral posterior (VLp/VLPN) subdivisions. Examining thalamus volume for migraine diagnosis via machine learning is a highly active and promising area of neuroimaging research.

Findings and Conclusion
An examination of the study's findings reveals that the VLAN_Right nucleus had a substantially higher impact on differentiating migraine patients from controls than other nuclei, followed in order by VLPN_Right, VLPN_Left, VLAN_Left, and the age variable. The obtained findings are consistent with similar studies in the literature, suggesting that ventral lateral nuclei may play a role in pain modulation due to their connections with motor circuits and trigeminothalamic pathways. Therefore, identifying the right VLAN as the most critical variable in the model for migraine patients represents a biologically plausible finding.
Keywords: Machine Learning, Migraine Diagnosis, Thalamus Volume

Introduction

Migraine is a highly disabling primary headache disorder with a 1- year prevalence of ~15% in the general population. According to the Global Burden of Disease Study, migraine is the second most prevalent neurological disorder worldwide and is responsible for more disability than all other neurological disorders combined. (Ashina, 2020; GBD 2016a, GBD 2016b, Eigenbrodt et al., 2021). Examining thalamus volume for migraine diagnosis via machine learning is a highly active and promising area of neuroimaging research.

While the ventral lateral anterior nucleus (VLAN) primarily receives inputs from the basal ganglia and connects with the premotor cortex and supplementary motor areas, the ventral lateral posterior nucleus (VLPN) is the principal motor thalamic nucleus that relays information from cerebellar nuclei to the primary motor cortex. Consequently, the ventral lateral complex plays a role not only in the regulation of motor control but also in the modulation of pain-associated motor responses, postural adaptation, and sensorimotor integration. Experimental studies suggest that trigeminothalamic pathways form

functional connections with the ventral lateral complex and that this nucleus may contribute to pain modulation (Younis et al., 2019).

It can be suggested that the right VLAn plays a more prominent role in the diagnosis of migraine compared to other nuclei, and that migraine leads to a reduction in the volume of this nucleus. The volume reduction (atrophy or microstructural loss) observed in the right VLAn of individuals with migraine may represent a neurodegenerative/plastic response (a consequence) resulting from excitotoxicity, neurogenic inflammation, and chronic pain load induced by recurrent migraine attacks; alternatively, it may serve as a pre-existing structural factor (a cause) predisposes the individual to migraine or the chronification of attacks.

Materials and Methods

MRI scans from 72 migraine patients and 51 control subjects from Balıkesir University Neurology Clinic were uploaded to the Volbrain system and digitized. The flow diagram of the study is given in Figure 1.

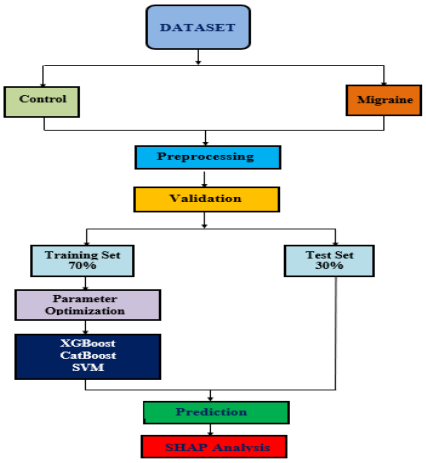


Figure 1. Flow Diagram of the Study

To improve model interpretability, SHAP (SHapley Additive exPlanations) analysis was employed. (Lundberg and Lee, 2017). SHAP addresses the “black box” limitation of ML models by quantifying the contribution of individual features to prediction outcomes, thereby enhancing clinical interpretability, particularly in biomedical research settings (Rodríguez-Pérez and Bajorath, 2020; Tunca and Saraçlı, 2026). The volumes of the Ventral Lateral Anterior and Ventral Lateral Posterior thalamic nuclei were evaluated using SHAP analysis to identify the nuclei that were significant in distinguishing between the control and migraine groups.

Findings

The ROC analysis results and confusion matrix for the CatBoost method, which yielded the best results among the three different deep learning methods, are given in Figure 2 and Figure 3.

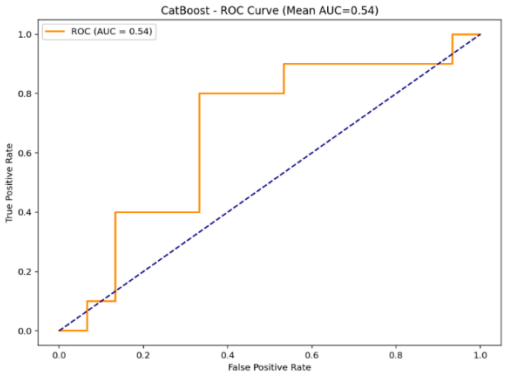


Figure 2. ROC Curve of the CatBoost Model

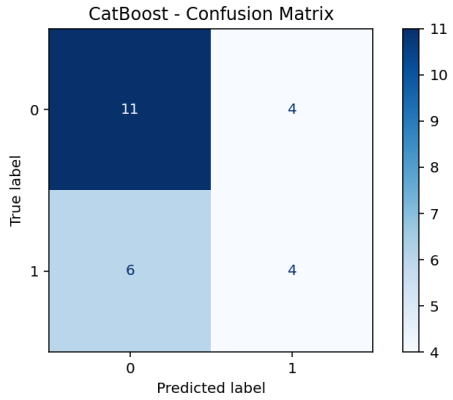


Figure 3. Confusion Matrix for CatBoost Model

Figure 2 and Figure 3. indicate that even the models classification ability is not much enough (0,54) classification probability of migraine patients is 11/17.
Results of SHAP analysis and Effects of right and left parts of VLAN and VLPN and Age on Migraine and control discrimination are given in Figure 4 and Figure 5.

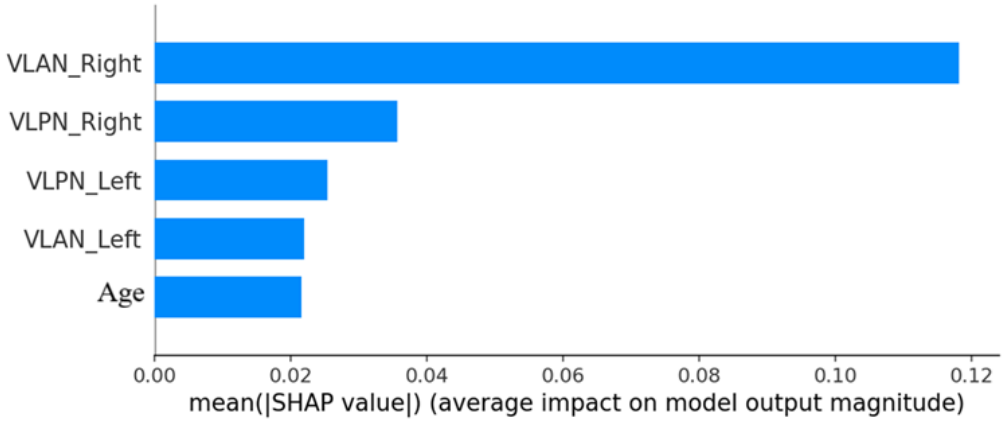


Figure 4. Effects of VLAN and VLPN and Age on Migraine and control discrimination.

As can be seen from Figure 4, among the variables considered in distinguishing between the migraine and control groups, right part of VLAN is the most effective variable; the other variables, ranked by effect size, are As can be seen from Figure 4, among the variables considered in distinguishing between the migraine and control groups, VLAN_Right is the most effective variable; the other variables, ranked by effect size, are VLPN_Right, VLPN_Left, VLAN_Left and Age respectively.

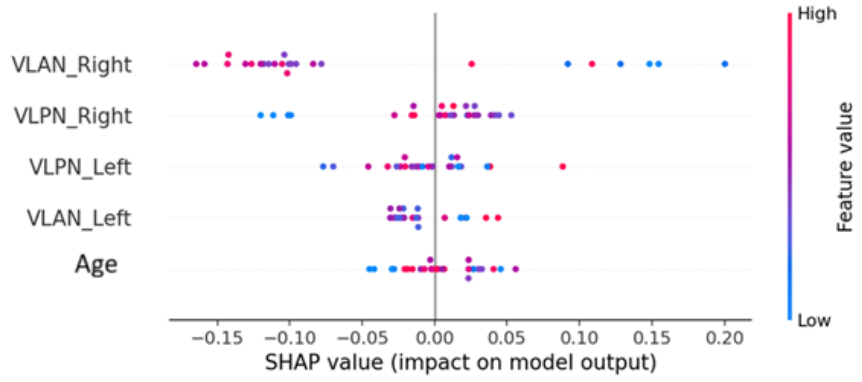


Figure 5. SHAP results

Conclusion

As the results of the analysis indicate that while the right part of ventral lateral anterior nuclei is the most effective variable in distinguishing between the migraine and control groups, it can be said that a decrease in the volume of this nuclei is associated with belonging to the migraine group, whereas a decrease in the volume of the right part of ventral lateral posterior nuclei is associated with belonging to the control group.

The obtained findings are also consistent with similar studies in the literature, suggesting that ventral lateral nuclei may play a role in pain modulation due to their connections with motor circuits and trigeminothalamic pathways. Therefore, identifying the right VLAN as the most critical variable in the model for migraine patients represents a biologically plausible finding.

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EFFECTS OF DROUGHT SHOCKS ON RURAL HOUSEHOLD WELFARE, CREDIT ACCESS AND BORROWING BEHAVIOR

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ABSTRACT
Drought is a multidimensional welfare shock that affects not only agricultural output but also rural households' consumption, asset, labor, migration and financing decisions. This paper reviews the international literature on how drought shocks affect rural household welfare, access to credit and borrowing behavior, and identifies the gaps that remain. Contributions from rural development economics, agricultural finance and climate risk research are synthesized narratively and discussed under seven headings: consumption smoothing and asset depletion, credit demand and informal finance, credit supply and lender behavior, indebtedness and default, public assistance and debt relief, interlinked insurance-credit instruments, and long-run and gendered outcomes. The reviewed evidence indicates that drought lowers income and weakens access to liquidity, that households draw down grain stocks and sell assets although these buffer cover only part of the shortfall, and that households facing weather risk make low-risk, low-return production choices, while lenders reduce agricultural lending in drought-exposed local markets. Evidence on the demand side is nonetheless thin: few studies track actual loan volumes, interest rates, rationing status and informal credit terms for the same households before and after a drought. Index insurance and state-contingent loan contracts confirm the importance of joint risk and liquidity constraints, yet their measured effects are sensitive to institutional context, cropping patterns and contract design. Household-level work on the drought-credit nexus is especially scarce for Türkiye and the wider Mediterranean basin. The paper concludes that drought relief, agricultural insurance and credit policy should be designed not as separate instruments but as complementary components of an integrated risk management framework.
Keywords: Drought, rural household welfare, agricultural credit, borrowing behavior, climate risk

ÖZET
Kuraklık, tarımsal üretim kayıplarının ötesinde kırsal hanelerin tüketim, varlık, emek, göç ve finansman kararlarını eş zamanlı olarak etkileyen çok boyutlu bir refah şokudur. Bu bildiri, kuraklık şoklarının kırsal hane refahı, krediye erişim ve borçlanma davranışı üzerindeki etkilerini uluslararası literatür temelinde derlemekte ve alandaki boşlukları ortaya koymaya çalışmaktadır. Kırsal kalkınma ekonomisi, tarımsal finansman ve iklim riski çalışmaları nitel biçimde sentezlenmiş ve yedi başlık altında tartışılmıştır: tüketimin düzeltilmesi ve varlıkların eritilmesi, kredi talebi ve informel finansman, kredi arzı ve kredi verme davranışı, borçluluk ve geri ödememe, kamu yardımları ve borç affı, sigorta-kredi bağlantılı araçlar, uzun dönemli ve toplumsal cinsiyete duyarlı sonuçlar. İncelenen çalışmalar kuraklığın geliri azalttığını ve hanelerin likiditeye erişimini zayıflattığını, hanelerin tahıl stoklarını eritip varlık sattığını ancak bu uygulamaların açığın yalnızca bir bölümünü kapattığını, hava riskiyle karşı karşıya kalan hanelerin düşük riskli ve düşük getirili üretim tercihlerine yöneldiğini, borç verenlerin ise kuraklığa maruz yerel piyasalarda tarımsal kredi arzını daralttığını göstermektedir. Buna karşılık talep yönlü kanıtlar sınırlıdır; fiili kredi tutarı, faiz oranı, kredi kısıtlanma durumu ve informel kredi koşullarını aynı haneler için şok öncesi ve sonrasında izleyen çalışma sayısı azdır. Endeks bazlı sigorta ve şoka bağlı kredi sözleşmelerine ilişkin bulgular, risk ve likidite kısıtlarının birlikte önemini doğrulamakla birlikte, ölçülen etkiler ülkeye, ürün desenine ve sözleşme tasarımına duyarlıdır. Türkiye ve geniş Akdeniz havzasında hane düzeyinde kuraklık-kredi etkileşimini inceleyen çalışmalar sınırlıdır. Bildiri, kuraklık yardımı, tarımsal sigorta ve kredi politikalarının ayrı araçlar olarak değil, bütünleşik bir risk yönetimi çerçevesinin birbirini tamamlayan bileşenleri olarak tasarlanması gerektiği sonucuna ulaşmıştır.
Anahtar Kelimeler: Kuraklık, kırsal hane refahı, tarımsal kredi, borçlanma, iklim riski

Introduction

Drought differs from most other natural hazards in the way it reaches rural households. It arrives slowly, covers wide areas, and strikes the income of many neighboring farms at the same time, so that the local mechanisms households normally rely on to absorb a bad year, such as selling an animal, borrowing from a relative or working for a neighbor, are weakened precisely when they are needed most. A drought is therefore not only a production shock; it is simultaneously a shock to consumption, to asset positions, to labor allocation and to the functioning of local credit and insurance arrangements. Understanding how these dimensions interact is essential for designing drought relief, agricultural insurance and rural credit policy.

The question has gained urgency in the Mediterranean context. Reviewing the state of drought assessment across the region, Tramblay et al. (2020) record that Mediterranean droughts carry heavy environmental and socio-economic costs, above all where farming depends on rainfall, and that model experiments run under future climate scenarios converge closely on drought becoming both more frequent and more severe throughout the basin. The damage, they expect, will weigh most on the developing countries of its southern and eastern shores. Türkiye sits squarely within this geography, and its room for action through irrigation is bounded: the State Hydraulic Works puts the economically irrigable area of the country at 8.5 million hectares and reports that the area opened to irrigation, including areas developed by other institutions, had reached 6.96 million hectares by the end of 2022 (DSİ, n.d.). Irrigation expansion alone therefore cannot carry the adjustment to a drier climate.

At the same time, the financial dimension of drought risk remains institutionally underdeveloped in much of the world. Cole and Xiong (2017) point out that farmers are exposed to a range of serious risks, and that the only insurance products ever to have reached scale were ones the state paid part of the bill for. Where formal insurance is thin, credit becomes the main financial instrument through which households try to carry a drought year, which places rural credit markets at the center of the welfare analysis of drought. Morduch (1995) sets out the behavioral logic beneath this. A risk-averse household can defend the level of its consumption in two ways: by borrowing and calling on insurance, or, as happens commonly where incomes are low, by spreading its activities across several sources and choosing cautiously what to produce and where to work. The second route leaves the household open only to the kind of setback its available credit and insurance can absorb. Credit access thus shapes not only how households cope after a drought but also what they plant, invest and risk before one.

This paper reviews the international literature on the effects of drought shocks on rural household welfare, access to credit and borrowing behavior. It synthesizes contributions from rural development economics, agricultural finance and climate risk research in a narrative form and organizes them under seven headings: consumption smoothing and asset depletion; credit demand, informal finance and risk sharing; credit supply and lender behavior; indebtedness and default; public assistance and debt relief; interlinked insurance-credit instruments; and long-run and gendered outcomes. A separate section discusses the Turkish and Mediterranean context and the research gap there. The final section draws the policy conclusions together.

Consumption Smoothing and Asset Depletion

The oldest strand of the literature asks whether rural households can protect consumption when drought cuts income, and at what cost. A first insight is that smoothing begins before the shock. Morduch (1995) separates the smoothing of consumption from the smoothing of income, observing that in low-income economies households frequently hold several activities at once and pick their crops and their employment cautiously, which keeps their exposure within what credit and insurance can absorb.

When the shock nonetheless arrives, productive assets become the buffer of last resort. Rosenzweig and Wolpin (1993) estimate a finite-horizon structural model of how farm households invest, built around three features of poor agricultural settings: income that cannot be foreseen, limited access to borrowing and to rental markets, and assets that both earn a return and buffer consumption. Fitting it to Indian panel data on farm profits, bullock holdings and pump sets, they use the estimated parameters to trace what complete markets, liquid bullock holdings, and second-best interventions offering farmers an assured income stream and weather insurance would each do to lifetime bullock accumulation, to farm profits and to welfare. Their setting is income uncertainty in general rather than drought in particular, but the tension their framework captures carries over: the same asset, a plough animal, is both a production input and a store of value, so that selling it to absorb a bad income year undermines future income.

Whether livestock actually perform this buffer role as well as is often assumed has been questioned empirically. Fafchamps, Udry and Czukas (1998) put to the test a claim of long standing, that herds in the West African semi-arid tropics work as a reserve households run down to hold consumption steady when income falls. Their results cut the claim back: trading animals does less of this work than has usually been supposed, sales offsetting at most thirty percent, and more likely nearer twenty percent, of the income lost to village-level shocks alone. Kazianga and Udry (2006) ask how far herds, stored grain and transfers between households served to steady consumption in rural Burkina Faso between 1981 and 1985. Severe drought fell inside that window, which puts the mechanisms to the test at the moment they matter most. What they find is little steadying: risk sharing is all but absent, and households fall back almost entirely on their own grain stores. The two coping strategies the literature leads one to expect, risk sharing and buffer stocks, did not work over the period surveyed.

The welfare consequences of this incomplete smoothing are not confined to the drought year itself. Working with panel data from rural Ethiopia, Dercon (2004) finds that shortfalls in rainfall weigh substantially on the growth of consumption and that their mark lasts for years, with the large-scale famine of the 1980s leaving a persistent and significant imprint of its own. What follows, he argues, is that the welfare cost of going uninsured and unprotected runs far beyond whatever is lost to short-term swings in consumption. Taken together, this strand establishes the premise for everything that follows: households cannot fully self-insure against drought, the informal mechanisms are weakest against exactly this kind of covariate shock, and the resulting demand for external liquidity flows directly into local credit markets.

Credit Demand, Informal Finance and Risk Sharing

If self-insurance is incomplete, the next question is what households ask of others, and of lenders, when drought strikes. The classic village-economy studies show that informal arrangements carry part of the burden. Townsend (1994) puts the full insurance model to data from three poor, high-risk villages in the semi-arid tropics of southern India. Statistically the model fails, yet it serves as a surprisingly good benchmark: what a household consumes moves with the village average, and once village-level risk is held constant, its own current income, illness, spell out of work and other individual misfortunes explain little. In one of the three villages he also finds the landless less well covered than their neighbors. The finding is double-edged for drought analysis: village-level risk sharing works reasonably well against idiosyncratic shocks, but a drought is by construction the kind of shock that moves village average consumption itself, so the village pool cannot be the mechanism that absorbs it. Townsend does not study drought, and this reading of his benchmark is ours.

Informal credit itself often embeds insurance. Drawing on a year-long survey in Zaria, northern Nigeria, Udry (1994) finds loan agreements themselves doing the work of pooling risk across households: what a borrower ends up owing turns on how chance has treated both sides of the contract. Payments conditioned on those outcomes are, on his estimates, large enough to matter, though the pooling they achieve stops short of full efficiency. Fafchamps and Lund (2003) trace a different pattern in the rural Philippines: adverse events move gifts and informal loans sharply while leaving sales of animals and grain largely untouched. Insurance there is not a village-wide arrangement but something that runs along lines of friendship and kinship, and what they observe fits quasi-credit models in which close networks share risk through interest-free loans of flexible terms alongside outright transfers. Informal borrowing after a shock is therefore best read not as pure debt but as a hybrid of credit and insurance whose terms adjust to the borrower's misfortune.

Risk also shapes production and investment decisions before any shock occurs, through the portfolio choices it induces. Rosenzweig and Binswanger (1993) draw on Indian panel data to ask how the make-up of a farmer's assets shifts with total wealth and with the degree of weather risk faced. They estimate how risky a portfolio is by how sensitive it proves to variation in the weather, and estimate how wealth conditions the response of both portfolio risk and farm profitability to weather risk that lies outside the farmer's control. Their framework connects weather risk, wealth and the profitability of the farm enterprise. Read alongside the credit-market literature reviewed below, this suggests that the same weather risk should also move the collateral base and repayment capacity that lenders observe, although Rosenzweig and Binswanger do not make that point themselves.

Reading these studies together suggests an important gap. The literature documents richly how informal transfers and credit-like financing respond to shocks, but studies that track actual loan volumes, interest rates, rationing status and informal credit terms for the same households before and after a specific

drought remain rare. Most evidence on the demand side is inferred from consumption or asset movements rather than observed directly in credit records, which limits what can be said about how much additional credit drought-affected households seek, at what price, and how often they are refused.

Credit Supply and Lender Behavior

The supply side of the market reacts to the same covariate risk that undermines village insurance. Because a drought hits many borrowers of the same local lender simultaneously, it confronts lenders with spatially correlated default risk. The empirical literature on natural disasters documents that credit access tightens after such events; that the tightening operates through a deliberate reassessment of correlated risk is our reading of that literature rather than a mechanism these studies test directly.

Berg and Schrader (2012) match client records from an Ecuadorian microfinance institution against geophysical readings of volcanic activity. Eruptions raise the demand for credit and narrow access to it at the same time, but an existing relationship softens the restriction: borrowers the institution already knows are about as likely to be lent to once eruptions have occurred as they were before. The pattern is exactly the scissors that matters for drought: demand for liquidity rises just as approval tightens, and relationship capital partly determines who is rationed.

Evidence from the United States shows how the structure of the banking system transmits and redistributes these shocks. Cortés and Strahan (2017) show banks operating across several markets shifting capital when a disaster lifts credit demand in one of them. Instrumenting lending growth with property damage, they put the withdrawal from untouched but connected markets at slightly under 50 cents for every additional dollar lent where the disaster struck. Core markets come through protected, because the bulk of the retreat falls on places where the bank holds no branches. Rehbein and Ongena (2022), whose shock is a flood rather than a drought, show thin bank capital magnifying the way a local shock spreads. Following a disaster as it reaches firms outside the stricken area through their lenders, they find firms banking with a heavily exposed institution in the bottom quartile of capitalization cutting total borrowing by 6.6% and tangible assets by 6.9%, reductions that are significant against comparable firms whose bank was well capitalized. Banks, for their part, pull back afterwards from areas this event spared but that are prone to such events generally. Their outcome units are firms rather than farm households.

Drought-specific evidence on bank lending has recently begun to accumulate. Merging bank balance sheets with county-level readings from the U.S. Drought Monitor for 2000–2020, Brei, Kowalewski, Śpiewanowski and Strobl (2026) find agricultural lending falling significantly where local credit markets meet drought, the effect gathering in the severe episodes. The fall runs deepest where banks are geographically concentrated, single-county institutions above all, and shallower where lenders are spread across more territory. Counties that irrigate more heavily lose less lending when drought turns extreme; the contractions gather instead where crops are less resistant to begin with; and counties with drought behind them react more strongly, which the authors read as persistent climate risk working its way into local credit conditions. For rural households the implication is concerning: the more local and specialized their lender, and the more drought-prone their county, the more procyclical their credit supply.

Indebtedness and Default

Weather shocks reach lenders through the repayment behavior of their borrowers, and a smaller literature examines this link directly in loan portfolios. Pelka, Musshoff and Weber (2015) find that too much rain over the rice harvest raises the credit risk carried by loans made to smallholders in Madagascar. Weather, they conclude, is a leading reason lenders in developing countries read smallholders as risky, while index-based weather insurance might hold the potential to take some part of that risk out of agricultural lending. Although the shock in their setting is excess rainfall rather than drought, the mechanism, weather-driven harvest failure translating into arrears, is the same one drought activates.

Collier, Katchova and Skees (2011) examine the portfolio of a microfinance institution in Northern Peru, where a severe El Niño brings catastrophic flooding rather than drought. The 1997-1998 event significantly raised problem loans, and the level of restructured ones in particular: restructured loans had averaged 0.5 percent of the portfolio beforehand, and the estimated cumulative effect puts a further 3.6 percent of portfolio value into restructuring on account of the event. Their emphasis falls on two things: where many small borrowers carry correlated risk the lender itself can be significantly affected,

and the restructuring a lender turns to in order to limit losses may run long enough to carry the disaster forward into the community. The shock is a flood, but the configuration on the lending side, one portfolio struck by a single covariate event, is the configuration drought produces. For the United States, Escalante, Song and Dodson (2016) look at Farm Service Agency borrowers whom their ordinary lenders had marked as marginal, across the Southeast and the Midwest. Larger loan balances, falling commodity prices and more severe drought all told against these farms, both in whether they survived and in how long they held on without slipping into delinquency. Drought relatively less heavily on the Midwestern farms than on the Southeastern ones.

At the extreme end of the indebtedness spectrum, the welfare stakes become existential. Reviewing the farmer suicide crisis in India, Merriott (2016) concludes that what is associated with these deaths is socioeconomic rather than psychiatric, with rising indebtedness the predominant factor. On the research available to him, the problem has grown sharper of late through an agrarian crisis bearing on the most vulnerable farmers, one that shows itself in too little agricultural investment and too little improvement in irrigation, in the turn toward cash crops, in greater recourse to credit from outside the institutional system, and in lowered trade barriers. He states plainly that the available literature does not permit a single defining cause to be identified. Two of the manifestations he lists, the increased use of noninstitutional credit and the absence of irrigation improvement, are the same two margins that recur throughout this review, although Merriott neither orders them causally nor links them to drought episodes.

Public Assistance and Debt Relief

Governments respond to drought-driven distress with two broad families of instruments: transfers to households and relief of their debts. The evidence suggests that the two work very differently.

Large-scale debt relief has been evaluated most rigorously in India. Studying India's bailout for rural households, Kanz (2016) finds relief reshaping household balance sheets substantially while leaving saving, consumption and investment where theories of debt overhang or balance-sheet distress would have predicted movement. What follows instead is heavier recourse to informal credit, less investment and lower agricultural productivity; and, as moral hazard from the bailout would imply, those who benefited worry significantly less about what defaulting again would cost their reputation. Taking up the same program from the credit market side, Giné and Kanz (2018) find credit significantly reallocated and defaults higher, with nothing on the other side of the ledger for productivity, for wages or for consumption. Loan performance after the program worsened faster the more a district had been exposed to it, and not because banks had taken on more risk. Defaults also came to track the electoral cycle more closely once relief had been granted, which the authors read as strategic default in response to the bailout. Unconditional debt forgiveness, in other words, can poison the future functioning of the very credit market on which drought-affected households depend.

Expectations of assistance can also distort behavior before any shock. Deryugina and Kirwan (2018) carry the Samaritan's dilemma, the worry that people lean on free assistance in place of their own effort, into U.S. agriculture. Anticipating a bailout turns out to matter for the insurance decision both qualitatively and quantitatively, and where aid is expected, spending on farm inputs falls and so does the crop revenue that comes after. These results suggest that poorly designed ex post relief can weaken precisely the ex ante instruments, insurance and input investment, that would reduce the need for relief.

Transfers targeted at poor households fare better in the evidence. Evaluating a multi-year cash transfer program in rural Niger, Premand and Stoeffler (2022) find household consumption rising by about 10 percent on average, with most of that gain sitting among the households a drought had struck. For those households the welfare gain exceeds what was handed over, because the transfers strengthen their capacity to defend earnings from farming and from off-farm business when a shock lands. The authors take their results to suggest that transfer programs running over several years can build resilience among poor households by making saving and income smoothing easier. The contrast with debt relief is instructive: predictable transfers appear to strengthen households' own risk management, while unpredictable forgiveness appears to weaken the credit relationship.

Interlinked Insurance and Credit Instruments

Because drought is a joint shock to income and to creditworthiness, a natural policy idea is to interlink insurance and credit rather than offer them separately. Over the past decade a contractual innovation, tying payouts to the weather actually realized rather than to a farmer's assessed loss, has drawn a great

deal of research (Cole & Xiong, 2017). The experimental literature that followed offers a nuanced picture of when such interlinkage works.

Bundling insurance into loans is not automatically attractive to borrowers. In a randomized field experiment in Malawi, Giné and Yang (2009) asked whether covering a loan against the main risk to production would draw farmers into borrowing for a new crop technology. The answer ran the other way. Attaching insurance to the loan lowered take-up by 13 percentage points, set against take-up of 33.0% where the loan came uninsured, and the suggestive evidence points to farmers already holding implicit cover through the limited liability clause of the loan contract. Where borrowers can default in a disaster state, an insurance premium simply prices what limited liability already gave them.

Offered separately, however, insurance appears to relax the binding constraint on investment. Karlan, Osei, Osei-Akoto and Udry (2014), working in northern Ghana, find index insurance in strong demand, and find that holding it moves farmers toward significantly larger agricultural investment and riskier choices about what to grow. What binds farmer investment, they conclude, is uninsured risk: once covered against the catastrophic risk that dominates their exposure, farmers prove able to find the resources to spend more on their farms. How they invest, and how much insurance they buy, both fit a setting marked by substantial basis risk, incomplete trust that a promised payout will actually arrive, and too much weight placed on recent events. Cole, Giné and Vickery (2017) find much the same: supplying insurance pushes farmers toward heavier investment in cash crops that pay better but hang on the rain, a shift most pronounced among the educated, and one that happens ex ante, while the eventual monsoon rainfall is still uncertain. Financial innovation, they conclude, can take the edge off what uninsured production risk does in the real economy.

Contract design determines whether these gains materialize. Casaburi and Willis (2018) show, in Kenyan contract farming, how much turns on when the premium falls due: 72 percent take the pay-at-harvest policy against 5 percent for the conventional contract paid up front, and the gap is widest among the poorer farmers. Further experiments and outcomes bear on the roles of liquidity constraints, present bias and counterparty risk, and show that letting a farmer commit to paying the premium just one month later lifts demand by 21 percentage points. The same liquidity logic underlies credit-based alternatives to insurance. Lane (2024) gives a randomly chosen group of Bangladeshi farmers a guarantee of credit, an emergency loan to be issued once a climate shock has landed. Those holding the guarantee adapt in less costly ways and come through a flood in better shape; households left outside the scheme show no sign of being hurt by it; and the loan proves profitable for the microfinance institution to offer, which makes it something the private sector could take up in comparable circumstances. Although the shock in that setting is flooding, the instrument, a pre-committed contingent credit line triggered by a covariate shock, is directly transferable to drought.

The overall lesson of this literature is that risk and liquidity constraints must be addressed jointly, but that the measured effects of any particular interlinked product are sensitive to institutional context, cropping patterns and contract design, from limited liability clauses to premium timing and basis risk.

Long-Run and Gendered Outcomes

When smoothing fails, droughts leave marks that outlast the weather, and these marks are not distributed equally within the household.

The human-capital evidence is sharp. Drawing on household panel data from rural Zimbabwe, Hoddinott and Kinsey (2001) find that in the wake of a drought children between 12 and 24 months of age forgo 1.5–2 cm of growth, and that what they later make up is limited enough to leave the shortfall permanent. Older children, by contrast, show no such slowdown. There is some sign that the loss falls unevenly, bearing hardest on children in poorer households and on the children of women who are daughters of the household head. For Indonesia, and for variation in early-life rainfall rather than drought episodes as such, Maccini and Yang (2009) find more rain in the first year of life telling strongly on women's adult outcomes and not at all on men's: a woman whose birth year brought rainfall 20 percent above the local norm stands 0.57 centimeters taller, has completed 0.22 more grades of schooling, and lives in a household 0.12 standard deviations higher on an asset index. Schooling appears to be what carries the effect through to adult women's socioeconomic standing.

The schooling channel, however, is not monotonic, because rainfall also moves the opportunity cost of children's time. Using test scores and schooling records from rural India, Shah and Steinberg (2017) show higher wages raising investment in human capital very early on, from the womb to age 2, and lowering it between ages 5 and 16, as children leave school for productive work in the wetter years.

What schooling costs a family in earnings foregone, even from children still fairly young, is an important factor in determining how much human capital gets built overall. Read against the infant-health results, these two findings suggest to us that the timing of a drought in a child's life matters for its direction: in infancy the binding channel is growth faltering, whereas at school age lower rainfall lowers the wage a child can earn and so lowers the opportunity cost of remaining in school. Neither study makes this comparison, and the inference is ours.

Drought also moves marriage markets, in directions that depend on the institution of marriage payments. In an equilibrium model in which parents choose when their children marry and marriage payments are a source of consumption smoothing, particularly for a woman's family, Corno, Hildebrandt and Voena (2020) show droughts, which cut annual crop yields by 10 to 15% and aggregate income by 4 to 5%, pulling marriage behavior in opposite directions across a sample of 400,000 women drawn from the two regions: in Sub-Saharan Africa the annual hazard of entering child marriage rises by 3%, whereas in India it falls by 4%. The age of marriage thus responds to short-term changes in aggregate economic conditions, and marriage payments determine the sign of the response, which places the timing of daughters' marriages among the margins on which households adjust to drought.

Finally, at the level of whole regional economies, adjustment can take generations. Studying the American Dust Bowl, Hornbeck (2012) estimates that the catastrophe cut agricultural land values and revenues in the more-eroded counties at once, substantially, and for long afterwards, measured against counties less eroded. Adjustments within agriculture won back less than 25 percent of the cost gap that had opened up in those counties. The economy adjusted chiefly by another route: large relative falls in their population, running through the 1930s and on into the 1950s. Migration, not local adaptation, carried the burden of adjustment, a finding with evident relevance for drought-prone rural regions today.

Drought, Agriculture and Rural Finance in Türkiye and the Mediterranean Basin

The Mediterranean basin faces a strongly projected deterioration in drought conditions. As noted above, Tramblay et al. (2020) report the models converging closely on more frequent and more severe drought across the basin, and note that the burden falls particularly where agriculture leans on rainfall. The same review stresses that considerable uncertainty remains, given how complex the phenomenon is, and that it weighs more on hydrological than on meteorological drought because of human influence and water withdrawal. For Türkiye specifically, a substantial climatological literature has characterized drought occurrence: Türkeş and Tatlı (2009) propose a modified Standardized Precipitation Index for examining Turkish droughts along several dimensions at once, how intense they are, how often they come, and where and when they fall. They argue the method carries over to other semi-arid, dry sub-humid and semi-humid regions whose precipitation is strongly seasonal and varies markedly from one year to the next, the Mediterranean macro-climate region among them.

On the institutional side, Türkiye has built a formal agricultural insurance. Burhan (2023) traces conventional agricultural insurance in the country back to 1957 and marks the founding of the Insurance of Agricultural (TARSIM) in 2005 as the decisive step, with the lines TARSİM writes running from crop, greenhouse and poultry cover through to drought yield insurance. The same study observes that natural disasters have grown both more frequent and more severe of late, and that this can be put down to climate change, global warming and ecological degradation acting together. Expert assessments of Turkish agriculture point in the same direction: in a SWOT analysis built on in-depth interviews with fifteen expert academics and agricultural field professionals, Kortak and Çakır (2025) report their participants naming environmental and climatic pressures, global warming and climate change above all, together with migration, food insecurity and heavy reliance on imports, as severe threats to the future and the sustainability of agricultural production. A sustainable future for the sector, they conclude, turns on holding on to advantages such as the country's climatic diversity, on repairing shortfalls in infrastructure and in education, and on building strategic resilience against import dependence, drought and the other climatic threats. Their stated aim is to arrive at policy recommendations in light of projections that climate-change-induced drought will grow more severe and more frequent in the Mediterranean Basin.

What is conspicuously missing, in our reading of this literature, is the household-level financial evidence that exists for South Asia, Sub-Saharan Africa and the United States. We could not identify studies for Türkiye that track rural households' actual loan volumes, interest rates, credit rationing status and informal borrowing before and after specific drought episodes, in the way that Udry (1994) did for northern Nigeria or Kanz (2016) for India, nor portfolio-level studies of Turkish agricultural lenders'

drought exposure comparable to Collier, Katchova and Skees (2011) or Brei et al. (2026). Given that TARSIM already includes a dedicated drought yield insurance line and that credit is central to how farm households finance production, this is a significant gap: the interaction between drought shocks, TARSIM coverage, formal agricultural credit and informal borrowing in Turkish villages is, to the best of our knowledge, essentially unmeasured at the household level. The same appears true for much of the wider Mediterranean basin, precisely the region where drought risk is projected to intensify most.

Conclusion

Drought lowers income across whole regions at once, which is exactly the configuration against which informal risk sharing is weakest; households respond by drawing down grain stocks and selling assets, but these buffers compensate for only a fraction of the shortfall, and the anticipation of such shocks pushes households toward conservative production and employment choices that are safer but carry lower average returns. On the other side of the market, lenders reduce agricultural lending in drought-exposed local markets just as demand for liquidity peaks, and the contraction is sharpest where lenders are local and undiversified. The parallel finding that thinly capitalized banks amplify shock spillovers comes from a flood setting and from firm borrowers rather than farm households, so we read the two strands together as suggestive rather than as a single established regularity. Repayment distress then feeds back into lender behavior. At the extreme end of the indebtedness spectrum, the Indian literature associates indebtedness with farmer suicides, although that literature neither traces the link back to drought nor connects it to lender behavior.

The policy evidence reviewed suggests three design principles. First, ex post generosity is not a substitute for ex ante insurance: unconditional debt relief in India improved balance sheets without restoring investment and was followed by faster-deteriorating loan performance and defaults suggestive of strategic behavior, while in the United States expectations of aid shaped insurance decisions and reduced input spending. Second, predictable, multi-year transfers and pre-committed contingent credit lines performed markedly better, protecting consumption and enabling cheaper adaptation without harming lenders. Third, insurance and credit must be designed jointly rather than bundled mechanically: bundling insurance into loans reduced loan take-up in a setting where, on the suggestive evidence available, limited liability already provided implicit insurance, whereas stand-alone index insurance increased agricultural investment and risk-taking, and liquidity-sensitive contract features such as pay-at-harvest premiums dramatically raised insurance take-up.

For Türkiye, these findings argue for treating drought relief payments, TARSIM drought insurance and subsidized agricultural credit not as three separate administrative programs but as complementary components of an integrated risk management framework, in which the terms of credit respond to insured status, relief is predictable and rule-based rather than discretionary, and contingent liquidity is available when a drought is declared. Building the household-level evidence base for such a framework, panel data following the same rural households' formal and informal borrowing through drought cycles, is in our view the most urgent research task this review identifies for Türkiye and the Mediterranean basin.

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FACTORS AFFECTING YOUNG PEOPLE'S ENTRY INTO AND RETENTION IN AGRICULTURE

GENÇLERİN TARIMA GİRİŞİNİ VE TARIMDA KALMASINI ETKİLEYEN FAKTÖRLER

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Abstract
The ageing of the farming population and the withdrawal of young people from agriculture have become central concerns for agricultural continuity, rural vitality and the future of food systems. This paper reviews the economic, social and institutional factors shaping young people's entry into and retention in farming, with emphasis on land access, finance, farm profitability, income uncertainty and succession. It is a critical narrative review of peer-reviewed research and institutional reports published mainly between 2010 and August 2026. Three findings recur. First, entry barriers are interdependent rather than additive: land prices and insecure tenancy raise start-up capital requirements, limited collateral constrains access to finance, and volatile incomes raise the opportunity cost of farming relative to non-farm employment. Second, entry and retention are analytically distinct outcomes that respond to different instruments; delayed succession in particular may deny young people effective managerial authority even where they are formally registered as holders. Third, the category of young farmer suppresses heterogeneity by entry route, gender, sector, farm size and region, so that a uniform grant may over-subsidise one group while under-serving another. Single-instrument programmes centred on start-up grants therefore cannot secure long-term retention. The review argues that policy should span the full pathway from orientation and entry through establishment and growth to persistence, combining land, finance, markets, social protection, rural services, advice and mentoring in a sequenced package. For Türkiye, it recommends secure access to land, credit guarantees, phased farm succession, stronger producer organisations, independent business development advice, mentoring and investment in the rural quality of life.
Keywords: Young farmers, farm succession, land access, agricultural finance, rural development

Özet
Tarımsal nüfusun yaşlanması ve gençlerin tarımdan uzaklaşması, tarımsal üretimin sürekliliği, kırsal ekonomilerin canlılığı ve gıda sistemlerinin geleceği bakımından temel politika sorunlarından birisidir. Bu çalışma, gençlerin tarıma girişini ve tarımda kalmasını etkileyen ekonomik, sosyal ve kurumsal faktörleri; özellikle araziye erişim, finansman, işletme karlılığı, gelir belirsizliği ve çiftlik devri ekseninde incelemektedir. Çalışma, ağırlıklı olarak 2010–Ağustos 2026 döneminde yayımlanan hakemli araştırmalar ile ulusal ve uluslararası kurum raporlarının eleştirel biçimde değerlendirildiği bir literatür derlemesidir. Literatürde üç bulgu öne çıkmaktadır. Birincisi, sektöre giriş engelleri birbirinden bağımsız değil, karşılıklı olarak bağımlıdır; arazi fiyatları ve güvencesiz kiracılık başlangıç sermayesi ihtiyacını artırmakta, teminat eksikliği finansmana erişimi zorlaştırmakta, değişken tarımsal gelir ise tarım dışı istihdamın fırsat maliyetini yükseltmektedir. İkincisi, tarıma giriş ile tarımda kalma farklı araçlara yanıt veren ayrı sonuçlardır; çiftlik devrinin gecikmesi, gençlerin resmi işletme yöneticisi olsalar bile gerçek karar yetkisine ulaşmasını engelleyebilmektedir. Üçüncüsü, genç çiftçi kategorisi, sektöre giriş yolu, cinsiyet, ürün kolu, işletme büyüklüğü ve bölge bakımından farklılıkları göz ardı etmektedir; bu nedenle, tek tip bir hibe bir grubu gereğinden fazla desteklerken diğer gruba yetersiz destek sunabilir. Bu nedenle yalnızca kuruluş hibesine dayanan tek araçlı politikalar uzun dönemli kalıcılığı güvence altına alamamaktadır. Derleme, genç çiftçi politikasının yönelim ve girişten kuruluş, büyüme ve kalıcılığa uzanan bütün bir süreci kapsamasını; arazi, finansman, pazar, sosyal güvenlik, kırsal hizmetler, danışmanlık ve mentorluk araçlarının sıralı bir paket halinde birleştirilmesini savunmaktadır. Türkiye için araziye güvenli erişim, kredi garantileri, aşamalı çiftlik devri, güçlendirilmiş üretici örgütleri, bağımsız iş geliştirme danışmanlığı, mentorluk ve kırsal yaşam kalitesini yükseltecek yatırımlar önerilmektedir.
Anahtar kelimeler: Genç çiftçi, çiftlik devri, araziye erişim, tarımsal finansman, kırsal kalkınma

Introduction

Generational renewal in agriculture involves considerably more than replacing older farm managers with younger ones. It requires the transfer of productive assets, managerial responsibility, local knowledge, market relationships and innovation capacity to a new cohort, and therefore matters for rural employment, land use and food security as well as for production continuity. The young farmer question is thus not merely demographic; it concerns the economic and institutional reproduction of the sector (Coopmans et al., 2021; Sutherland, 2023). International assessments indicate that young people can act as agents of transformation in agrifood systems while facing constraints in land, credit, training and voice in decision-making (FAO, 2025), and that inadequate rural infrastructure and limited social protection coverage further weaken the appeal of rural and agricultural careers (ILO, 2024).

Policy debate frequently treats the "young farmer" as a single, homogeneous category. In practice, a successor expected to take over a family farm, an entrepreneur entering from outside agriculture, a young woman working unrecognised on a family holding and a young person in a remote region facing weak services do not share the same constraints, and a uniform instrument will not serve them equally. This paper assesses, through a critical narrative review, the principal factors shaping young people's entry into and retention in agriculture. Three questions guide it: which factors recur across the literature and through which mechanisms do they operate; how do they differ by entry route, gender, sector and region; and what design principles follow for an integrated generational renewal policy, particularly in the Turkish context. The paper integrates literatures usually treated separately, distinguishes entry from retention as distinct policy objectives, and translates the resulting principles into a context-specific discussion for Türkiye, a setting under-represented in a predominantly European literature.

Conceptual framework and review method

In most support programmes the young farmer is defined by an age threshold that varies across countries and institutions. Age simplifies administration but conveys little about agricultural experience, effective control of the holding or inherited assets; the OECD accordingly defines new entrants regardless of their age or entry path and notes that the European Union tends to conflate young farmers with new entrants (Campi et al., 2024). A family successor takes over a holding belonging to a parent or close relative together with part of its assets and relationships; a newcomer enters without inheriting land, machinery, customer relationships or occupational knowledge. The successor's advantage is access to assets and established relationships, whereas the newcomer must build a business without them; survey evidence from several European countries indicates that the feeling of being "established" as a farmer is influenced by the mode of entry, and that successors and newcomers differ in their contributions to agriculture and rural development and in their dependency on public support, which underscores the importance of considering entry methods when designing support schemes (Stork et al., 2025). Generational renewal is accordingly a multi-year process rather than a single transaction, so programmes that intervene only at the formal transfer cannot capture the actual transition (Coopmans et al., 2021; Latruffe et al., 2025).

Two analytical points organise the review. The first is complementarity: without land, credit may not create productive capacity; without working capital, land may not be used; without market access, higher output may not raise income; without managerial authority, an educated young person may be unable to innovate. This explains why removing a single constraint does not reliably produce the expected outcome, and why sequencing matters (Coopmans et al., 2021). The second is additionality: support granted to a person who would in any case inherit sufficient land and capital may subsidise a planned transfer rather than generate a new entry, since most audited beneficiaries had set up before knowing that they would receive the aid (European Court of Auditors, 2017); support that presupposes own savings and off-farm income may exclude the most constrained groups (Calo & Corbett, 2024); and area-based payments are associated with higher land sale and rental prices and affect the value of land in ways that can hinder entry (European Court of Auditors, 2017; OECD, 2025).

The study is designed as a critical narrative review, treating the literature review as a research method in its own right (Snyder, 2019); the approach suits a subject lying at the intersection of economics, rural sociology, agricultural policy, land management, finance and family business, where findings cannot be reduced to a single common effect size. The search combined the terms "young farmer", "new entrant", "farm succession", "generational renewal", "land access", "agricultural finance", "farm profitability", "rural youth" and "farm transfer" with their Turkish equivalents, across Web of Science, Scopus, ScienceDirect, SpringerLink, the OECD iLibrary, the FAO Knowledge Repository, EU institutional

portals, DergiPark and official Turkish policy documents, with priority given to material published between 2010 and August 2026. Sources had to relate directly to entry, transfer or retention and to address at least one of land, credit, income, markets, skills, family relations, gender or rural living conditions; institutional reports were included only where they offered evidence-based assessment or an explicit policy framework. No original dataset was constructed and no statistical or meta-analytic analysis was performed. Three limitations follow: the review reports no numerical flow of records and applies no formal quality appraisal; definitions of "young", "new entrant" and "remaining in agriculture" vary across countries and programmes; and the strength of the European literature constrains generalisation to different property and labour regimes. The paper therefore develops context-sensitive principles rather than a universal prescription.

Factors shaping entry into and retention in agriculture

Table 1 sets out the principal factors identified in the literature and the mechanisms through which they operate, organised to emphasise the connections between problems rather than the assumption that each can be addressed by a separate programme.

Table 1. Principal factors shaping young people's entry into and retention in agriculture

Factor domain	Principal economic or institutional mechanism	Key risk or inequality	Appropriate support approach
Access to land	Determines productive capacity, the location of investment and the collateral base.	High prices, fragmented ownership, short-term tenancy, exclusion of entrants from outside the family	Long-term leasing, land banks, matching services, transparent allocation of public land
Finance	Enables establishment investment and working capital to be met.	Lack of collateral and credit history, high debt burden, own-funds requirements	Credit guarantees, staged grant-loan packages, grace periods and business advice
Profitability and income stability	Determines the attractiveness of farming relative to non-farm careers and the capacity to service debt.	Low margins, price and climate risk, input costs, delayed revenue	Market linkage, risk management, value addition and enterprise diversification
Farm succession	Determines the timing of the transfer of management, ownership and knowledge.	Delayed transfer, intergenerational conflict, absence of real authority for the young person	Staged succession plans, independent mediation, alignment of pension and tax rules
Knowledge and mentoring	Strengthens technical, financial and entrepreneurial capacity.	Standardised training, advice ill-adapted to local context, absence of non-family networks	Tailored advisory services, peer learning, long-term mentoring
Markets and producer organisation	Affects prices, input supply, logistics and bargaining conditions.	Small scale, weak bargaining power, high transaction costs	Cooperatives, producer organisations, shared services, contracts and short chains
Rural quality of life	Affects the willingness of the young person and their family to remain in rural areas.	Deficits in health, education, housing, transport, internet access and social life	Place-based rural service packages and infrastructure supporting family life
Gender	Affects the distribution of land, credit, decision-making authority and care work.	Invisibility of women's labour, inequality in inheritance and management	Gender-responsive rights, finance, advisory services and outcome monitoring

Source: Compiled by the author on the basis of the literature reviewed.

Land, finance and profitability

Access to land is the most widespread barrier to entry. Where land is priced by the real estate market, prices can be far higher than what production can justify, so that newcomers struggle to meet purchase costs while family succession remains the most common route to land; support measures are moreover perceived as benefiting primarily those already in a favourable position through family links or high investment capacity (Eistrup et al., 2019). The problem is not confined to price. Short-term, verbal or readily terminable tenancy makes investment in irrigation, soil improvement, perennial crops and buildings risky and raises lenders' assessment of risk; land access is therefore a question of tenure security, contract quality and legal protection of improvements, and not only of ownership. Area-based payments are moreover associated with higher land sale and rental prices and affect the value of land in ways that can hinder entry (European Court of Auditors, 2017; OECD, 2025), which implies that part of any area-linked support may accrue to landowners rather than to the entrant. Land banks, long-term leasing and matching services widen the options, but matching partners solely by business attributes is insufficient: in the Cornwall Fresh Start initiative, differing expectations and concerns about responsibilities and the legal validity of agreements deterred formal joint ventures except where a relationship already existed, so policy should facilitate and formalise existing partnerships with professional business and legal support rather than orchestrate matches between strangers (Ingram & Kirwan, 2011). Comparative evidence from Belgium, Ireland and Poland indicates that new farms formed without inheritance begin with limited land and expand much later than other farms, and that identified successors already display substantial land expansion before transfer (Bertolozzi-Caredio et al., 2026).

Establishment requires machinery, livestock, irrigation, structures, licences, insurance and working capital in addition to land, while revenue is realised only after the production period. Farming demands substantial upfront investment in land, equipment, technologies and infrastructure, which poses particular challenges for those with limited credit history (Campi et al., 2024); where collateral cannot be offered, economically sound projects may therefore fail to start. Access to finance cannot be measured by loan rejection alone. EU survey evidence reports that "fear of possible rejection as a reason of not applying for bank loans is reported by 9% of younger and 7% of older farmers", and that "unfavourable financing costs and lending conditions remained broadly stable, affecting 27% of young farmers in 2024 compared to 30% in 2022" (European Investment Bank, 2026); self-exclusion and unsuitable terms must therefore be considered alongside observed demand. Start-up grants reduce the equity gap but have limited effect where total investment requirements and early-year cash flow are not addressed together, and qualifying thresholds may push young farmers into over-investment. Credit guarantees, longer maturities, repayment aligned to the production cycle, grace periods and income insurance are complementary, and should be delivered alongside independent business plan appraisal, since plans prepared by vendors are oriented towards the sale rather than the net return to the farmer.

Retention additionally requires that the holding generate a regular and adequate income. Price and input-cost volatility, climatic events, disease and marketing losses create substantial year-to-year variation, which is more damaging where the young farmer began with high debt. Because non-farm employment offers regular wages, defined hours and social protection, it raises the opportunity cost of farming, particularly for the educated. Turkish evidence indicates that having personal income or assets, and larger land and livestock holdings in the household, increase the likelihood of staying in agriculture, whereas out-migration from the household and higher education levels decrease it (Ayyıldız et al., 2025). This should not be read as evidence that education is of no value in farming: education widens outside options while strengthening capacity for innovation and financial management, and the binding problem is that many holdings offer neither the scale nor the autonomy to reward those skills. Behavioural analysis of the young farmer payment likewise finds that the payment affects the willingness to stay mainly through non-economic motivations, and that pessimism about farming, integration in family and community, and participation in decision-making weigh more heavily than the payment itself (May et al., 2019). Income stability is also a matter of social protection: informal status leaves rural young workers without protection in the event of shock or crisis, and expanding social protection coverage in rural areas is treated as key to including them in social insurance mechanisms (ILO, 2024); a holding that appears profitable in the short run may therefore be unattractive as a lifetime career.

Markets, succession and managerial authority

Small and newly established holdings have limited bargaining power. Low volumes raise unit transport costs, and quality standards, cold chain and delivery requirements can bar entry to certain markets, so that market access is a starting condition of the business plan rather than a secondary matter. Cooperatives and producer organisations reduce the disadvantage of scale through input supply, shared machinery, storage, processing and marketing; assessments of the Young Farmer Project in Türkiye likewise identify organisation as the most effective route to making the project's effects permanent (Unakıtan & Başaran, 2018) and recommend strengthening organisation among the measures needed to keep young people in rural areas (Kızılaslan & Dağdelen, 2023). Organisation is not, however, a matter of legal registration alone: it requires transparent governance and services grounded in members' actual needs. Contract production can offer sales security, technical support and access to finance while carrying risks of price setting, quality rejection, input debt and single-buyer dependence, so contract literacy and independent legal advice matter.

Farm succession lies at the centre of generational renewal yet is often delayed: older generations may hesitate to pass on the business for lack of retirement provision or out of concern about how it will be run once handed over (Campi et al., 2024), and without legal and advisory support transfer can be delayed or poorly managed, leading to conflict and uncertainty (European Commission, 2025). That a young person works on the holding does not mean that authority has been transferred: cropping, investment, credit and sales decisions may remain with the previous generation, and a young person who assumes responsibility without a share of income and decision-making may conclude that no independent career is possible. Effective transfer therefore requires the phased sharing of income, information and authority, not only of workload. Ownership and management need not transfer on the same date: a gradual transition through alternative business structures such as partnerships is under way as a route to generational renewal (Shin et al., 2024), and a period of overlap or collaborative working before the transfer is finalised is beneficial to a successful succession (Latruffe et al., 2025). The concerns about the legal security of joint arrangements reported by Ingram and Kirwan (2011) indicate that responsibilities, profit shares, investment authority, debt obligations and exit conditions should be set out in writing. Where the older farmer's retirement income is inadequate, land is retained as security and a start-up grant will not deliver control of the holding; pension, tax and inheritance rules designed independently of young farmer policy may preserve incentives that delay transfer, and Irish microsimulation results indicate that under current policy retaining a farm until death may be more economically beneficial to the farmer than transferring it before death (Leonard et al., 2017). Independent advisers and mediators can render visible the questions of ownership, sibling balance and elder care that families find difficult to discuss, and evidence from French cattle farming identifies three distinct successor profiles and calls for policies adapted to the needs of those entering from outside farming (Latruffe et al., 2025).

Knowledge, rural quality of life and uncertainty

The knowledge young farmers require extends well beyond production technique: farm business owners still need operational and financial management skills alongside new entrepreneurial and digital skills (Campi et al., 2024), and demand for entrepreneurial and management skills, digital know-how and marketing is expected to increase (OECD, 2025). Training focused on technique alone therefore risks producing holdings that farm well but remain financially fragile. Extension must be adapted to local crop, climate and market conditions and timed to the producer's decision point, and a continuing learning relationship should replace the single training certificate. Mentoring (a development relationship of defined duration between an experienced producer or specialist and a young entrant) extends beyond technical problem-solving to decision-making, occupational identity and network building, and is especially valuable to entrants from outside agriculture who lack the networks that arise naturally within farming families. Mentor selection should not rest on production experience alone: communication and feedback skills should be developed and commercial conflicts of interest disclosed. Young people's decision to remain in rural areas depends on services provided beyond the holding. Where healthcare, childcare, eldercare, transport, housing, education and employment opportunities lag behind urban standards, young people hesitate to stay in or return to farming (European Commission, 2025), and rural youth are constrained by the lack of effective infrastructure and quality services, with childcare deficits a particular barrier for young women (ILO, 2024); in such settings even a profitable holding may not retain a young household.

These costs do not appear in the farm account but reduce the real return to an agricultural career, which makes rural infrastructure a core rather than incidental element of young farmer policy; the OECD recommends both changing social perceptions of farming and investing in public services and digital infrastructure while reducing barriers to entry (OECD, 2025); reading the evidence reviewed here together, however, image campaigns are unlikely to strengthen the standing of the occupation durably unless they are matched by fair income, decision autonomy and access to public services. Workload and mental wellbeing are frequently neglected: studies in Ireland and the United Kingdom show that social life, the ability to take time away from the farm, gendered pressures, confidentiality concerns and help-seeking behaviour all shape young farmers' wellbeing, so rural mental wellbeing services must be accessible and confidential, offered in informal social settings and in forms that do not require travel (Rose et al., 2024). Young farmers also enter with long investment horizons while facing climate shocks, and their limited equity means that a given shock has more severe consequences than for an established holding, so generational renewal support should be linked to climate adaptation instruments. Policy continuity matters equally: irregular calls, frequent rule changes and payment delays disrupt the timing of land rental and investment, and administrative inconsistency burdens newcomers more than established holdings.

Heterogeneity within the young farmer population

Family successors and newcomers of the same age hold different starting packages. Inheritance may grant the successor access to land but not necessarily the resources to farm it, whereas newcomers can bring skills, networks, financial capital and new organisational and business models from outside farming and are more likely to engage in alternative and value-added farming (Campi et al., 2024); the two groups also differ in their contributions to agriculture and rural development and in their dependency on public support (Stork et al., 2025). The newcomer's most significant deficit is local embeddedness: rental opportunities, reliable workers and service providers, informal market information and neighbourhood relationships are largely unavailable on the open market, older farmers value people they know or who are known in the community, and only where a relationship had already been established did participants commit to a formal joint venture, so matching programmes must help build and formalise relationships rather than merely advertise holdings (Ingram & Kirwan, 2011). The successors' resource advantage does not justify directing all support to that group, since newcomers tend to be more innovative and bring advanced skills, and young farmer supports are in practice often farm successor supports, so support for succession and for new entry should be distinguished (Sutherland, 2023). Incubator farms, shared infrastructure and mentor matching matter most for newcomers, whereas succession planning, ownership arrangements among siblings, taxation and managerial autonomy matter most for successors, a distinction a single "young farmer grant" cannot target, and one that monitoring systems must record if additionality is to be assessed.

Although women make a substantial labour contribution, they are considerably less visible in ownership, farm management and formal decision-making. Gender norms in farm succession continue to privilege sons and dismiss daughters, and the commitment to keeping the family farm intact takes priority (Sheridan et al., 2021); where family labour is classified as help, experienced women may in addition go unrecognised as young farmers or successors, which constrains their access to land, collateral and hence finance. Gender in farm transfer is not only a matter of inheritance shares: who operates machinery, goes to market, deals with banks and participates in strategic decisions shapes managerial identity, and formal applications made in a husband's or father's name prevent women from building their own credit history, social security entitlements and professional networks. Comparative evidence indicates that new female farmers face greater difficulties in expanding their land base after installation (Bertolozzi-Caredio et al., 2026), so support should extend beyond additional application points to visibility in ownership and tenancy contracts, individual bank accounts, credit guarantees, childcare and demonstrated managerial authority. Programme reporting should monitor rights over land, participation in income and investment decisions, social security coverage and actual management, rather than the number of women among applicants.

Risk profiles also vary by sector, farm size and region. Livestock farming entails high daily workload and building capital; fruit production a long establishment period and climatic risk; arable farming land scale and machinery costs; vegetable and protected cultivation labour and market access. Uniform grant amounts and business plan criteria are therefore problematic. Farm size does not explain support needs in a single direction either: small holdings require less start-up capital but face high unit costs, while

large holdings offer greater income potential alongside greater debt and management risk, so programmes should assess resource efficiency, income stability, workload and market position rather than treating growth in size as success in itself. In remote, mountainous and arid regions land is cheaper but irrigation, transport, internet, health and market services are often inadequate; in peri-urban regions market opportunities are strong but land prices and non-agricultural use pressure rise. Generational renewal is thus a place-based policy, in which a national framework sets common rights and standards while implementation instruments are adapted to regional conditions.

Towards an integrated generational renewal policy

The most consistent conclusion of the literature is that generational renewal cannot be achieved through a single instrument: the factors interact, many of the relevant rules lie outside agricultural policy (inheritance and tax regulations, tenure legislation, rural planning), and national and local policies do not always form a legislative context that is constructively supportive of renewal (Coopmans et al., 2021). Policy design should therefore focus on the sequencing, targeting and institutional coherence of instruments rather than on the number of programmes. The European Union's 2025 Strategy for Generational Renewal in Agriculture moves in this direction, addressing access to finance, skills, land, living conditions and succession together, and setting out instruments such as national generational renewal strategies and a European Land Observatory (European Commission, 2025).

Five design principles follow. First, support should be organised around the developmental stages of the holding rather than the moment of application: orientation and appraisal of the business proposition before entry; land, investment and working capital at establishment; markets, advisory services and risk management in the early years; productivity, value addition and managerial capacity at growth. Staged support should not mean rigid performance penalties, since weather and markets lie beyond the young farmer's control, and the advisory and inspection functions should be clearly separated. Second, land instruments should widen options beyond purchase: land banks and matching systems with transparent listing, standard contracts and dispute resolution; long-term leasing with explicit treatment of tenant investments at contract end; priority in public land allocation that also considers land quality, water and market access, since offering unviable land as "young farmer support" transfers the risk of failure to the young person; and coherence with consolidation, inheritance and land-use policy.

Third, financial instruments should be combined rather than sequenced by institution: grants to reduce the equity gap, guarantees to relieve collateral shortfalls, long-term credit for fixed investment and working capital for the first production period, with repayment adapted to the cash flow of the product concerned and rules for grace periods and restructuring defined in advance. Risk sharing should prevent collapse in the face of shocks beyond the young farmer's control without encouraging imprudent borrowing, which requires procedural coherence among insurance, disaster support and credit programmes. Fourth, succession should be treated as a two-generational and staged process: tax and support advantages linked to the acquisition of managerial responsibility, income share and decision-making authority rather than to the transfer of title alone; written regulation of investment, debt, workload, profit, social security and termination in partnership arrangements; adequate pension, housing and care options for the older generation; and impartial valuation and mediation in non-family transfers. Fifth, advisory services, mentoring and peer networks should convert individual support into durable capacity, through a one-stop system that directs the young farmer to the appropriate specialist and networks accessible to women and to entrants from outside agriculture. Underpinning all five, rural health, education, childcare, transport, housing and internet services, spousal employment opportunities and relief-worker arrangements determine whether the household remains in the countryside at all. Evaluation should accordingly track retention, effective management, real income, debt sustainability, tenure security and women's decision-making authority rather than counting beneficiaries and assets.

Implications for Türkiye

In Türkiye, young people's retention in agriculture is shaped by the joint influence of farm structure and rural living conditions: small and fragmented holdings, income uncertainty, the attractiveness of non-farm employment, access to social services and occupational status. Ayyıldız et al. (2025) report that having personal income or assets, and larger land and livestock holdings in the household, increase the likelihood of staying in agriculture, whereas out-migration from the household and higher education levels decrease it, indicating the need for policies that improve income, asset and career conditions rather than simply expecting young people to take an interest in agriculture. Evidence from the Young Farmer

Project is consistent with the entry-retention distinction: in the Turhal district of Tokat a substantial proportion of beneficiaries already operated a holding before support, and a considerable share retained an intention to migrate to urban areas, so that receiving support is not equivalent to new entry or to long-term persistence (Kızılaslan & Dağdelen, 2023). Programmes should therefore be assessed against pre-support status and a follow-up period rather than payment and asset delivery alone. Provision of livestock, greenhouses or equipment can create productive capacity while deficits in feed, husbandry, energy, veterinary services, marketing and working capital persist; where project selection is not linked to local market and service infrastructure, the same investment yields very different outcomes across regions, which argues for regional value chain analysis and staged business plans in place of standard investment packages.

Access to land is a fundamental problem area. Fragmentation through inheritance, shared ownership, long-unused parcels and unwritten tenancy relationships all reduce investment security. Alongside consolidation and registration, secure leasing and the transparent return of idle land to production are needed, with standard contracts protecting both the landowner's rights and the young farmer's long-term investments. On the financial side, deficits in equity and collateral make credit guarantees and long-term repayment models important; although IPARD III and national rural development support provide investment opportunities, application preparation capacity, co-financing requirements and pre-implementation cash needs may favour stronger holdings, so advisory support should address the consistency of the investment with the real capacity of the holding rather than the preparation of project files. Producer organisations can improve market and service access, and the proposal for young farmer cooperatives, owned and managed by young farmers themselves, aims to offset the small and fragmented structure of individual holdings through bargaining power in input supply, joint marketing, the consolidated cultivation of fragmented parcels and the leasing of idle land (Unakıtan & Başaran, 2018); establishing new cooperatives is not always necessary, however, and opening management, services and decision-making space to young members within existing cooperatives and unions may prove more sustainable.

The extension system should combine technical knowledge with farm management. The working documents of the Fourth Agriculture and Forestry Council and the Fourth National Rural Development Strategy indicate that rural extension, infrastructure, employment and living conditions should be addressed together (Ministry of Agriculture and Forestry, 2024, 2025), and within this framework joint mentoring networks could be established at provincial and district level among young farmer advisers, universities and producer organisations. Mentoring may be particularly useful for young people without family experience in agriculture, for holdings shifting to new products and for women entrepreneurs; programmes should not depend on mentors selling their own products, and in product-intensive regions such as Mersin, Adana and Antalya mentor pools could be formed for fruit growing, beekeeping, protected cultivation and livestock farming, with mentors trained in farm management and communication. The numerical visibility of young women in support programmes should not be equated with economic empowerment: ownership of land and livestock, the income account, social security coverage, investment decisions and control over sales should be monitored, and childcare, transport, safe working conditions, credit guarantees and participation in cooperative governance should form part of the programme.

Rural quality of life cannot be considered independently of farm income. The Fourth National Rural Development Strategy and the Council documents emphasise infrastructure, education, health, access to digital services, social programmes for women and young people and the diversification of the rural economy beyond agriculture for the attractiveness of rural areas (Ministry of Agriculture and Forestry, 2024, 2025). Where a settlement receiving young farmer investment support has weak access to schooling, transport or health care, the household may continue to gravitate towards urban areas. The institutional model proposed here is a "young farmer transition plan" combining national standards with local implementation, in which the applicant's entry route, land rights, financing requirements, product and market plan, training and mentoring needs and household living conditions are assessed together, divided into three- or five-year phases with scope for revision, and supported by a local adviser independent of banking and inspection functions. For evaluation, linking the Farmer Registration System with support, social security and business records within a legal and ethical framework would allow independent comparison of the long-term situation of supported and comparable non-supported young people.

Conclusion

Securing young people's entry into and retention in agriculture is not simply a matter of lowering the average age of the farming population. Generational renewal requires that productive assets, managerial responsibility, knowledge and market relationships be transferred to a new cohort in a manner that is economically viable and socially sustainable, so that young farmer policy must pursue objectives of job quality, income, rights and decision autonomy alongside demographic targets. The central finding of the literature is complementarity: investment cannot be secured without secure land, production cannot be sustained without working capital, income cannot be generated without markets, innovation cannot be implemented without managerial authority, and household retention cannot be achieved without rural services. A one-off grant addresses only one component of this whole.

Four priorities follow for policy design. Young people should not be treated as a homogeneous group: distinct entry routes and support combinations are required for family successors, newcomers, young women and young people in different production systems, and the age criterion should be complemented by criteria capturing differences in resources and authority. Support should extend across the orientation-entry-establishment-growth-persistence pathway, with monitoring that assesses whether the young farmer has acquired effective managerial control and economic resilience rather than only whether the investment was made. Farm transfer should be managed as a two-generational and staged process, with early planning, written allocation of duties and income, independent mediation and retirement security for the older generation. And rural quality of life should be placed at the centre of the policy. Critical scholarship on "predatory inclusion" is a useful corrective here: policy that invites newcomers into precarious and uncompensated labour, or grants short-term access to land at the price of long-term financial liability, increases the number of entries without securing the conditions of a viable career (Calo & Corbett, 2024).

Four gaps merit attention in future research: the scarcity of longitudinal evidence tracking supported and comparable non-supported young farmers over periods long enough to separate entry from retention; the underdeveloped measurement of effective managerial authority as distinct from formal holdership; the thinness of evidence from middle-income and non-European settings, including Türkiye; and the limited attention to the interaction between generational renewal instruments and climate adaptation policy. In Türkiye, a new approach should combine the National Rural Development Strategy, the development plan, IPARD, national investment support, agricultural extension and social policy within a common transition plan, and success should be assessed by young people's continuation in farming, the viability of their holdings, tenure security, decision-making authority, the empowerment of women and improvements in rural quality of life. Retaining young people in agriculture ultimately requires that they be seen not as inexpensive labour filling gaps in an existing structure but as rights-bearing farm managers and agents of rural transformation.

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ALTERNATİF DOĞUM YÖNTEMLERİ: SUDA DOĞUM, PLANLI EVDE DOĞUM, SEZARYEN SONRASI VAJİNAL DOĞUM VE EPİDURAL DOĞUM

ALTERNATIVE BIRTH METHODS: WATER BIRTH, PLANNED HOME BIRTH, VAGINAL BIRTH AFTER CESAREAN, AND EPIDURAL BIRTH

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ABSTRACT

Objective

Although the physiology of birth has remained unchanged for thousands of years, the ways in which birth is managed have evolved significantly. Alternative birth methods such as water birth, planned home birth, vaginal birth after cesarean (VBAC), and epidural birth have become increasingly popular with the common goals of careful monitoring, reducing unnecessary interventions, involving parents in decision-making, and supporting women's autonomy. This narrative review aims to examine the benefits, risks, eligibility criteria, and current evidence regarding these alternative birth methods.

Materials and Methods: This narrative review was conducted by synthesizing current national and international guidelines and evidence-based literature on water birth, planned home birth, vaginal birth after cesarean (VBAC), and epidural analgesia. Key sources included recommendations from ACOG and other professional organizations, along with recent clinical studies and systematic reviews related to maternal and neonatal outcomes of these alternative birth methods.

Results: Water immersion during the first stage of labor is associated with reduced pain perception, decreased need for pharmacological analgesia, shorter labor duration, and higher maternal satisfaction; however, evidence regarding the second stage remains limited, and ACOG recommends delivery out of water. Planned home birth, when conducted for low-risk women with appropriate preparation, can reduce rates of induction, episiotomy, and cesarean section while improving psychological outcomes. VBAC success rates generally range between 60% and 80%, with previous vaginal birth history being the strongest predictor, along with maternal height, estimated fetal weight, and cervical dilatation. Modern low-dose epidural analgesia provides effective pain relief with minimal impact on labor progress and operative delivery rates, and large-scale evidence suggests it may reduce severe maternal morbidity.

Conclusion: In conclusion, the safe implementation of alternative birth methods requires evidence-based protocols and woman-centered care. When appropriate eligibility criteria are applied and continuous monitoring is ensured, these methods can support maternal autonomy, reduce unnecessary interventions, and improve birth experiences without compromising safety.

Keywords: Water birth; Planned home birth; Vaginal birth after cesarean; Epidural analgesia

ÖZET

Amaç: Doğumun fizyolojisi değişmemiş olsa da yönetim şekilleri yıllar içinde çeşitlenmiştir. Suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum (SSVD/VBAC) ve epidural doğum gibi alternatif yöntemler, gereksiz müdahaleleri azaltma, ebeveynlerin karar alma süreçlerine katılımını artırma ve kadın merkezli bakım sunma amacıyla giderek daha fazla tercih edilmektedir. Bu derleme, söz konusu alternatif doğum yöntemlerinin yararları, riskleri, uygulama kriterleri ve güncel kanıtlar ışığında incelenmesini amaçlamaktadır.

Materyal ve Yöntem

Bu anlatısal derleme, suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum (SSVD) ve epidural analjezi konularındaki güncel ulusal ve uluslararası kılavuzlar ile kanıta dayalı literatürün sentezlenmesiyle gerçekleştirilmiştir. Kaynaklar arasında ACOG önerileri, mesleki örgütlerin rehberleri ve bu alternatif doğum yöntemlerinin maternal ve neonatal sonuçlarına ilişkin klinik çalışmalar ile sistematik derlemeler yer almaktadır.

Bulgular
Suda doğum, özellikle doğumun birinci evresinde ağrı algısını azaltmakta, farmakolojik analjezi ihtiyacını düşürmekte ve doğum memnuniyetini artırmaktadır; ancak ikinci evrede su altında doğum konusunda kanıtlar sınırlıdır ve ACOG su dışında doğumu önermektedir. Planlı evde doğum, düşük riskli gebelerde indüksiyon, epizyotomi ve sezaryen oranlarını azaltırken, uygun hazırlıklarla gerçekleştirildiğinde güvenli bir seçenek olabilir. SSVD başarı oranı genel olarak %60-80 arasında değişmekte olup, önceki vajinal doğum öyküsü, maternal boy, fetal ağırlık ve servikal dilatasyon gibi faktörler başarıyı belirlemektedir. Epidural analjezi etkili ağrı kontrolü sağlarken, modern düşük doz tekniklerle doğum süresi ve operatif doğum riski üzerindeki olumsuz etkiler büyük ölçüde azalmıştır; ayrıca şiddetli maternal morbiditeyi azaltıcı etkisi bildirilmektedir.

Sonuç
Sonuç olarak, alternatif doğum yöntemlerinin güvenli uygulanması için kanıta dayalı protokoller ve kadın merkezli danışmanlık kritik öneme sahiptir. Uygun seçim kriterleri uygulandığında ve sürekli izlem sağlandığında, bu yöntemler maternal özerkliği destekleyebilir, gereksiz müdahaleleri azaltabilir ve doğum deneyimini iyileştirebilir.
Anahtar Kelimeler: Suda doğum; Planlı evde doğum; Sezaryen sonrası vajinal doğum; Epidural doğum

GİRİŞ
Doğum, insanlık tarihi boyunca var olan doğal bir süreç olmasına rağmen, modern tıbbın gelişmesiyle birlikte doğum yönetimi önemli ölçüde değişmiştir. Hastane temelli, müdahaleci yaklaşımların yaygınlaşmasıyla birlikte, birçok kadın daha az müdahaleli, kadın merkezli ve özerkliğini destekleyen alternatif doğum yöntemlerine yönelmiştir.[1] Suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum (SSVD) ve epidural analjezi eşliğinde doğum, bu alternatif yaklaşımların başlıcaları arasında yer almaktadır. Bu yöntemlerin ortak hedefleri; gereksiz tıbbi müdahaleleri azaltmak, ebeveynlerin karar alma süreçlerine aktif katılımını sağlamak, maternal memnuniyeti artırmak ve güvenli koşullarda fizyolojik doğumu desteklemektir.[2] Ancak her yöntemin kendine özgü yararları, riskleri ve uygulama kriterleri bulunmaktadır. Kanıta dayalı uygulamalar ve uygun aday seçimi, bu yöntemlerin güvenli şekilde sunulabilmesi için temel koşullardır. Bu anlatısal derlemenin amacı, suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum ve epidural doğum yöntemlerini güncel kılavuzlar ve bilimsel kanıtlar ışığında incelemek; yararları, riskleri, uygunluk kriterleri ve ebelik uygulamaları açısından değerlendirmektir.

GELİŞME
1. Suda Doğum
Suda doğum, doğum eyleminin birinci ve/veya ikinci evresinin ılık su dolu bir küvette gerçekleşmesini ifade eder. Birinci evrede suya daldırma (immersion), ağrı algısını azaltma, farmakolojik analjezi ihtiyacını düşürme, doğum süresini kısaltma ve maternal memnuniyeti artırma ile ilişkilendirilmiştir.[3],[4] ACOG, sağlıklı, komplike olmayan gebeliklerde (37 0/7 – 41 6/7 hafta) birinci evrede su immersiyonunu önerebileceğini belirtmektedir.[5]
İkinci evrede (bebeğin su içinde doğması) ise kanıtlar daha sınırlıdır. Sistematik derlemeler ve meta-analizler, düşük riskli gebelerde maternal enfeksiyon riskinin artmadığını, postpartum kanama riskinin azaldığını ve bazı neonatal sonuçların (düşük Apgar skoru, NICU yatışı) olumlu etkilendiğini bildirmektedir. Ancak kordon avülsiyonu riskinde hafif artış gözlenmiştir.[6] ACOG, ikinci evrede su içinde doğum için yeterli veri olmadığını vurgulayarak, doğumun karada gerçekleşmesini önermektedir.[5]
Uygun aday seçimi (düşük riskli gebelik, tekil, baş gelişi, term), hijyenik koşullar, deneyimli ekip ve acil durum protokollerinin hazır olması suda doğumun güvenliği için kritik öneme sahiptir. Ebeler, su immersiyonu sırasında sürekli izlem, pozisyon desteği ve anne-bebek bağlanmasının desteklenmesi konusunda önemli rol oynar.

2. Planlı Evde Doğum
Planlı evde doğum, düşük riskli gebelerin, deneyimli ebe veya doğum ekibi eşliğinde, önceden planlanmış şekilde ev ortamında doğum yapmasıdır. Literatürde planlı evde doğumun, hastane doğumuna kıyasla daha az müdahale (indüksiyon, epizyotomi, epidural, sezaryen) ile ilişkili olduğu gösterilmiştir.[7] Maternal memnuniyet ve psikolojik sonuçlar genellikle daha olumludur.

Ancak bazı meta-analizler, planlı evde doğumlarda neonatal mortalite riskinin hafif artış gösterebileceğini bildirmiştir. Bu nedenle, uygun aday seçimi (düşük risk, multiparite avantajı, acil transfer planı), deneyimli ekip, acil durum ekipmanı ve hastaneye hızlı transfer imkanı zorunludur.[8] ACOG, sezaryen sonrası vajinal doğum (TOLAC) adaylarının evde doğum için uygun olmadığını vurgulamaktadır.[9]

Türkiye'de planlı evde doğum uygulamaları sınırlı olup, yasal ve kurumsal altyapının güçlendirilmesi gerekmektedir. Ebeler, risk değerlendirmesi, bilgilendirilmiş onam, doğum planı hazırlığı ve postpartum izlem süreçlerinde merkezi rol üstlenir.

3. Sezaryen Sonrası Vajinal Doğum (SSVD / VBAC)

Sezaryen sonrası vajinal doğum (SSVD), önceki sezaryen doğumu olan kadınların sonraki gebeliklerinde vajinal doğum denemesidir (TOLAC – Trial of Labor After Cesarean). Başarı oranı genel olarak %60-80 arasında değişmekte olup, en güçlü öngörücü faktör önceki vajinal doğum öyküsüdür. Maternal boy, tahmini fetal ağırlık, servikal dilatasyon ve önceki kesi tipi de başarıyı etkileyen faktörler arasındadır.[10]

ACOG, tek düşük transvers kesi öyküsü olan çoğu kadının SSVD için aday olduğunu ve danışmanlık alması gerektiğini belirtmektedir. Kontrendikasyonlar arasında klasik veya T tipi kesi, önceki uterus rüptürü ve vajinal doğumu engelleyen diğer durumlar yer alır. Uterus rüptürü riski yaklaşık %0,5-1 civarındadır ve acil sezaryen imkanı olan merkezlerde uygulama önerilir.[11]

Epidural analjezi SSVD sırasında kullanılabilir. Evde SSVD ise yüksek risk nedeniyle önerilmemektedir. Ebeler, aday değerlendirmesi, risk-yarar bilgilendirmesi, doğum eylemi sırasında yakın izlem ve acil durum yönetiminde aktif rol alır.

4. Epidural Doğum (Epidural Analjezi)

Epidural analjezi, doğum sırasında en sık kullanılan farmakolojik ağrı kontrol yöntemidir. Modern düşük doz epidural teknikler, etkili ağrı giderimi sağlarken doğum süresi ve operatif doğum riski üzerindeki olumsuz etkileri büyük ölçüde azaltmıştır.[12] Epidural, sezaryen doğum riskini artırmamaktadır.

Yararları arasında yüksek maternal memnuniyet, ağrı kontrolü ve bazı çalışmalarda şiddetli maternal morbiditede azalma yer alır. Olası yan etkiler arasında hipotansiyon, motor blok, idrar retansiyonu ve nadiren ciddi nörolojik komplikasyonlar bulunur. Bebek üzerindeki etkiler genellikle geçicidir.[13]

Epidural uygulaması anestezi uzmanı tarafından gerçekleştirilmekle birlikte, ebeler doğum eylemi sırasında sürekli destek, pozisyon değişikliği, mesane yönetimi ve maternal-fetal izlem konularında kritik rol oynar. Kadın merkezli yaklaşımda epidural, "doğal doğumu bozan" bir müdahale olarak değil, bilinçli bir seçenek olarak sunulmalıdır.

5. Ebelik Açısından Değerlendirme ve Ortak İlkeler

Tüm alternatif doğum yöntemlerinde ortak olan temel ilkeler şunlardır:

- Kanıta dayalı uygunluk kriterlerinin uygulanması,
- Bilgilendirilmiş onam ve paylaşımlı karar verme,
- Sürekli risk değerlendirmesi ve acil durum hazırlığı,
- Kadın merkezli, saygılı ve destekleyici bakım,
- Multidisipliner ekip çalışması.

Ebeler, bu süreçlerin her aşamasında eğitici, danışman, savunucu ve bakım verici rollerini üstlenerek maternal özerkliği ve güvenli sonuçları destekler.

Suda doğum uygulamalarında ebelik bakımı, suyun sıcaklık kontrolü, annenin hidrasyonu, pozisyon değişikliklerinin desteklenmesi ve continuous support prensiplerinin uygulanmasını içerir. Ayrıca, doğum sonrası ilk emzirmenin su içinde veya hemen çıkış sonrası desteklenmesi maternal-infant bağlanmayı güçlendirir.

Planlı evde doğumda başarıyı etkileyen en önemli faktörler arasında multiparite, önceki vajinal doğum öyküsü, düşük risk profili ve acil transfer için hazırlıklı olunması yer alır. Ev ortamında doğum yapan kadınlar, hastane ortamına göre daha fazla hareket özgürlüğü, mahremiyet ve kontrol hissi bildirmektedir. Ancak perinatal mortalite riskindeki olası artış nedeniyle, seçim süreci dikkatli bilgilendirme ve risk-yarar analizini gerektirir.

SSVD sürecinde ebelik bakımı, doğum eyleminin yakın izlemi, uterus rüptürü belirtilerinin erken tanınması (ani ağrı, fetal kalp hızı değişiklikleri, kanama) ve acil sezaryene hazırlıklı olunmasını kapsar.

Başarı oranını artırmak için, doğum eyleminin doğal seyrinin desteklenmesi, gereksiz indüksiyonlardan kaçınılması ve kadın merkezli destek önemlidir.

Epidural analjezi uygulanan kadınlarda ebelik bakımı, motor bloğun derecesine göre pozisyon değişikliği, mesane kateterizasyonu ihtiyacının değerlendirilmesi, kan basıncı izlemi ve ikinci evrede ıkınma desteğini içerir. Modern düşük doz epidural teknikler sayesinde kadınlar sıklıkla hareket edebilmekte ve aktif ıkınabilmektedir. Bu durum, operatif doğum riskinin azalmasına katkı sağlar.

Alternatif doğum yöntemlerinin güvenli şekilde yaygınlaştırılması için sağlık sistemlerinde altyapı, eğitim ve protokol geliştirme çalışmalarına ihtiyaç vardır. Ebelerin bu yöntemler konusunda yeterli bilgi ve beceriye sahip olması, sürekli mesleki gelişim programları ile desteklenmelidir. Ayrıca, kadınların bilinçli seçim yapabilmesi için antenetal dönemde kapsamlı bilgilendirme ve danışmanlık hizmetleri sunulmalıdır.

Sonuç olarak, suda doğum birinci evrede güçlü kanıtlarla desteklenirken ikinci evrede ihtiyatlı yaklaşım gerektirir; planlı evde doğum düşük riskli multiparlarda avantaj sağlarken neonatal riskleri dikkate almayı zorunlu kılar; SSVD uygun adaylarda yüksek başarı oranına sahiptir; epidural analjezi ise modern tekniklerle güvenli ve etkili bir seçenektir. Tüm bu yöntemlerde ortak nokta, kadın merkezli, kanıta dayalı ve güvenli bakım sunulmasıdır.

Literatürde alternatif doğum yöntemlerine ilişkin kanıt düzeyi yöntemler arasında farklılık göstermektedir. Suda doğumun birinci evresi için güçlü kanıtlar mevcutken, ikinci evre için daha fazla randomize kontrollü çalışmaya ihtiyaç vardır. Planlı evde doğum için seçim biası ve transfer oranları sonuçları etkileyebilmektedir. SSVD için prospektif kohort çalışmaları başarı oranlarını netleştirmiştir. Epidural analjezi için ise büyük ölçekli çalışmalar modern tekniklerin güvenliğini desteklemektedir.

Ebelik eğitiminde alternatif doğum yöntemlerine yer verilmesi, mezuniyet sonrası eğitim programlarının güçlendirilmesi ve klinik protokollerin standartlaştırılması, bu yöntemlerin güvenli şekilde sunulmasına katkı sağlayacaktır. Ayrıca, kadınların doğum tercihlerini etkileyen sosyokültürel faktörlerin anlaşılması ve danışmanlık süreçlerinde dikkate alınması önemlidir.

Gelecek araştırmalarda, Türkiye koşullarında alternatif doğum yöntemlerinin uygulanabilirliği, ebelik uygulamalarının etkinliği ve maternal-neonatal sonuçların değerlendirildiği çok merkezli çalışmaların yapılması önerilmektedir. Bu sayede ulusal kılavuzların geliştirilmesi ve kanıta dayalı uygulamaların yaygınlaştırılması mümkün olacaktır.

SONUÇ

Suda doğum, planlı evde doğum, sezaryen sonrası vajinal doğum ve epidural analjezi, uygun koşullarda uygulandığında maternal özerkliği destekleyen, gereksiz müdahaleleri azaltan ve doğum deneyimini olumlu etkileyen alternatif yöntemlerdir. Her yöntemin kendine özgü yarar ve risk profili bulunmaktadır; bu nedenle bireyselleştirilmiş risk değerlendirmesi ve kanıta dayalı protokoller zorunludur. Güvenli uygulama için; düşük riskli aday seçimi, deneyimli ekip, acil durum planları, sürekli izlem ve kadın merkezli danışmanlık temel unsurlardır. Ebeler, bu alternatif yöntemlerin güvenli ve saygılı şekilde sunulmasında kilit role sahiptir. Gelecekte, yerel koşullara uygun protokollerin geliştirilmesi ve ebelik uygulamalarına entegrasyonunun güçlendirilmesi önerilmektedir

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SAĞLIKLI YAŞAM BİÇİMİ DAVRANIŞLARININ FERTİLİTE ÜZERİNDEKİ ETKİSİ VE FERTİLİTENİN DESTEKLENMESİNDE EBENİN ROLÜ

THE IMPACT OF HEALTHY LIFESTYLE BEHAVIORS ON FERTILITY AND THE ROLE OF MIDWIVES IN SUPPORTING FERTILITY

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ABSTRACT

Objective

Infertility is a global public health issue affecting approximately 10–15% of reproductive-aged couples and is defined by the World Health Organization (WHO, 2025) as a disease of the reproductive system. Alongside organic and pathological causes, modifiable lifestyle behaviors—including nutrition, body weight, physical activity, tobacco/alcohol/substance use, psychological stress, environmental toxins, endocrine-disrupting chemicals (EDCs), sleep disturbances, and electromagnetic exposure—play a critical role in infertility etiology. This narrative review aims to examine the biological and hormonal mechanisms through which healthy lifestyle behaviors influence fertility and to highlight the key roles of midwives as educators, counselors, and care providers in protecting reproductive health and supporting fertility.

Materials and Methods

A comprehensive literature search was conducted across PubMed, Web of Science, Scopus, ScienceDirect, CINAHL, and the YÖK Thesis Center databases using combinations of keywords including infertility, fertility, lifestyle factors (BMI, nutrition, exercise, toxic exposures), endocrine disruptors, and midwifery care. Current national and international clinical guidelines (WHO, 2025; ASRM, 2024; ESHRE) alongside evidence-based literature published between 2021 and 2026 were retrieved and synthesized in accordance with APA referencing standards.

Results

The synthesized literature demonstrates that obesity (BMI ≥ 30 kg/m²) and low body weight (BMI < 18.5 kg/m²) impair ovulation and oocyte quality in women while decreasing sperm concentration and motility in men. Adherence to a Mediterranean diet rich in antioxidants and omega-3 fatty acids positively correlates with improved semen parameters and higher IVF success rates. Moderate physical activity supports fertility; however, strenuous or elite exercise can negatively affect ovarian function and semen quality. Active and passive smoking, alcohol abuse, high caffeine intake (>300 mg/day), chronic stress, sleep deprivation, exposure to EDCs (phthalates, parabens, heavy metals in cosmetics), and elevated scrotal temperature are consistently associated with increased sperm DNA fragmentation, reduced ovarian reserve, and prolonged time-to-pregnancy.

Conclusion

Healthy lifestyle interventions represent cost-effective, high-impact strategies that significantly improve both natural conception rates and assisted reproductive technology outcomes. Midwives, operating on the frontline of primary healthcare and reproductive health services, are uniquely positioned to screen for lifestyle risk factors, deliver individualized counseling, facilitate stress and weight management, and foster sustainable health behavior changes. Integrating midwife-led holistic lifestyle coaching into preconception and infertility care pathways is strongly recommended.

Keywords: Infertility; Fertility; Lifestyle Behaviors; Endocrine Disruptors; Midwifery Care

ÖZET

Amaç: İnfertilite, üreme çağındaki çiftlerin yaklaşık %10-15'ini etkileyen küresel bir halk sağlığı sorunudur ve Dünya Sağlık Örgütü (WHO, 2025) tarafından üreme sisteminin bir hastalığı olarak tanımlanmaktadır. Organik ve patolojik nedenlerin yanı sıra, beslenme, vücut ağırlığı, fiziksel aktivite, tütün/alkol/madde kullanımı, psikolojik stres, çevresel toksinler, endokrin bozucu kimyasallar (EDC'ler), uyku bozuklukları ve elektromanyetik maruziyet gibi değiştirilebilir yaşam biçimi davranışları infertilite etiyolojisinde kritik rol oynamaktadır. Bu derlemenin amacı, sağlıklı yaşam biçimi davranışlarının fertiliteyi etkilediği biyolojik ve hormonal mekanizmaları incelemek ve ebelerin üreme sağlığını koruma ile fertilitenin desteklenmesindeki eğitici, danışman ve bakım verici rollerini vurgulamaktır.

Materyal ve Yöntem

Bu anlatısal derleme için PubMed, Web of Science, Scopus, ScienceDirect, CINAHL ve YÖK Tez Merkezi veritabanlarında infertilite, fertilite, yaşam biçimi faktörleri (BKİ, beslenme, egzersiz, toksik maruziyetler), endokrin bozucular ve ebelik bakımı anahtar kelimeleri kullanılarak kapsamlı bir literatür taraması yapılmıştır. 2021-2026 yılları arasında yayımlanan kanıta dayalı literatür ile güncel ulusal ve uluslararası klinik kılavuzlar (WHO, 2025; ASRM, 2024; ESHRE) AMA referans standartlarına uygun şekilde taranmış ve sentezlenmiştir.

Bulgular

Sentezlenen literatür, obezite (BKİ ≥ 30 kg/m²) ve düşük vücut ağırlığının (BKİ < 18,5 kg/m²) kadınlarda ovulasyon ve oosit kalitesini bozduğunu, erkeklerde ise sperm konsantrasyonu ve motilitesini azalttığını göstermektedir. Antioksidan ve omega-3 yağ asitlerinden zengin Akdeniz diyetine uyum, semen parametrelerinde iyileşme ve daha yüksek IVF başarı oranları ile pozitif ilişkilidir. Orta düzeyde fiziksel aktivite fertiliteyi desteklerken, aşırı/elit düzeyde egzersiz over fonksiyonunu ve semen kalitesini olumsuz etkileyebilmektedir. Aktif ve pasif sigara kullanımı, alkol kötüye kullanımı, yüksek kafein alımı (>300 mg/gün), kronik stres, uyku yoksunluğu, EDC'lere (kozmetiklerdeki fitalatlar, parabenler, ağır metaller) maruziyet ve artmış skrotal sıcaklık; artmış sperm DNA fragmantasyonu, azalmış over rezervi ve uzamış gebe kalma süresi ile tutarlı şekilde ilişkilendirilmiştir.

Sonuç

Sağlıklı yaşam biçimi müdahaleleri, hem doğal konsepsiyon oranlarını hem de yardımcı üreme teknikleri sonuçlarını önemli ölçüde iyileştiren maliyet-etkin ve yüksek etkili stratejilerdir. Birinci basamak sağlık hizmetleri ve üreme sağlığı hizmetlerinin ön saflarında yer alan ebeler, yaşam biçimi risk faktörlerini tarama, bireyselleştirilmiş danışmanlık sunma, stres ve kilo yönetimini kolaylaştırma ve sürdürülebilir sağlık davranışı değişikliklerini teşvik etme konusunda benzersiz bir konuma sahiptir. Ebe liderliğindeki bütüncül yaşam tarzı koçluğunun prekonsepsiyonel ve infertilite bakım yollarına entegre edilmesi güçlü şekilde önerilmektedir.

Anahtar Kelimeler: İnfertilite; Fertilite; Yaşam Biçimi Davranışları; Endokrin Bozucular; Ebelik Bakımı

GİRİŞ

İnfertilite, Dünya Sağlık Örgütü tarafından üreme sisteminin bir hastalığı olarak tanımlanmakta olup, dünya genelinde üreme çağındaki bireylerin yaklaşık altıda birini etkilemektedir.[1] Bu durum yalnızca bireysel ve ailevi düzeyde psikososyal yük oluşturmakla kalmayıp, aynı zamanda önemli bir halk sağlığı sorunu olarak kabul edilmektedir. Organik nedenler (tubal faktör, erkek faktörü, ovulatuar disfonksiyon, endometriozis vb.) yanında, modifiye edilebilir yaşam biçimi faktörlerinin infertilite etiyolojisindeki rolü son yıllarda giderek daha fazla dikkat çekmektedir.[2,3]

Beslenme alışkanlıkları, vücut kitle indeksi (BKİ), fiziksel aktivite düzeyi, tütün ve alkol kullanımı, psikolojik stres, uyku kalitesi, çevresel toksinler ve endokrin bozucu kimyasallara (EDC) maruziyet gibi faktörler, hem kadın hem de erkek üreme sağlığını doğrudan veya dolaylı yoldan etkilemektedir. Bu faktörlerin büyük kısmı değiştirilebilir niteliktedir ve prekonsepsiyonel dönemde yapılan müdahalelerle hem doğal gebelik şansı hem de yardımcı üreme teknikleri (YÜT) başarı oranları artırılabilmektedir.[4,5]

Ebelik mesleği, birinci basamak sağlık hizmetleri ve üreme sağlığı hizmetlerinin ön saflarında yer alması nedeniyle, yaşam biçimi risk faktörlerinin erken dönemde taranması, bireyselleştirilmiş danışmanlık

verilmesi ve davranış değişikliğinin desteklenmesi açısından kritik bir konumdadır. WHO'nun 2025 tarihli infertilite kılavuzu da düşük maliyetli yaşam biçimi danışmanlığının infertilite tedavi süreçlerine entegrasyonunu önermektedir.[1]
Bu anlatısal derlemenin amacı, sağlıklı yaşam biçimi davranışlarının fertilite üzerindeki biyolojik ve hormonal etkilerini güncel kanıtlar ışığında incelemek ve ebelerin fertilitenin desteklenmesindeki rollerini ortaya koymaktır.

GELİŞME

1. Vücut Ağırlığı ve Beden Kitle İndeksinin Fertilite Üzerindeki Etkisi

Hem fazla kilo (obezite) hem de düşük vücut ağırlığı, kadın ve erkek üreme fonksiyonlarını olumsuz etkilemektedir. Kadınlarda BKİ ≥30 kg/m² olduğunda, insülin direnci, hiperandrojenemi ve kronik düşük dereceli inflamasyon yoluyla ovulatuar disfonksiyon, oosit kalitesinde bozulma ve endometrial reseptivitede azalma görülmektedir.[6] Obezite, anovulatuar infertilite riskini yaklaşık üç kat artırmakta ve IVF sikluslarında daha düşük gebelik ve canlı doğum oranlarıyla ilişkilendirilmektedir.[7,8]
Düşük vücut ağırlığı (BKİ <18,5 kg/m²) ise hipotalamik-hipofizer-ovaryan aksın baskılanmasına, gonadotropin salınımının bozulmasına ve amenoreye yol açabilmektedir. Erkeklerde obezite, artmış aromatizasyon yoluyla östrojen düzeylerini yükseltirken, testosteron ve seks hormon bağlayıcı globulin (SHBG) düzeylerini düşürmekte; sperm konsantrasyonu, motilite ve morfolojide bozulmaya neden olmaktadır.[9,10] Prekonsepsiyonel dönemde %5-10 oranında kilo kaybı bile ovulasyonun yeniden başlamasına ve doğal gebelik şansının artmasına katkı sağlamaktadır.[11]

2. Beslenme ve Diyet Örüntüleri

Akdeniz tipi diyet (yüksek miktarda sebze, meyve, tam tahıl, baklagil, kuruyemiş, zeytinyağı ve balık; sınırlı kırmızı et ve işlenmiş gıda) fertilite açısından en tutarlı olumlu sonuçları gösteren diyet örüntüsüdür. Antioksidanlar, omega-3 yağ asitleri ve bitkisel proteinler oksidatif stresi azaltarak oosit ve sperm kalitesini desteklemektedir.[12,13] Gözlemsel çalışmalar ve meta-analizler, yüksek Akdeniz diyeti uyumunun klinik gebelik ve canlı doğum oranlarını artırdığını, özellikle YÜT uygulanan kadınlarda embriyo kalitesini iyileştirdiğini bildirmektedir.[14,15] Tersine, Batı tipi diyet (yüksek işlenmiş gıda, şeker, doymuş yağ ve kırmızı et) ovulatuar infertilite riskini artırmaktadır. Folat, D vitamini, çinko, selenyum ve koenzim Q10 gibi mikrobesinlerin yetersiz alımı da üreme sağlığını olumsuz etkileyebilmektedir. Prekonsepsiyonel dönemde folik asit suplementasyonu nöral tüp defektlerini önlemenin yanı sıra, genel üreme sağlığını da desteklemektedir.[16]

3. Fiziksel Aktivite

Orta düzeyde düzenli fiziksel aktivite (haftada en az 150 dakika orta yoğunlukta aktivite), hem kadın hem erkek fertilitesini olumlu etkilemektedir. İnsülin duyarlılığını artırarak, vücut kompozisyonunu iyileştirerek ve stres düzeyini azaltarak üreme fonksiyonlarını destekler.[17] Ancak aşırı veya elit düzeyde egzersiz (özellikle dayanıklılık sporları), kadınlarda hipotalamik amenore, luteal faz yetmezliği ve azalmış over rezervi; erkeklerde ise testosteron düşüklüğü ve semen parametrelerinde bozulma ile ilişkilendirilmiştir.[18] Dengeli ve sürdürülebilir bir aktivite programı önerilmektedir.

4. Tütün, Alkol ve Kafein Kullanımı

Sigara içmek (aktif ve pasif), kadınlarda over rezervinin azalması, oosit kalitesinin bozulması, ektopik gebelik ve erken menopoz riskinin artması; erkeklerde ise sperm DNA fragmantasyonu, azalmış motilite ve konsantrasyon ile ilişkilidir.[19,20] Sigara içen kadınlarda IVF başarı oranları belirgin şekilde düşmektedir. Alkol tüketimi, özellikle ağır kullanım, sperm morfolojisini olumsuz etkilemekte ve kadınlarda hormonal dengeyi bozabilmektedir. Kafein alımının günde 300 mg'ın üzerinde olması, gebelik süresini uzatabilmektedir.[21] Prekonsepsiyonel dönemde tütün bırakma danışmanlığı ve alkol sınırlaması kritik öneme sahiptir.

5. Psikolojik Stres, Uyku ve Diğer Faktörler

Kronik psikolojik stres, hipotalamik-hipofizer-adrenal aksın aktivasyonu yoluyla gonadotropin salınımını baskılayarak ovulasyonu ve sperm üretimini olumsuz etkileyebilmektedir. Uyku bozuklukları ve yetersiz uyku süresi de hormonal ritimleri bozarak fertiliteyi azaltmaktadır.[22] Elektromanyetik alan maruziyeti ve artmış skrotal sıcaklık (laptop kullanımı, dar giysiler) erkek fertilitesini olumsuz etkileyebilmektedir.

6. Endokrin Bozucu Kimyasallar (EDC'ler)

Fitalatlar, parabenler, bisfenol A (BPA), ağır metaller ve pestisitler gibi EDC'ler, hormon reseptörlerine bağlanarak veya hormon sentezini bozarak üreme sistemini etkilemektedir. Kozmetik ürünler, plastik ambalajlar, temizlik malzemeleri ve tarım ürünleri yoluyla maruziyet söz konusu olabilmektedir. EDC maruziyeti, kadınlarda over rezervinin azalması, endometriyozis ve PCOS riskinin artması; erkeklerde ise sperm kalitesinde bozulma ile ilişkilendirilmiştir.[23],[24] Prekonsepsiyonel dönemde EDC maruziyetinin azaltılmasına yönelik danışmanlık (plastik kullanımını sınırlama, doğal kozmetik tercih etme vb.) önerilmektedir.

7. Fertilitenin Desteklenmesinde Ebenin Rolü

Ebeler, kadın sağlığı ve üreme sağlığı hizmetlerinin birinci basamağında yer almaları nedeniyle, prekonsepsiyonel danışmanlık ve yaşam biçimi müdahaleleri için ideal konumdadır. WHO ve ASRM kılavuzları, prekonsepsiyonel bakımın rutin jinekolojik ve ebelik hizmetlerine entegre edilmesini önermektedir.[1],[25] Ebelerin rolleri şunları kapsamaktadır:

• Yaşam biçimi risk faktörlerinin (BKİ, beslenme, sigara, alkol, stres, uyku, EDC maruziyeti) sistematik taranması,
• Bireyselleştirilmiş, kanıta dayalı danışmanlık ve motivasyonel görüşme teknikleriyle davranış değişikliğinin desteklenmesi,
• Kilo yönetimi, beslenme düzenlemesi ve fiziksel aktivite planlamasında rehberlik,
• Stres yönetimi ve ruh sağlığı desteği için uygun yönlendirme,
• Yardımcı üreme teknikleri sürecinde çiftlere bütüncül destek sağlanması,
• Toplum temelli eğitim programları ve sağlık okuryazarlığının artırılması.

Ebe liderliğindeki prekonsepsiyonel yaşam tarzı koçluğu programları, hem doğal gebelik oranlarını hem de YÜT başarılarını artırma potansiyeline sahiptir. Ayrıca, bu yaklaşımlar maliyet-etkin olup, sağlık sistemleri üzerindeki yükü azaltmaya katkı sağlamaktadır.[26],[27]

SONUÇ

Sağlıklı yaşam biçimi davranışları, fertiliteyi etkileyen değiştirilebilir risk faktörlerinin başında yer almaktadır. Optimal vücut ağırlığının korunması, Akdeniz tipi beslenme örüntüsünün benimsenmesi, orta düzeyde fiziksel aktivite, tütün ve aşırı alkolden uzak durma, stres yönetimi, yeterli uyku ve EDC maruziyetinin azaltılması; hem doğal konsepsiyon şansını hem de yardımcı üreme tekniklerinin başarısını anlamlı ölçüde artırmaktadır. Ebeler, birinci basamak ve üreme sağlığı hizmetlerindeki konumları sayesinde, bu müdahalelerin etkili bir şekilde uygulanmasında kilit rol oynamaktadır. Prekonsepsiyonel bakım ve infertilite yönetim süreçlerine ebe liderliğindeki bütüncül yaşam tarzı danışmanlığının entegre edilmesi, kanıta dayalı, maliyet-etkin ve sürdürülebilir bir yaklaşım olarak önerilmektedir. Gelecekte, ebelik uygulamalarına özgü yaşam biçimi müdahale modellerinin etkinliğini değerlendiren randomize kontrollü çalışmaların artırılması, bu alandaki kanıt düzeyini güçlendirecektir.

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FEMTECH IN WOMEN'S HEALTH: SMART RINGS, OVULATION TRACKING WITH WEARABLE DEVICES, AND DIGITAL NURSING

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ABSTRACT
Digital technologies developed for women's health have expanded rapidly under the concept of FemTech. Mobile health applications, smart rings, smartwatches, and other wearable devices are increasingly used for menstrual cycle monitoring, ovulation prediction, fertility awareness, and pregnancy planning. These technologies continuously or periodically measure physiological indicators such as skin temperature, heart rate, heart rate variability, respiratory rate, sleep, and physical activity. Current research indicates that wearable technologies may provide useful information for identifying physiological changes associated with ovulation and estimating the fertile window. However, their performance differs according to the sensors and algorithms used, menstrual cycle characteristics, adherence to device use, and the reference methods used to confirm ovulation. Wearable devices do not directly visualise ovulation but generate estimates from physiological changes. Therefore, their results should not be interpreted as stand-alone diagnostic findings. The increasing use of FemTech also raises concerns regarding data privacy, measurement accuracy, affordability, and digital inequality. Women's health nurses have important responsibilities in assessing women's purposes for using these devices, explaining their intended uses and limitations, supporting the appropriate interpretation of device-generated data, and providing guidance regarding data privacy. FemTech should be integrated into women's health care as a complementary tool that supports professional assessment and person-centred nursing rather than as a replacement for clinical care.
Keywords: FemTech, women's health, smart ring, wearable device, ovulation tracking, digital nursing

INTRODUCTION
Digital health technologies allow individuals to monitor health-related indicators outside clinical settings and during their daily lives. These technologies include mobile applications, wearable sensors, telehealth systems, websites, and other digitally connected tools. The World Health Organization reports that digital health technologies may improve women's access to health services and essential health information, support maternal health, and increase women's participation in health-related decisions. Positive outcomes have been reported particularly in gynaecology, obstetrics, psychiatry, nutrition, and physical activity. Nevertheless, socioeconomic, cultural, and geographical barriers may affect women's ability to benefit from these technologies.[1]

Digital products and services developed to address women's health needs are commonly described using the term FemTech. The concept includes mobile applications, software, diagnostic technologies, wearable devices, and digital health services focusing on health issues that are specific to women or affect women disproportionately. Menstrual and fertility-tracking applications, smart rings, wearable sensors, pregnancy-monitoring platforms, and digital pelvic health technologies are among the tools included within this field.[2]

A scoping review of person-generated health data in women's health evaluated 406 publications. The review identified the use of mobile applications, wearable devices, websites, smart devices, two-way messaging systems, interactive voice-response systems, and implantable devices. The included publications most frequently addressed pregnancy and the postpartum period, followed by cancer and other areas of women's health. Accessibility, connectivity, design, functionality, measurement accuracy, reliability, and user characteristics were identified as factors affecting the adoption of these technologies.[3]

FemTech applications may help women record menstrual cycles, fertility-related indicators, and symptoms over extended periods. These records may enable women to recognise changes in their bodies and provide health professionals with more detailed information during clinical consultations. However, the clinical value of digital technologies depends on the reliability of the measurements, the appropriateness of the intended use, and the manner in which the resulting data are incorporated into professional health care.[3]

SMART RINGS AND WEARABLE DEVICES

Smart rings, smartwatches, sensor-equipped wristbands, ear-worn devices, and vaginal sensors can continuously or periodically measure physiological indicators. These indicators may include skin temperature, heart rate, heart rate variability, respiratory rate, sleep duration, sleep patterns, physical activity, and skin perfusion. Wearable reproductive health technologies use changes in these measurements to estimate menstrual cycle phases and the fertile window.[4]

One advantage of wearable technologies is their ability to collect multiple measurements automatically. Traditional basal body temperature monitoring usually requires a woman to measure her temperature manually at approximately the same time each morning. In contrast, smart rings and other wearable devices can collect numerous data points throughout the night. This may reduce problems associated with forgotten measurements, differences in measurement time, and inconsistent user adherence.

However, most wearable devices measure peripheral skin temperature rather than core body temperature. Skin temperature may be influenced by environmental conditions, physical activity, sleep, food and alcohol consumption, and other individual factors. Consequently, individual measurements should generally be interpreted as part of a longer-term physiological pattern rather than as isolated findings.

Maijala et al conducted a pilot study involving 22 women who used a smart ring for an average of 114.7 days. Ovulation was monitored using urinary luteinising hormone tests. Nocturnal finger skin temperature was, on average, 0.30°C higher during the luteal phase than during the follicular phase. The best-performing algorithm demonstrated 83.3% sensitivity within a 6-day period extending from 3 days before to 2 days after the confirmed day of ovulation. The researchers concluded that nocturnal finger skin temperature had potential for menstrual cycle monitoring under real-life conditions. However, they also emphasised the need for validation in larger samples because of the small, pilot nature of the study.[5]

Wearable devices may also assess several physiological indicators simultaneously. Goodale et al initially recruited 237 women who were attempting to become pregnant and monitored wrist skin temperature, heart rate, heart rate variability, respiratory rate, and skin perfusion. The performance of the algorithm was validated using 85 cycles from 24 participants who wore the device at the recommended frequency. The 6-day fertile window was identified in 90% of these cycles.[6]

The study demonstrated the potential value of using several physiological signals rather than relying exclusively on calendar calculations or a single temperature measurement. Nevertheless, most of the authors were current or former employees of the company that manufactured the device, and one author served on the company's medical advisory board. The results therefore require confirmation through studies conducted by independent research groups and in different populations.[6]

OVULATION TRACKING USING WEARABLE DEVICES

Methods used for ovulation monitoring include menstrual calendars, cervical mucus assessment, basal body temperature measurement, urinary luteinising hormone testing, and ultrasonography. Wearable devices use algorithms to evaluate physiological changes occurring before and after ovulation. These technologies do not directly visualise the release of an oocyte from the ovary. Instead, they estimate the probable timing of ovulation from patterns detected in physiological data.[4]

Zhu et al compared continuously measured wrist skin temperature with oral basal body temperature in 193 menstrual cycles obtained from 57 healthy women. Of these cycles, 170 were classified as ovulatory and 23 as anovulatory. Home urinary luteinising hormone tests were used as the reference method. The sensitivity of wrist skin temperature for detecting ovulation was 0.62, whereas the sensitivity of oral basal body temperature was 0.23. In contrast, the specificity of wrist skin temperature was 0.26, compared with 0.70 for oral basal body temperature. The false-positive rate was 8.8% for wrist skin temperature and 3.6% for oral basal body temperature. These findings indicate that wrist skin temperature detected more temperature changes associated with ovulation but also produced more false-positive results.[7]

The results demonstrate why sensitivity and specificity should be considered together when evaluating wearable technologies. A device may identify a greater proportion of possible ovulations while simultaneously classifying physiological changes as ovulation when ovulation has not occurred. Device performance should therefore not be evaluated solely by the percentage of ovulations detected.

A systematic review of wearable reproductive health technologies found that finger-, wrist-, ear-, and vaginally placed devices had been used to estimate menstruation, ovulation, and different phases of the menstrual cycle. Most devices assessed temperature, heart rate, heart rate variability, respiratory rate, or

combinations of these parameters. The authors reported promising findings but noted substantial differences in device types, algorithms, study samples, and ovulation-validation methods. They concluded that further independent validation was necessary.[4]

A systematic review and Bayesian network meta-analysis published by Shi et al included 27 studies with 6244 participants. Thirteen studies evaluated wearable digital technologies for ovulation tracking. The pooled accuracy of wearable technologies in detecting the fertile window was 0.88, while pooled sensitivity and specificity were 0.79 and 0.80, respectively. The best performance was generally observed within a period extending approximately 3 days before and after ovulation.[8]

The meta-analysis also found that systems combining multiple physiological parameters could achieve greater accuracy than systems using temperature alone. However, potential publication bias was identified, and the certainty of evidence regarding ovulation detection was rated as very low because of risk of bias, inconsistency, and imprecision. The findings should therefore be interpreted cautiously.[8]

Thigpen et al evaluated 1155 ovulatory menstrual cycles obtained from 964 participants. The physiology-based algorithm of a smart ring detected 1113 of the 1155 ovulations, representing a detection rate of 96.4%. The mean absolute error between the estimated and reference ovulation dates was 1.26 days. In comparison, the mean absolute error for the calendar-based method was 3.44 days.[9]

Despite these findings, the study included only cycles in which ovulation was considered to have occurred. Therefore, the performance of the algorithm in anovulatory cycles and its false-positive rate could not be determined. The reference ovulation date was based on participant-reported home luteinising hormone tests rather than confirmation by transvaginal ultrasonography. The researchers also stated that failure of the device to detect ovulation should not, by itself, be interpreted as evidence of anovulation.[9]

All authors of the study were employees of the company manufacturing the smart ring, and the data were obtained from the company's commercial user database. These methodological and commercial characteristics do not invalidate the findings, but they should be considered when applying the reported performance to other populations, particularly women with irregular cycles, anovulatory cycles, or conditions affecting ovulation.[9]

DIFFERENCE BETWEEN OVULATION PREDICTION AND CONTRACEPTION

The ability of a device to estimate ovulation or the fertile window does not necessarily mean that it is suitable for contraception. A device developed to support ovulation prediction and pregnancy planning has a different intended use from a digital medical device evaluated specifically as a contraceptive method.

The US Food and Drug Administration documentation for the Ava Fertility Tracker states that the device measures physiological parameters such as body temperature, resting pulse rate, heart rate variability, and respiratory rate. Its intended use is to assist in ovulation prediction and facilitate conception. The same documentation explicitly states that the device should not be used for contraception.[10]

A prediction error of several days may affect the timing of sexual intercourse in women attempting to conceive. However, the same degree of error may carry a greater consequence for women attempting to avoid pregnancy. Women should therefore be informed of the official intended use and regulatory status of the application or device they use. A menstrual or ovulation-tracking application should not automatically be regarded as an effective contraceptive method.

OPPORTUNITIES AND LIMITATIONS OF FEMTECH

FemTech applications may help women monitor menstrual patterns, fertility indicators, sleep, physical activity, and symptoms. Long-term records may make changes in menstrual intervals or symptom patterns more visible and may facilitate the communication of detailed information to health professionals.

Digital records may be particularly useful when symptoms vary throughout the menstrual cycle or cannot be fully recalled during a single clinical consultation. However, device-generated information should be used to support the medical history and clinical assessment rather than being treated as diagnostic evidence.

The accuracy of wearable measurements may be affected by environmental conditions, physical activity, sleep patterns, exercise near bedtime, food, coffee, and alcohol consumption. Illnesses, medication use, hormonal contraceptives, and conditions affecting menstrual cycles may also influence physiological patterns.[5,6,8]

Anovulatory cycles and irregular menstrual cycles present additional challenges for algorithms developed using data obtained primarily from ovulatory cycles. The failure of a device to identify ovulation is not sufficient to establish a diagnosis of anovulation. Similarly, a predicted ovulation date does not provide definitive clinical confirmation that ovulation has occurred.[9]

Consequently, device-generated findings should be interpreted together with the woman's medical history, menstrual characteristics, medication use, pregnancy intentions, symptoms, and relevant clinical findings. Professional evaluation remains necessary when a woman experiences prolonged amenorrhoea, excessive menstrual bleeding, severe pelvic pain, substantial cycle irregularity, or possible infertility.

DATA PRIVACY AND DIGITAL INEQUALITY

Reproductive health applications may collect information concerning menstruation, fertility, pregnancy, sexual activity, symptoms, and other aspects of personal health. The storage or sharing of such information may create privacy risks, particularly when users do not clearly understand which data are collected, why they are collected, and whether they are shared with third parties.

Zadushlivy et al evaluated the privacy policies of 4 popular reproductive health applications: Clue, Flo, Period Tracker by GP Apps, and Stardust. Concerns identified in the study included IP address tracking, the involvement of third-party advertising and marketing services, and insufficient transparency regarding data use. The researchers recommended that applications collect only the minimum data necessary and clearly explain their data storage and sharing procedures. They also emphasised the importance of encryption and anonymisation.[11]

An example of privacy concerns in practice involved Flo Health. The Federal Trade Commission alleged that the company shared sensitive information belonging to millions of users with marketing and analytics companies, including Facebook and Google, despite statements suggesting that users' health data would remain private. Under the settlement, the company was required to obtain users' explicit consent before sharing personal health information, inform affected users, and arrange an independent assessment of its privacy practices.[12]

Women should be supported in examining which data an application collects, how the data are used, whether information is shared with third parties, and whether options are provided for deleting stored information. Data privacy counselling should therefore form part of health education concerning FemTech.

Access to FemTech is also influenced by the costs of smart devices, smartphones, internet services, and subscription-based platforms. These technologies may not be equally accessible to all women. Limited internet access, digital health literacy, language options, and financial resources may restrict the potential benefits of FemTech. The WHO has consequently emphasised that socioeconomic, cultural, and geographical barriers should be considered when digital health technologies are incorporated into women's health services.[1]

DIGITAL NURSING AND THE ROLE OF THE WOMEN'S HEALTH NURSE

Women's health nurses should not regard information generated by a smart ring or mobile application as an independent clinical diagnosis. Digital data should be considered alongside the woman's menstrual history, symptoms, age, medication use, pregnancy intentions, contraceptive needs, and clinical findings.

A study involving 611 nurses recruited from teaching hospitals in Saudi Arabia found that participants generally held positive attitudes towards artificial intelligence-enabled wearable health technologies. Participants believed that these technologies could support personalised care, chronic disease management, and health-service efficiency. However, data accuracy, affordability, technical reliability, data privacy, overreliance on artificial intelligence, and reduced human interaction were reported as concerns.[13]

The researchers recommended structured education, institutional support, and clear implementation guidelines to promote the safe integration of wearable technologies into clinical care.[13] These findings demonstrate that the adoption of digital technologies requires not only access to devices but also professional knowledge regarding their accuracy, intended use, limitations, and ethical implications.

Based on the available literature, the suggested responsibilities of women's health nurses include assessing why a woman uses a device and what she expects from it; explaining which physiological variables are measured; clarifying the difference between an algorithmic estimate and a clinical

diagnosis; and interpreting device-generated findings together with the woman's symptoms and clinical history.

Nurses should also explain that a device developed for ovulation prediction may not be suitable for contraception. They should provide guidance concerning the collection, storage, and sharing of reproductive health data and refer women for clinical assessment when symptoms or menstrual changes require professional evaluation.

Digital technologies should not replace communication between the nurse and the woman. Instead, they should be used as complementary tools that support person-centred care, improve continuity of monitoring, and facilitate discussion of symptoms and menstrual patterns.

CONCLUSION

FemTech provides new opportunities for personalised monitoring in menstruation, ovulation, and fertility. Smart rings and other wearable devices can continuously monitor physiological indicators and generate estimates concerning menstrual cycle phases and the probable timing of ovulation.

Current evidence indicates that wearable technologies may provide more individualised information than traditional calendar-based methods. However, these devices do not directly confirm ovulation, and their performance varies according to the sensors, algorithms, samples, adherence patterns, and validation methods used. Although a recent meta-analysis reported relatively high pooled accuracy, the certainty of the evidence was rated as very low.[8]

Some studies reporting high performance have also been conducted by researchers affiliated with the manufacturers of the devices. Independent validation in different populations, including women with irregular or anovulatory cycles, remains necessary.

Smart rings and other wearable devices should not replace clinical assessment, hormonal testing, or ultrasonography when these procedures are indicated. Devices developed for ovulation prediction should not be assumed to be suitable for contraception.

The increasing use of FemTech also requires attention to privacy, affordability, measurement accuracy, and digital inequality. Women's health nurses have important responsibilities in explaining the intended purposes and limitations of devices, improving digital health literacy, supporting data privacy, interpreting digital information within its clinical context, and providing appropriate referrals.

FemTech should therefore be used not as a replacement for women's health nursing or professional clinical assessment but as a complementary tool that supports person-centred care and informed health decisions.

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GÖÇ VE YOKSULLUK BAĞLAMINDA ÇOCUK GELİŞİMCİNİN TOPLUM TEMELLİ SOSYAL HİZMET ÇALIŞMALARINDAKİ KONUMU

THE ROLE OF CHILD DEVELOPMENT SPECIALIST IN COMMUNITY-BASED SOCIAL WORK IN THE CONTEXT OF MIGRATION AND POVERTY

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ÖZET

Göç ve yoksulluk, çocukların gelişim süreçlerini olumsuz etkileyen önemli risk faktörleri arasında yer almaktadır. Bu koşullarda yaşayan çocuklar; eğitim hizmetlerine erişimde güçlük, psikososyal sorunlar ve ev ortamında yeterli gelişimsel uyaranlara ulaşamama gibi nedenlerle gelişimsel eşitsizliklerle karşı karşıya kalabilmektedir. Bu durum çocukların bilişsel, dil, sosyal-duygusal ve fiziksel gelişimlerini olumsuz etkileyerek uzun vadeli dezavantajlara yol açabilmektedir.

Toplum temelli sosyal hizmet uygulamaları dezavantajlı çocuk ve ailelerin desteklenmesinde önemli bir rol üstlenmesine rağmen, gelişimsel değerlendirme ve erken müdahale çalışmaları çoğu zaman geri planda kalmaktadır. Bu nedenle toplum temelli sosyal hizmet çalışmalarında çocuk gelişimcilerin daha aktif rol aldığı ve gelişimsel destek süreçlerini içeren erken müdahale bileşenlerinin güçlendirilmesine ihtiyaç duyulmaktadır.

Bu çalışmanın amacı, göç ve yoksulluk koşullarında yaşayan çocukların gelişimsel risklerini çocuk gelişimi perspektifinden ele alarak, çocuk gelişimcinin toplum temelli sosyal hizmet çalışmalarındaki rolünü incelemektir. Ayrıca gelişimsel tarama, risk belirleme ve erken müdahale süreçlerinin toplum temelli hizmetlere nasıl entegre edilebileceğine ilişkin bir çerçeve sunulması amaçlanmaktadır.

Göç ve yoksulluk kaynaklı gelişimsel eşitsizlikler, çocukların yaşam boyu gelişimlerini etkileyebilmekte ve kuşaklar arası aktarılabilmektedir. Bu nedenle koruyucu ve önleyici toplum temelli hizmetlerin gelişim odaklı olarak yürütülmesi büyük önem taşımaktadır. Çalışma, çocuk gelişimcinin bu alandaki rolünü ortaya koyması ve uygulama ile politika geliştirme süreçlerine katkı sağlaması bakımından önemlidir.

ABSTRACT

Migration and poverty are among the major risk factors that negatively affect children's developmental processes. Children living under these conditions may face developmental inequalities due to difficulties in accessing educational services, psychosocial problems, and insufficient developmental stimulation in the home environment. This situation can adversely affect children's cognitive, language, socio-emotional, and physical development, leading to long-term disadvantages.

Although community-based social service practices play an important role in supporting disadvantaged children and families, developmental assessment and early intervention efforts often remain in the background. Therefore, there is a need to strengthen early intervention components that include developmental support processes and enable child development specialists to take a more active role in community-based social service practices.

The aim of this study is to examine the role of child development specialists in community-based social service practices by addressing the developmental risks faced by children living in conditions of migration and poverty from a child development perspective. In addition, the study aims to provide a framework for integrating developmental screening, risk identification, and early intervention processes into community-based services.

Developmental inequalities arising from migration and poverty can affect children's lifelong development and may be transmitted across generations. Therefore, it is of great importance that preventive and protective community-based services are implemented with a developmental focus. This study is significant in highlighting the role of child development specialists in this field and contributing to practice and policy development processes.

1.1 Göç ve Yoksulluk Kavramları

Göç, toplulukların veya bireylerin çeşitli toplumsal, ekonomik ve siyasi nedenlerle bir ülkeden başka bir ülkeye ya da bir yerleşim alanından farklı bir bölgeye taşınması olarak tanımlanabilir.

Bu süreç, insanların daha kaliteli yaşam koşulları, güvenli bir ortam, iş fırsatları veya siyasi istikrar arayışı gibi gerekçelerle gerçekleşmektedir (Tekgün vd., 2025).
Türk Dil Kurumu'na (TDK) göre göç, bireylerin ya da toplulukların ekonomik, siyasal ve sosyal nedenlerle bir ülke sınırları içinde yer değiştirmesi ya da bir ülkeden başka bir ülkeye taşınarak yeni bir yerleşim alanına geçmesi şeklinde tanımlanmaktadır (Demirci, 2022).
İç göç, adından da anlaşılacağı gibi belirli bir ülke veya siyasi birim içindeki coğrafi hareketlilik modellerini ifade eder. Bireylerin yer değiştirmelerinin kararı, gerekçesi ve varış noktası kısmen finansal, mesleki, sosyal, kültürel ve siyasi faktörlerden etkilenir (Dias et al., 2025). İç göç ise bir ülke sınırları içerisinde yer alan bölge, kent, kasaba veya köylerden başka bir yerleşim birimine, çoğunlukla büyükşehirlere doğru gerçekleşen nüfus hareketlerini ifade etmektedir. Buna karşılık dış göç, ülke sınırlarının aşılmasıyla gerçekleşen ve genellikle uzun süreli yerleşim ya da çalışma amacı taşıyan göç türü olarak tanımlanmaktadır (Çetik, 2025). Dış göç, en az iki ülkenin yerleşim birimleri arasında gerçekleşen nüfus hareketi olarak tanımlanmakta; özellikle devletlerin resmi sınırları içerisindeki idari bölgeler arasındaki yer değiştirme süreci şeklinde ele alınmaktadır (Güreşci, 2016).
Yoksulluk yalnızca ekonomik bir kategori olarak değerlendirilemez; bireylerin içinde yaşadığı, anlamlandırdığı ve bu durumla baş edebilmek için farklı stratejiler geliştirdiği toplumsal bir olgudur (Ak, 2016). Benzer şekilde yoksulluk tek bir tanım üzerinden açıklanması güç bir kavramdır. Bu nedenle bir kategori olarak ele alınmaktan ziyade, yoksulluk; bireylerin deneyimlediği, anlam yüklediği ve çeşitli baş etme yöntemleri geliştirdiği toplumsal bir "durum" olarak da tanımlanmaktadır (Çelik, 2024). Çok boyutlu yoksulluk yaklaşımı ise bireylerin yaşam standartlarını etkileyen farklı alanlardaki yoksunlukların birlikte değerlendirilmesini esas almaktadır. Bu kapsamda yoksulluk; ekonomik boyutun yanı sıra sosyal, kültürel, politik, fiziksel ve psikolojik boyutları da içeren geniş bir çerçevede ele alınmaktadır (Toper & Aslan, 2023).
Çok boyutlu yoksulluk; sınırlı finansal kaynaklar, maddi yoksunluk, sosyal izolasyon, dışlanma, fiziksel ve psikolojik hastalıklar gibi özellikleri kapsamaktadır. Yoksulluk yaşayan bireyler bu durumu yalnızca ekonomik değil; eğitim, sağlık, barınma, güçlenme, dışlanma/aşağılanma, istihdam ve kişisel güvenlik gibi alanları da içeren çok yönlü bir olgu olarak değerlendirmektedir. Bu nedenle gelir veya tüketim gibi tek bir gösterge, yoksulluğun farklı boyutlarını tam olarak ortaya koymakta yetersiz kalmaktadır (Güneş & Yenihan, 2023).

1.2 Gelişimsel Eşitsizlik Kavramı

Gelişimsel eşitsizlik, çocukların gelişim fırsatlarına erişimindeki farklılıklar nedeniyle ortaya çıkan dezavantajları ifade etmektedir. Yoksulluk, göç, düşük gelir düzeyi ve eğitim olanaklarına erişimde yaşanan sorunlar, çocukların bilişsel, sosyal-duygusal ve fiziksel gelişimlerini olumsuz etkileyebilmektedir (Özpolat & Aktuna, 2023).
Erken çocukluk dönemi, bireyin yaşam boyu gelişimini etkileyen kritik bir süreçtir. Bu dönemde yaşanan olumsuz deneyimler, çocukların sağlık, eğitim ve sosyal yaşama katılımlarını olumsuz etkileyebilmektedir. Buna karşılık, erken müdahale programları ve koruyucu hizmetler çocukları yoksulluğun olumsuz sonuçlarından koruyarak gelişimsel eşitsizliklerin azaltılmasına katkı sağlamaktadır (Çebi ve ark., 2024).
Ayrıca, erken çocukluk döneminde sosyoekonomik eşitsizliklerin çocukluk boyunca nasıl değiştiğine ilişkin çalışmalar sınırlıdır. Bu eşitsizliklerin zaman içindeki seyrinin anlaşılması, yaşam boyu sağlık ve refah üzerindeki etkilerinin değerlendirilmesi açısından önem taşımaktadır (Houweling ve ark., 2022).
Araştırmalar, sosyoekonomik farklılıkların çocukların gelişim düzeylerinde eşitsizliklere yol açtığını göstermektedir. Düşük sosyoekonomik düzeydeki çocuklar, daha sınırlı gelişim fırsatlarına sahip olduklarından okul hazırlık düzeylerinde dezavantaj yaşayabilmektedir. Bu nedenle erken yaşta yapılan gelişim yatırımları, gelişimsel eşitsizliklerin azaltılmasında önemli bir rol oynamaktadır (Karaoğlan ve ark., 2024).

1.3 Ekolojik Sistem Yaklaşımı

Ekolojik Sistemler Kuramı: Gelişim psikolojisinin önde gelen isimlerinden Urie Bronfenbrenner tarafından ortaya atılmıştır. Bu kuram, insan davranışlarının gelişimini farklı çevresel sistemler çerçevesinde inceleyen bir yapı sunar. Bu kuramsal temel doğrultusunda, bireyin gelişimi farklı çevresel sistemler üzerinden açıklanmaktadır (Türkoğlu & Şahin, 2021). Mikrosistem, bireyin rol aldığı etkinlikleri, kişilerarası ilişkileri ve günlük yaşam deneyimlerini doğrudan yaşadığı, yüz yüze etkileşimin bulunduğu yakın çevre olarak tanımlanmaktadır (Balaban Öztürk, 2023).

Mezosistem ise bireyin aile, okul ve akran grupları arasındaki ilişkilerin birbirini nasıl etkilediğini açıklayan bir sistem düzeyidir (Sarıgül, 2025). Makrosistem, toplumsal normlar, kültürel değerler, ekonomik yapılar ve yasal düzenlemeler gibi daha geniş ölçekli yapısal unsurları kapsamaktadır. Bu sistemlerin tümü birlikte ele alındığında, bireyin gelişimini şekillendiren bütüncül bir yapı ortaya çıkmaktadır (Elver & Türgay, 2025).

Bu sistemlerin her biri çocuk gelişimi açısından risk ve koruyucu faktörler içerebilmektedir. Özellikle mikrosistem, çocuğun günlük yaşamındaki doğrudan etkileşimleri nedeniyle gelişim üzerinde önemli bir belirleyici olarak kabul edilmektedir Dolayısıyla ekolojik sistemler kuramı, çocuk gelişimini yalnızca bireysel değil çevresel sistemler bütününde ele alan kapsamlı bir açıklama sunmaktadır. (Antony, 2022).

Ekolojik Yaklaşım, sosyal hizmet alanında birey ile çevresi arasındaki karşılıklı etkileşimi esas alan bütüncül bir perspektif sunmaktadır. Ekolojik sistemler kuramına dayanan bu yaklaşım, bireyi içinde bulunduğu çevresel bağlamla birlikte ele alarak sosyal çalışmada hem bireye hem de çevreye odaklanan bir bakış açısı geliştirmektedir. Bu bağlamda ekolojik yaklaşım, teorik çerçeve ile uygulama alanı arasında köprü kurarak sosyal hizmette bütüncül değerlendirmeyi mümkün kılar (Erbaş, 2025).

Göç ve Yoksulluk Bağlamında Erken Çocukluk Riskleri

2.1 Eğitim ve Okul Öncesi Erişim Sorunları

Göç ve yoksulluk, çocukların okul öncesi eğitime erişimini olumsuz etkileyen önemli risk faktörleri arasında yer almaktadır. Ekonomik yetersizlikler, ailelerin eğitim imkanlarına ulaşmasını zorlaştırırken çocukların gelişim süreçlerini de etkileyebilmektedir. Özellikle dezavantajlı bölgelerde yaşayan çocukların kaliteli okul öncesi eğitime erişimde daha fazla sorun yaşadığı belirtilmektedir (Eroğlu & Şimşek, 2021).

Bunun yanında yoksulluk nedeniyle birçok ailenin çocuklarını okul öncesi eğitime gönderemediği ve bunun eğitimde fırsat eşitsizliğini artırdığı ifade edilmektedir. Erken çocukluk döneminde eğitime erişimin artırılması, çocukların bilişsel ve sosyal gelişimleri açısından önemli görülmektedir (Öztürk, 2017).

2.2 Psikososyal Riskler

Göç sonrasında ailelerin, çoğunlukla kentlerin kenar mahallelerinde, sosyal ve fiziksel imkânların sınırlı olduğu alanlarda yoğunlaştığı ve bunun yeni bir sosyal dışlanma döngüsünü beraberinde getirdiği görülmektedir. Bu bağlamda travmatik göç deneyimi ile kronik kent yoksulluğunun iç içe geçtiği bu süreçte, mevcut literatür hem göç olgusunun (örneğin kültürel uyum güçlükleri ve sosyal dışlanma) hem de yoksulluğun (örneğin maddi yetersizlikler ve kısıtlı fırsatlar) yaşam kalitesi üzerinde olumsuz etkiler oluşturduğunu ortaya koymaktadır (Havle, 2025).

Öte yandan bazı ailelerin okullar tarafından sunulan psikososyal destek hizmetlerini kabul etmemesi de önemli bir sorun olarak öne çıkmakta olup, bunun nedenleri arasında bu tür hizmetlerin damgalayıcı olarak algılanması, maddi yetersizlikler, okuldan uzaklaştırılma kaygısı ve dil engelleri bulunmaktadır. (Karaman & Bulut, 2018).

2.3 Ev Ortamında Uyarıcı Yetersizliği

Son yıllarda yapılan araştırmalar, ev ortamının niteliğinin çocuk gelişimi üzerinde belirleyici bir rol oynadığını göstermektedir. Özellikle düşük sosyoekonomik düzeydeki ailelerde ev içi öğrenme fırsatlarının daha sınırlı olduğu ve bunun çocukların gelişimsel çıktıları üzerinde olumsuz etkiler oluşturduğu belirtilmektedir (Bayrakdar, 2023).

Ayrıca ev ortamında sunulan motor ve sosyal uyarıcıların yetersizliğinin çocukların sosyal-duygusal gelişimini de etkileyebileceği ifade edilmektedir (Yıldız et al., 2026). Bunun yanında Türkiye'de yapılan çalışmalar, ev ortamı kalitesinin çocukların gelişimsel işlevleriyle doğrudan ilişkili olduğunu ve uyarıcı zenginliğin gelişimi desteklediğini ortaya koymaktadır (Ömercioğlu et al., 2024).

Ebeveyn desteği yetersiz olan çocukların dezavantajlı bir konumda olduğu söylenebilir. Çocukların gelişimini ve eğitimini desteklemek isteyen anne babaların temel görevi, onların karşısındaki keşif dünyasının kapılarını aralamak ve zengin uyaranlarla desteklenmiş bir çevre sunmaktır. Tüm bu noktalar göz önünde bulundurulduğunda, ev ortamının çocukların gelişim düzeylerine ve ihtiyaçlarına uygun, güvenli, sağlıklı ve ilgi çekici şekilde yapılandırılması gerekmektedir (Aydoğan, 2006).

Toplum Temelli Sosyal Hizmet Çalışmaları

3.1 Toplum Temelli Yaklaşımın İlkeleri

Toplum temelli hizmet yaklaşımı, birey ve toplulukların sosyal, ekonomik ve kültürel ihtiyaçlarına yerel düzeyde çözüm üretmeyi amaçlayan; katılımı, güçlendirmeyi ve yerel kaynakların etkin kullanımını esas alan bir yaklaşımdır. Özellikle göç ve yoksulluk gibi risk faktörlerinden etkilenen çocuklar ve ailelerin toplumsal yaşama uyumlarını desteklemesi bakımından önemli bir yere sahiptir (Altuntaş, 2025).

Bu yaklaşımın temel ilkelerinden biri olan katılım ilkesi, bireylerin hizmet süreçlerine ve karar alma mekanizmalarına aktif olarak dahil edilmesini ifade etmektedir (Baxter ve ark., 2022). Güçlendirme ilkesi ise bireylerin kendi yaşamları üzerinde daha fazla söz sahibi olmalarını ve sorunlarla baş etme kapasitelerini geliştirmeyi amaçlamaktadır (Tören & Açan Aslan, 2024).

Toplum temelli sosyal hizmet anlayışı, koruyucu ve önleyici hizmetlerle doğrudan ilişkilidir. Bu hizmetler; bireylerin olumsuz koşullardan etkilenmesini önlemeyi, psikososyal gelişimlerini desteklemeyi ve baş etme becerilerini güçlendirmeyi amaçlamaktadır (Doğan & Yücer, 2025). Toplum temelli uygulamalarda yerel kurumlar, sivil toplum kuruluşları ve meslek elemanları arasında iş birliğinin geliştirilmesi önem taşımaktadır. Bu sayede özellikle dezavantajlı çocuklar ve aileler için daha kapsayıcı ve sürdürülebilir hizmetlerin sunulması mümkün olmaktadır (Acar ve ark., 2023).

3.2 Dezavantajlı Gruplara Yönelik Müdahale Modelleri

Sosyal destek, bireylerin psikososyal iyi oluşunu koruyan önemli bir unsur olarak ele alınmakta ve duygusal, araçsal ve bilgilendirici destek türleri üzerinden açıklanmaktadır. Sosyal destek düzeyinin artmasının yalnızlık ve sosyal izolasyon riskini azalttığı, özellikle algılanan destek kalitesinin bu süreçte belirleyici olduğu belirtilmektedir (Kırlıoğlu, 2019). Yetersiz sosyal ilişkiler ise bireylerde yalnızlık riskini artırmakta ve sosyal katılımı olumsuz etkilemektedir (Erbay, 2019).

Sosyal destek, yalnızlığa karşı önemli bir koruyucu faktör olarak değerlendirilmekte ve duygusal, araçsal ve bilgilendirici destek bileşenlerinden oluşmaktadır. Araştırmalar, sosyal destek düzeyi arttıkça yalnızlık düzeyinin azaldığını ve bu iki değişken arasında negatif bir ilişki bulunduğunu göstermektedir. Ayrıca yalnızlığın azaltılmasında yalnızca sosyal ağın büyüklüğünün değil, ağ içindeki ilişkilerin niteliğinin de belirleyici olduğu, bireyin kendini değerli ve anlaşılmış hissetmesinin daha koruyucu bir etkiye sahip olduğu belirtilmektedir (Huang ve ark., 2026).

Toplum merkezleri, dezavantajlı gruplara yönelik sosyal hizmet müdahalelerinde önemli bir uygulama alanı olarak değerlendirilmektedir. Toplum temelli hizmetlerin bireylerin sosyal uyumunu güçlendirdiği, özellikle kırılgan grupların güçlendirilmesinde önemli bir araç olduğu vurgulanmaktadır (Buz & Artam Ayyıldız, 2019).

Bu merkezler, bireylerin sosyal yaşama katılımını artırmakta, toplumsal dayanışmayı güçlendirmekte ve sosyal adaletin sağlanmasına katkı sunmaktadır (Tuncay, 2006). Ayrıca göçmenler ve dezavantajlı gruplara yönelik psikososyal destek, eğitim ve yönlendirme hizmetleri sunarak çok boyutlu müdahale modelleri geliştirmektedir (Altuntaş, 2025).

3.3 Mevcut Uygulamalarda Gelişim Boyutunun Yeri

Mevcut toplum temelli sosyal hizmet uygulamalarında gelişim boyutu, özellikle çocukların bilişsel, duygusal ve sosyal gelişimlerinin desteklenmesi açısından önemli bir yer tutmaktadır. Erken çocukluk döneminde sunulan koruyucu ve önleyici hizmetlerin, çocukların gelişimsel risklerini azalttığı ve yaşam boyu iyi oluşu desteklediği belirtilmektedir (Türkkent ve Özer, 2023).

Çocukların gelişimsel ihtiyaçlarının erken dönemde karşılanmasına yönelik uygulamaların etkili olduğu bilindiği süreçlerde, bu süreçte çocuğun gelişiminin yalnızca bireysel değil, aile ve çevresel faktörlerle birlikte ele alınmasının gerekli olduğu ve aile ortamlarının ve çocuklarının bireysel özellikleri ile birlikte uygun müdahale programlarının önemi ve gerekliliği de ifade edilmektedir (Kaya & Demir, 2022).

Güncel sosyal hizmet uygulamalarında çocukların gelişimsel durumu yalnızca risklerin belirlenmesi ile sınırlı kalmayıp, gelişim süreçlerinin aşama aşama izlenmesi ve uygun müdahalelerle desteklenmesi önem taşımaktadır. Çocuk gelişimciler, 0–18 yaş aralığındaki çocukların normal, riskli veya özel gereksinimli gelişim özelliklerini değerlendirerek aileler ve diğer meslek gruplarıyla iş birliği içinde müdahale planları oluşturmaktadır (Cesur & Köksal Akyol, 2018).

Çocuk Gelişimcinin Toplum Temelli Çalışmalardaki Rolü

4.1 Gelişimsel Tarama ve Risk Belirleme

Gelişimsel tarama uygulamaları, risk altındaki çocukların erken tespitinde kritik öneme sahiptir. Erken uyarı sistemleri, çocukların normal gelişim gösteren, risk altında olan veya özel gereksinim gösteren gruplar içinde sınıflandırılmasını sağlayarak uygun müdahale planlarının oluşturulmasına katkı sunar (Armutlu, 2026). Planlı sosyal hizmet müdahaleleri ile risk altındaki çocukların ihtiyaçları sistematik olarak değerlendirilerek desteklenir (Catulay & Uğurlu, 2023).

Sağlam çocuk izlemlerinde doktor takibinin yanı sıra, belirli aralıklarla standartlaştırılmış gelişimsel tarama araçlarının uygulanması erken tanı fırsatını artırmaktadır. Bu doğrultuda, değerlendirme, izlem ve destek süreçlerinde etkin görev üstlenecek klinisyenlerden oluşan multidisipliner ve transdisipliner ekiplerin yapılandırılması ve ekip üyelerinin bilimsel kanıta dayalı ölçme araçlarını kullanması büyük önem taşımaktadır (Özkan vd., 2024).

Değerlendirme sürecinde, çocuğun bakım sürecinde yer alan ebeveyn ve eğitimci gibi kaynaklardan elde edilen veriler, gelişimsel durumun saptanmasında önemli bir rol oynamaktadır. Bununla birlikte, bu bireylerin erken çocukluk dönemine ilişkin gelişimsel bilgi düzeylerinin her zaman yeterli olmaması, değerlendirme sürecinde eksikliklere ya da yanlış yorumlamalara neden olabilmektedir (Köroğlu ve Yılmaz Demirel, 2023).

4.2 Erken Müdahale Programlarının Yapılandırılması

Erken müdahale programları, 0–36 ay aralığındaki çocukların gelişimsel risklerinin erken dönemde belirlenerek bilişsel, dil, sosyal ve duygusal gelişimlerinin desteklenmesini amaçlayan uygulamalardır. Bebek kütüphanesi temelli erken müdahale programlarının özellikle dil ve sosyal gelişimi desteklediği, aile katılımını artırdığı ve ev ortamında öğrenmeyi güçlendirdiği belirtilmektedir. Ayrıca bu programların bebeklerin genel gelişimi üzerinde olumlu etkiler oluşturduğu ifade edilmektedir (Ceylan ve ark., 2025).

Erken müdahale programlarında aile katılımı önemli bir yer tutmakta olup, ebeveynlerin çocuklarıyla oyun temelli etkinlikler aracılığıyla nitelikli zaman geçirmesi, çocukların gelişimsel süreçlerini desteklemektedir. Bu kapsamda ebeveynlerin oyun ortamları oluşturarak çocuklarının yaratıcı düşünme becerilerini desteklemeleri, gelişimsel farkındalıklarını artırmaktadır (Tuğrul ve Niran, 2022).

4.3 Topluluk İçinde Kapasite Geliştirme

Topluluk içinde kapasite geliştirme, özellikle göç ve yoksulluk gibi risk faktörlerine maruz kalan aileler ve çocuklar için sosyal hizmet uygulamalarının önemli bir alanını oluşturmaktadır. Bu kapsamda grup temelli sosyal hizmet müdahaleleri, bireylerin psikososyal yönden güçlenmesine ve toplumsal uyum süreçlerinin desteklenmesine katkı sağlamaktadır. Yapılan araştırmalar, grup çalışmalarının bireylerin sosyal işlevselliğini artırdığını ve toplumsal kapasiteyi geliştirdiğini göstermektedir(Alataş ve Pak Güre, 2025). Göçmen ve dezavantajlı ailelerde güçlendirme yaklaşımının uygulanması, sosyal uyum süreçlerini destekleyen önemli bir sosyal hizmet müdahalesi olarak değerlendirilmektedir (Sırma ve Aslan, 2024).

Anne destek grupları, ailelerin psikososyal yönden güçlenmesine katkı sağlarken, gelişim atölyeleri ise çocukların ve ailelerin sosyal becerilerinin artırılmasında etkili bir yöntem olarak kullanılmaktadır. Ayrıca sosyal inovasyon temelli grup çalışmaları ve atölye uygulamalarının, bireylerin sosyal işlevselliğini artırdığı ve toplum içinde aktif katılımı güçlendirdiği belirtilmektedir (Erol vd., 2021).

4.4 Disiplinler Arası ve Kurumlar Arası İş Birliği

Sosyal hizmet uygulamaları, birey ve toplum refahını sağlamak amacıyla farklı meslek gruplarının ve kurumların birlikte çalışmasını gerektiren disiplinler arası bir yapıya sahiptir (Sırma & Aslan, 2024). Sosyal hizmet uzmanlarının özellikle risk altındaki gruplara yönelik çalışmalarda diğer meslek elemanları ile koordinasyon içinde olması, hizmetlerin etkinliğini artıran temel bir faktör olarak değerlendirilmektedir (Alataş ve Pak Püre, 2025).

Yerel yönetimler, sosyal hizmetlerin sahaya ulaştırılmasında önemli kurumsal aktörlerden biri olarak birey ve ailelere doğrudan destek sağlayan yapılar arasında yer almaktadır (Erol, Karasoy & Yıldırım, 2021). Sivil toplum kuruluşları ise dezavantajlı gruplara yönelik hizmetlerin çeşitlendirilmesinde ve toplumsal ihtiyaçların belirlenmesinde tamamlayıcı bir rol üstlenmektedir (Sırma & Aslan, 2024).

Bu doğrultuda sosyal hizmet alanında kurumlar arası iş birliğinin güçlendirilmesi, hizmetlerin daha kapsayıcı ve sürdürülebilir olmasını sağlamaktadır (Erol, Karasoy & Yıldırım, 2021).

Sonuç olarak sosyal hizmet uzmanları, yerel yönetimler ve sivil toplum kuruluşları arasındaki koordinasyon, toplumsal sorunlara yönelik müdahalelerin bütüncül bir şekilde yürütülmesinde kritik bir öneme sahiptir (Yılmaz & Demir, 2025).

Erken Müdahale Bileşeninin Yapılandırılması

5.1 Program Tasarımı

Yoksulluk, çocukların gelişimlerini olumsuz etkileyen önemli bir risk faktörüdür. Eğitim, sağlık ve sosyal hizmetlere erişimde yaşanan eşitsizlikler çocukların gelişimsel fırsatlardan yeterince yararlanamamasına neden olmaktadır. Ayrıca çocuk işçiliği gibi sorunlar çocukların eğitimden uzaklaşmasına ve gelişimlerinin olumsuz etkilenmesine yol açmaktadır. Bu nedenle erken müdahale programlarında risk altındaki çocuklara öncelik verilmesi önem taşımaktadır (Kalaycı & Karadeniz, 2023).

Erken müdahale programlarının etkili olabilmesi için çocukların gelişimlerinin düzenli olarak izlenmesi gerekmektedir. Erken çocukluk döneminde yapılan değerlendirmeler, gelişimsel risklerin erken belirlenmesine ve gerekli destek hizmetlerinin planlanmasına katkı sağlamaktadır (Aksoy & Yıldırım Parlak, 2023).

Çocukların gelişimsel gereksinimlerinin doğru belirlenebilmesi için değerlendirme süreçlerinin bütüncül bir yaklaşımla yürütülmesi önemlidir. Bilişsel, dil, motor ve sosyal-duygusal gelişim alanlarının birlikte ele alınması müdahalenin etkililiğini artırırken, aile katılımı da sürecin başarısını desteklemektedir (Leblebicier vd., 2024).

Aile katılımı erken müdahale programlarının temel bileşenlerinden biridir. Ailelerin sürece aktif olarak dahil edilmesi, çocukların gelişimsel kazanımlarını desteklemekte ve programların sürdürülebilirliğini artırmaktadır (Yıldırım & Keleş, 2023).

5.2 Ölçme ve Değerlendirme Süreçleri

Göç ve yoksulluk riski altındaki çocukların gelişimsel özelliklerinin erken dönemde belirlenmesi, olası gecikmelerin tespit edilmesi ve uygun destek hizmetlerine yönlendirilmesi açısından sistematik değerlendirmeler gereklidir. Bu süreçte çocuk gelişimciler, gözlem, aile görüşmeleri ve standart gelişimsel değerlendirme araçlarını birlikte kullanarak çocukların gelişim düzeylerini bütüncül bir bakış açısıyla ele almaktadır (Özkan vd., 2024).

Çocukların gelişimsel durumlarının belirlenmesinde gelişim tarama testleri önemli bir işlev görmektedir. Türkiye'de yaygın olarak kullanılan Denver II Gelişimsel Tarama Testi, çocukların kişisel-sosyal, dil, ince motor ve kaba motor gelişim alanlarının değerlendirilmesine olanak sağlamaktadır. Erken müdahale kapsamında gerçekleştirilen tarama çalışmalarının, gelişimsel gecikme riski taşıyan çocukların belirlenmesinde etkili olduğu ve müdahale planlarının oluşturulmasına katkı sağladığı belirtilmektedir (İmir vd., 2024).

Çocuk gelişimciler tarafından kullanılan değerlendirme araçları yalnızca gelişimsel gecikmelerin belirlenmesine değil, aynı zamanda çocuğun ihtiyaçlarının ayrıntılı biçimde ortaya konulmasına da yardımcı olmaktadır (Yılmaz Bursa, 2024).

Ölçme ve değerlendirme süreci yalnızca ilk değerlendirme aşamasıyla sınırlı değildir. Müdahale süreci boyunca yapılan düzenli izleme ve yeniden değerlendirmeler sayesinde çocuğun gelişimsel ilerlemesi takip edilmekte, uygulanan programların etkililiği değerlendirilmekte ve gerekli durumlarda müdahale planları güncellenmektedir. Erken müdahale programlarında sürdürülen izleme çalışmalarının, çocukların gelişimsel kazanımlarının kalıcılığını desteklediği ve hizmetlerin etkililiğini artırdığı ifade edilmektedir (Tercan ve Bayhan, 2020).

6. SONUÇ

Bu çalışmada, göç ve yoksulluk koşullarında büyüyen çocukların gelişim süreçlerinin çeşitli risk faktörlerinden etkilendiği ve bu durumun gelişimsel eşitsizliklerin ortaya çıkmasına neden olduğu görülmüştür. Eğitim olanaklarına erişimde yaşanan güçlükler, psikososyal sorunlar ve ev ortamındaki uyarıcı yetersizliği, çocukların bilişsel, dil, sosyal-duygusal ve fiziksel gelişimlerini olumsuz yönde etkileyebilmektedir. Bu nedenle göç ve yoksulluk yalnızca ekonomik bir sorun olarak değil, çocukların gelişimsel iyi oluşunu etkileyen çok boyutlu bir sosyal risk alanı olarak değerlendirilmelidir.

Araştırma kapsamında incelenen toplum temelli sosyal hizmet uygulamalarının, dezavantajlı çocuklar ve ailelerin desteklenmesinde önemli bir işleve sahip olduğu belirlenmiştir.

Ancak mevcut uygulamalarda gelişimsel değerlendirme ve erken müdahale çalışmalarının yeterince ön planda olmadığı görülmektedir. Çocukların gelişimsel ihtiyaçlarının erken dönemde belirlenmesi ve uygun destek hizmetlerine yönlendirilmesi açısından çocuk gelişimcilerin toplum temelli sosyal hizmet ekiplerinde daha aktif görev alması gerekmektedir.

Bu bağlamda çocuk gelişimciler; gelişimsel tarama ve değerlendirme, risk belirleme, aile danışmanlığı, erken müdahale programlarının planlanması ve uygulanması gibi alanlarda önemli sorumluluklar üstlenmektedir. Özellikle göç ve yoksulluk riski altındaki çocuklara yönelik koruyucu ve önleyici hizmetlerin geliştirilmesinde çocuk gelişimcilerin mesleki bilgi ve becerilerinden yararlanılması, hizmetlerin etkililiğini artıracaktır.

Toplum temelli sosyal hizmet çalışmalarında gelişim odaklı bir yaklaşımın benimsenmesi ve erken müdahale bileşeninin hizmet modellerine sistematik biçimde entegre edilmesi önem taşımaktadır. Yerel yönetimler, sosyal hizmet kuruluşları, eğitim kurumları ve sağlık hizmetleri arasında kurulacak iş birliği sayesinde çocukların gelişimsel gereksinimleri daha bütüncül şekilde karşılanabilecektir. Böylece göç ve yoksulluktan kaynaklanan gelişimsel eşitsizliklerin azaltılması, çocukların sağlıklı gelişimlerinin desteklenmesi ve toplumsal refahın güçlendirilmesi mümkün olacaktır.

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THE IMPACT OF INFLUENCER CULTURE ON CHILDREN'S IDENTITY DEVELOPMENT AND THE PROTECTIVE ROLE OF SOCIAL WORK

INFLUENCER KÜLTÜRÜNÜN ÇOCUK KİMLİK GELİŞİMİNE ETKİSİ VE SOSYAL HİZMETİN KORUYUCU ROLÜ

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ABSTRACT
With the digitalization process, new communication experiences offered by platforms such as Instagram have led to the redefinition of consumer culture through influencers. In this study, which is a qualitative literature review, the inclusion of children in digital content imposes significant responsibilities on the social work discipline in terms of protecting children's rights. The reflections of fundamental principles such as the "best interests of the child" and the ‘’right to privacy’’ in the digital world, in the light of developmental theories such as Erikson and Bandura, constitute the focus of this research. Especially the concept of *’’sharenting’’* and the commodification of children are evaluated as risky areas in the context of child neglect and abuse. Consequently, the transformative effect of digital platforms on identity construction increases the necessity for advocacy and protective-preventive interventions.
Keywords: Influencer Culture, *Sharenting*, Child Rights, Identity Development, Social Work.

ÖZET
Dijitalleşme süreciyle birlikte Instagram gibi platformların sunduğu yeni iletişim deneyimleri, influencerlar aracılığıyla tüketim kültürünün yeniden tanımlanmasına yol açmıştır. Bu dönüşüm içerisinde çocukların dijital içeriklere dahil edilmesi, çocuk haklarının korunması noktasında sosyal hizmet disiplinine önemli sorumluluklar yüklemektedir. Çocuk Hakları Sözleşmesi'nde yer alan ‘’çocuğun yüksek yararı’’ ve ‘’mahremiyet hakkı’’ gibi temel ilkelerin, dijital dünyadaki yansımaları bu çalışmanın odağını oluşturmaktadır. Özellikle ebeveynlerin çocuklarına ait görsel ve verileri paylaşması olarak tanımlanan çim"*sharenting*" kavramı ve çocukların ticari birer meta haline getirilmesi, çocuk ihmali ve istismarı bağlamında riskli alanlar olarak değerlendirilmektedir. Sonuç olarak, dijital platformların bireylerin kimlik inşası ve sosyal etkileşim dinamikleri üzerindeki dönüştürücü etkisi, savunuculuk ve koruyucu-önleyici müdahale gerekliliğini artırmaktadır.
Anahtar Kelimeler: Influencer Culture, *Sharenting*, Child Rights, Identity Development, Social Work.

GİRİŞ
Tüketim çağı olarak nitelendirilen günümüzde toplumsal yaşam; yalnızca sosyal etkileşim biçimlerini değil, çocukluk, aile ve ebeveynlik gibi temel kurumları da kapsayan radikal bir dönüşüm sürecinden geçmektedir. Bu süreç, yeni iletişim araçlarının yaygınlaşmasıyla birlikte mahremiyet sınırlarının belirsizleşmesine neden olurken, aile içi dinamikleri dijital kamusallığın bir parçası haline getirmektedir (Duman, 2024).

Bu dönüşümün en belirgin yansımalarından biri olan influencer kültürü, ebeveynlik rollerini geleneksel koruyucu işlevinden uzaklaştırarak çocukları dijital ekosistemin birer 'ekonomik aktörü' haline getirmiştir. Günümüzde ebeveynlerin çocuklarını "kidfluencer" olarak yetiştirip onlar aracılığıyla ekonomik kazanç sağladığı bir sürecin ivme kazandığı görülmektedir. Başlangıçta maddi bir amaç güdülmese bile, ebeveynlerin çocuklarının her anını paylaştıkları "sharenting" akımı, çocukların ticari birer nesne gibi konumlandırılmasına yol açabilmektedir. Bu durum, yeni nesil bir ‘’çocuk işçiliği’’ sorununu ortaya çıkararak çocukları fiziksel ve sosyal sömürüye açık hale getirmekte ve haklarının ihlal edilmesine zemin hazırlamaktadır (Gözen & Şaldırdak, 2023).

Dijitalleşmenin bu boyutu, çocuğun özel hayatının gizliliğini ihlal etmenin ötesinde; oyun oynaması ve eğitim alması gereken gelişimsel dönemlerinde 'ticari bir mesai' ile karşı karşıya kalmasına neden olmaktadır. Çocukların gerçek dünyayı deneyimlemeden sanal evrende bu denli yoğun yer alması,

sağlıklı bir kimlik inşası yerine dış odaklı ve tüketime dayalı bir benlik geliştirmelerine yol açabileceği değerlendirilmektedir (Baloğlu & Budak, 2025). Bu noktada sosyal hizmet disiplini, dijital dünyadaki bu hak ihlallerine karşı savunuculuk ve koruyucu-önleyici müdahale rollerini yeniden tanımlamak durumundadır. Bu makale, dijital mecralarda yer alan çocukların sadece birer pasif içerik üreticisi değil gelişimsel süreçleri ve psikososyal bütünlükleri risk altında olan 'hassas özneler' olduğunu savunmaktadır. Çalışma kapsamında önce influencer kültürünün kuramsal temelleri incelenecek, ardından risk faktörleri analiz edilerek sosyal hizmet disiplini için çözüm odaklı öneriler sunulacaktır.
Bu derlemede izlenen yol; Türkiye'deki sosyal medya fenomenlerinin çocukların psikososyal gelişim süreçleri üzerindeki etkilerini analiz etmek ve bu sürecin dijital hak ihlalleri boyutunu sosyal hizmet perspektifiyle değerlendirmektir. Çalışma, söz konusu etkileri sadece genel bir kültürel değişim olarak değil; disiplinlerarası bir bakış açısıyla ''sharenting'' uygulamaları ve ''dijital çocuk işçiliği'' riskleri üzerinden ele almayı amaçlamaktadır. Bu bağlamda çalışma, literatürdeki kavramsal boşluğu doldurarak sosyal hizmet uzmanları için proaktif ve koruyucu müdahale stratejileri sunması bakımından önem taşımaktadır.
Sharenting; ebeveynlerin çocuklarına ait fotoğraf, video veya yazılı içerikleri sosyal medyada paylaşması olarak tanımlanmaktadır. Ebeveynler bunu her ne kadar iyi niyetle yapsalar da çocuğun rızası alınmadığı için bu durum mahremiyet ihlaline yol açmaktadır (Avcı & Yalman Polatlar, 2025). Günümüzde çocuk ve ergenler, sanal alemde varlık göstererek kendi kimliklerini inşa etmeye başlamaktadır. Özellikle YouTube gibi platformlar üzerinden kurulan 'ideal kimlik' yaratma çabası, beraberinde toplum tarafından beğenilme ve arzulanma isteğini de getirmektedir (Karadağ, 2022). Çocukların henüz olgunlaşmamış düşünce yapıları ve dürtülerini kontrol etmekte zorlanmaları, onları sosyal medyadaki bilgilerden etkilenmeye daha açık ve savunmasız bir hale getirmektedir (Aydın & Gürbüz, 2024). Mevcut literatürdeki bu verilerden yola çıkarak, çalışmamız şu sorulara yanıt aramaktadır:

1. **Soru:** Ebeveynlerin *sharenting* paylaşımlarının, çocuğun kimlik gelişimi ve mahremiyet hakları üzerindeki etkileri nelerdir?
2. **Soru:** İnfluencer kültürü ve dijital etkileşimlerin, çocukların kimlik inşası ile özdeşim kurma süreçlerindeki temel rolleri nelerdir?
3. **Soru:** Sosyal medyadaki risklere ve çocuk haklarının ihlaline karşı sosyal hizmet uzmanlarının üstlendiği önleyici ve koruyucu roller nelerdir?
4. **Soru:** Sosyal medyada sergilenen 'mükemmel hayat' sunumları, çocuklar üzerinde ne tür psikososyal riskler oluşturmaktadır?

Türkiye'de en çok tercih edilen medya aracı YouTube'dur. Hem yetişkinler hem de çocuklar için farklı kanallar bulunmaktadır. Çocuklara yönelik kanallarda yapılan bazı çalışmalar mahremiyet konusunu ele alırken, bazıları da çocuk haklarının ihlal edildiğini göstermiştir. Özellikle ürün tanıtımı için çocukların videolarda kullanılması ailelere para kazandırsa da çocuk hakları göz ardı edilmektedir. Literatürde YouTube'daki reklam stratejilerinin çocuk gelişimi üzerindeki etkilerini sosyal hizmet perspektifiyle derinlemesine ele alan çalışmaların sınırlı olduğu görülmektedir; bu durum hem hukuki hem de sosyal müdahale süreçlerinde bir boşluk yaratmaktadır. Sosyal hizmet açısından bakıldığında çocukların güvenliği, hakları ve kimlik gelişimi büyük önem arz etmektedir. Bu yüzden Aile ve Sosyal Hizmetler Bakanlığı ile Millî Eğitim Bakanlığı'nın birlikte çalışıp çocuk hakları konusunda farkındalık yaratması gerekmektedir. Böylece çocuklar sosyal medyada daha güvenli hale gelecek ve sosyal hizmetin koruyucu rolünün güçlenmesi sağlanacaktır (Özcan, 2023). Literatürdeki bu boşluk, Baudrillard'ın (Özyurt, 2022) kuramsallaştırdığı nesneleşme sürecinin dijital platformlarda çocuk özneler üzerinden somutlaştığını göstermektedir. Bu bağlamda araştırma; YouTube'daki reklam stratejilerinin çocuğun sadece fiziksel güvenliğini değil, sağlıklı bir psikososyal kimlik inşası sürecini de nasıl tehdit ettiğini ortaya koyması bakımından sosyal hizmet disiplini için kritik bir önem taşımaktadır.

2.1.Kimlik Gelişimi

Kimlik gelişimi, doğumdan itibaren çevremizdeki önemli insanların bize yaklaşımıyla şekillenen; aile, inançlar ve toplumsal kültürle iç içe geçerek başkalarının bizim hakkımızdaki fikirlerinin bir yansıması olarak oluşan bütünsel bir süreçtir (Bilgin & Oksal, 2018). Bu gelişim sürecinde yer alan "beliren yetişkinlik" dönemi, bireyin henüz büyük sorumluluklar almadan kendisini özgürce keşfettiği kritik bir zaman dilimi olarak tanımlanmaktadır. Arnett (2000), söz konusu evrede yaşanılan her yeni tecrübe ve geliştirilen dünya görüşünün, karakterin son halini almasına yardımcı olan birer parça niteliğinde olduğunu belirtmektedir. Günümüzde bu tecrübe ve keşif süreci, fiziksel dünyadan ziyade dijital

mecralarda gerçekleşmekte; Arnett'in bahsettiği 'kendini keşfetme' süreci, influencerların sunduğu hazır kimlik modelleriyle etkileşime girmektedir.

2.1.1.Bireysel Kimlik

Bireysel kimlik, zihinde yer alan imajların bir bütünü olarak tanımlanmaktadır. Bireyi diğerlerinden ayıran ve özgün bir benlik inşasına imkân tanıyan temel özelliklerin bu kavram çerçevesinde belirlendiği görülmektedir. Bu süreç çocukluktan başlar ve çevre ile kurulan bağlarla şekillenerek devam eder. Kimliği tanımak ve geliştirmek için kimlik süreci kritik bir aşamadır (İncirkuş, 2020). Bu, kişinin kendisini nasıl gördüğü ve nasıl tanımladığı ile ilgili bir durumdur.
Erikson (1968), gençlik yıllarında farklı rollerin denendiği bir kimlik krizinden bahseder. Dijital çağda bu ‘’rol deneme ‘’süreci, çocukların influencerların yaşam tarzlarını, giyimlerini ve tüketim alışkanlıklarını taklit etmeleriyle yeni bir boyut kazanmıştır. Bu durum, bireysel kimliğin özgün bir şekilde inşasından ziyade, dijital modellerin birer kopyasına dönüşme riskini barındırmaktadır.

2.1.2.Sosyal Kimlik

Teknolojinin hızla gelişmesiyle birlikte sosyal kimlik kavramı da şekil değiştirmektedir. Artık gençler, yüz yüze iletişime gerek duymadan sanal ortamlarda da sosyalleşebilmektedir. Özellikle ergenler; diğer kullanıcılar tarafından onaylanma, kabul görme ve popüler kültüre ayak uydurma isteğiyle bu platformlarda daha fazla vakit geçirmektedir. Sosyal medya, her ne kadar çocukların yaratıcılığını ve dijital okuryazarlık becerilerini geliştirse de bu durum onları bazen gerçek hayattan kopuk bir hale getirmektedir. Ayrıca çevrim içi oyun platformları veya internet üzerinden kurulan yeni arkadaşlıklar, gençleri birçok riskle karşı karşıya bırakmaktadır (Yılmaz & Aktürk, 2024). Bu risklerin başında, sosyal kimlik inşasının sadece dijital beğeni ve 'takipçi' sayılarına indirgenmesi gelmektedir. Bu noktada influencerlar, çocukların sosyal kabul görmek için model aldıkları ana figürler haline gelerek, sosyal kimliğin oluşumunda aile ve okulun önüne geçmektedir.

2.1.3.Dijital Kimlik

Dijital kimlik, bireyin çevrimiçi ortamlarda kendisini sunma ve ifade etme biçimini kapsamaktadır. Sosyal medya platformları, bireyin yalnızca mevcut kimliğini görünür kıldığı değil, aynı zamanda farklı kimlik denemeleri gerçekleştirebildiği bir alan oluşturmaktadır (Kaya, 2021). Bu durum, Erik Erikson’un “psikososyal moratoryum” olarak tanımladığı kimlik deneme sürecinin dijital ortamlardaki bir yansıması olarak değerlendirilebilir. Ancak dijital kimlik inşasının beğeni, takip edilme ve çevrimiçi onay mekanizmaları üzerinden şekillenmesi, bireyin benlik sunumunu sürekli dış değerlendirmeye açık hale getirebilmektedir.

2.2.Çocukluk ve Ergenlik Döneminde Kimlik Gelişimi

Kimlik gelişimi, çocukluk döneminden itibaren şekillenmeye başlayan önemli bir süreçtir. Çocuklar, kimliklerini oluştururken yetişkinlere ihtiyaç duymaktadır. Başta anne ve baba olmak üzere çevredeki diğer yetişkin bireyler; çocukların kişisel, ahlaki, dini ve sosyal açıdan gelişiminde, onları erdemli birer yetişkin haline getirecek destekleri sunmaktadır. Ergenlik döneminde de gençler yetişkinliğe hazırlık sürecinde olduğundan, anne, baba ve öğretmenlerin ergene rol model olması gerekmektedir (Çiftçioğlu vd., 2016). Dijital medya ortamında influencerların görünürlüğünün artması, çocuk ve ergenlerin rol model algılarının dönüşmesine neden olmaktadır. Bu durum, kimlik gelişim sürecindeki bireylerin çevrimiçi figürlerle daha yoğun özdeşim kurabilmelerine zemin hazırlayabilmektedir.

2.3.Sosyal Medya ve Influencer Kültürü

Teknolojinin hızla gelişmesiyle birlikte sosyal medya mecraları, günümüzün en önemli iletişim araçlarından biri haline gelmiştir. Sosyal medya, ihtiyaçtan ziyade zevk ve eğlence amacı ile de kullanılmaktadır. Sosyal medyanın temel işlevleri arasında reklam ve pazarlama faaliyetleri ön planda yer almaktadır. Reklam ve pazarlama şirketleri, mal ve hizmetlerini daha görünür hale getirmek ve popülerliğini artırmak amacıyla İnfluencerları kullanmaktadırlar. İnfluencer kavramı ise sosyal medyada geniş bir takipçi kitlesi bulunan ve toplulukları etkileme kabiliyeti olan kişileri ifade etmektedir. Sosyal medyanın pek çok alanında İnfluencerlar bulunmaktadır; güzellik, moda, kozmetik ve yemek, bu alanlardan bazılarını oluşturmaktadır (Yardımcı, 2024). Yardımcı’nın (2024) işaret ettiği bu pazarlama düzeninde influencerlar, Bandura’nın (2006) kuramındaki ‘’sembolik modeller’’ haline gelmiştir. Tatlıoğlu (2021) ise modelin sahip olduğu yüksek statünün taklit edilme olasılığını artırdığını belirtir; bu bağlamda influencerların sunduğu idealize edilmiş yaşamlar, çocukların kimlik inşasında kontrolsüz bir sosyal öğrenme süreci başlatmaktadır.

2.3.1.Influencer Tanımı ve Türleri

Influencerlar; pazarlama, reklam ve günlük içerik paylaşımları yapan kişilerdir. Takipçi sayılarına göre beş gruba ayrılmaktadırlar: 1 milyondan fazla takipçisi olanlar "mega", 100 bin - 1 milyon arası olanlar "makro", 50 bin - 500 bin arası takipçisi olanlar "mid-tier", 5 bin - 100 bin arası olanlar "mikro" ve 1000 civarı takipçisi olup etkisi yüksek olanlar "nano" İnfluencerlardır. Reklam verenler, İnfluencerların verimliliğini bu şekilde beş kademede değerlendirmektedir. Özellikle mid-tier grubu eklenmediğinde, takipçi sayısı ve istenen ücretler arasında çok büyük farklar oluşmaktadır. Bu yüzden araştırmada, sektörde de kullanılan bu beşli sınıflandırma tercih edilmektedir (Çetintürk, 2024). Influencerların bu kademeli sınıflandırması, çocuk gelişimi açısından sadece takipçi sayısını değil, model alma sürecindeki psikolojik yakınlık düzeyini belirlemektedir. Takipçi sayısı azaldıkça artan ‘samimiyet’ algısı, çocukların sunulan içerikleri eleştirel bir süzgeçten geçirmeden içselleştirme riskini güçlendirmektedir.

2.3.2.Mikro ve Makro Influencerler

Mikro İnfluencerlar, 1.000 ile 10.000 arasında takipçisi olan ve belirli bir konuda uzmanlaşmış kişilerdir. Bu İnfluencerların marka ve reklam tanıtım olanakları, makro İnfluencerlara göre daha sınırlıdır. Mikro İnfluencerlar hakkında bazen olumsuz tespitler yapılsa da durum aslında böyle değildir; çünkü bu kişiler uzmanlaştıkları alanlarda takipçileri tarafından inandırıcı ve doğru bir kaynak olarak görülmektedir. Makro influencerlar ise 100.000 ve üzeri takipçi kitlesine sahip olan ‘’celebrity’’ (ünlü) kişilerdir. Bu grup, genellikle kendi şirketlerini kurmuş ve paylaşımları için belirli bir bütçe talep eden kişilerden oluşmaktadır (Gümüş, 2019). Mikro influencerların 'inandırıcı kaynak' olarak görülmesi, çocukların bu kişileri daha kolay içselleştirmesine ve sunulan yaşam tarzlarını sorgulamadan taklit etmesine zemin hazırlamaktadır. Makro influencerlar ise yarattıkları 'ünlü' imajıyla çocukta hayali bir standart oluşturarak, gerçeklikten kopuk bir benlik algısı gelişimini tetikleyebilmektedir.

2.3.3.Çocuk Influencer Fenomeni

“20 Kasım 2020 tarihinde Prof. Dr. İlber Ortaylı'nın YouTube programına konuk olan 7 yaşındaki Sedef'e, ‘Büyüyünce ne olacaksın?’ sorusu sorulduğunda Sedef, ‘YouTuber olacağım.’ yanıtını vermiştir. Bundan on yıl öncesine kadar doktor, avukat veya öğretmen olmak isteyen çocukların günümüzde YouTuber olmayı hayal etmesi, dijital çağın onlara sunduğu sınırsız seçeneklerin bir göstergesidir” (Gözen & Şaldırdak, 2023, s. 115). İnternet çağının getirdiği dijitalleşme sonucunda markalar, ürünlerini tanıtmak amacıyla ‘’influencer’’ kavramını ön plana çıkarmakta ve hedef kitle olarak çocukları seçmektedir. Ebeveynlerin de bu durumu ekonomik bir fırsat alanı olarak görmeleri sebebiyle çocuklarını "kidfluencer" olarak yetiştirdikleri belirtilmektedir (Gözen & Şaldırdak, 2023). Çocukların mesleki hayallerinin geleneksel rollerden (doktor, öğretmen) YouTuberlığa kayması, Erikson’un (1980) belirttiği toplumsal rol arayışının artık dijital ekosistemde şekillendiğini kanıtlamaktadır. Bu durum, Bandura’nın (2006) sosyal öğrenme kuramında vurguladığı üzere; dijital figürlerin çocuklar için sadece bir eğlence aracı değil, kimliklerini üzerine inşa ettikleri temel 'başarı modelleri' haline geldiğini göstermektedir.

3.1.Erikson’ un psikososyal gelişim kuramında kimlik ve rol karmaşası

Ergenlikten yetişkinliğe geçiş süreci, bireyin yoğun bir kendini keşfetme ve benlik tasarımı oluşturma evresi olarak nitelendirilmektedir. Bu dönemde birey tarafından kimlik karmaşasına yönelik sorgulamalar yapılmakta ve gelecekteki toplumsal rolüne dair cevaplar aranmaktadır. Kişisel kimliğin inşa edildiği bu arayış sürecinde, akran gruplarının birey üzerindeki etkisinin ve sosyal çevreden gelen dönütlerin belirleyici bir rol oynadığı gözlemlenmektedir (Esin, 2022). Kimlik kazanımı sürecinin ön plana çıktığı bu dönemde, başarılı bir kimlik gelişiminin en temel göstergesi olarak sorumluluk duygusu kabul edilmektedir. Kimlik gelişimi; bireyin diğerleriyle kurduğu ilişkilerdeki süreklilik, özgüven artışı ve belirlenen somut hedeflere ulaşılabileceğine dair gelişen inançla ilişkilendirilmektedir. Bu süreçte, bireyin yetkinliklerine dair duyduğu inancın ve başarı motivasyonunun kimlik inşasında belirleyici bir unsur olduğu vurgulanmaktadır (Erikson, 1980). Erikson’un işaret ettiği bu ‘’farklı rolleri deneme ‘’ve kimlik arama süreci, günümüzde dijital mecralarda Bandura’nın (2006) ‘’sosyal öğrenme’’ prensipleriyle somutlaşmaktadır. Çocuk ve ergen, kimlik karmaşasını aşmak için dijital dünyadaki popüler figürleri (influencerları) gözlemleyerek onları kendine model seçmektedir.

3.2.Bandura’ nın Sosyal Öğrenme Kuramı (Model Alma)

Bandura (2006), bireylerin yalnızca kendi doğrudan deneyimleriyle değil, başkalarını gözlemleme yoluyla da kapsamlı bir öğrenme süreci gerçekleştirdiklerini savunmaktadırBu öğrenme süreci

genellikle birini "model alma" veya taklit etme yoluyla gerçekleşmektedir. Bandura'ya göre bir davranışı taklit etmek için o kişinin statüsü ve birey üzerindeki etkisi önemlidir; bu modeller de canlı, sembolik veya sözlü yönlendirmeler şeklinde karşımıza çıkabilmektedir. Bandura, öğrenmenin sadece doğrudan değil, başkalarının başına gelenleri izleyerek de gerçekleştiğini savunmaktadır. Yani birinin ödüllendirildiği veya cezalandırıldığı görüldüğünde, kişinin o davranışı yapıp yapmama konusunda karar verdiği belirtilmektedir. Ancak bu model alma süreci sadece birey ve model arasındaki bir etkileşim değil, bireyin içinde bulunduğu çevresel sistemlerin bir sonucudur. Bronfenbrenner'ın (1979) Ekolojik Sistemler Kuramı, bu modellerin çocuğun yaşamındaki yerini ve önemini sistemli bir çerçevede sunmaktadır.

3.3.Ekolojik Sistemler Kuramı (Bronnfenbrenner)

Bronfenbrenner'ın (1979) ortaya koyduğu bu kurama göre,içinde yaşadığı çevreyi de tüm katmanlarıyla incelemek gerekmektedir. Bu sistemler; kişinin ailesi ve okulu gibi en yakın çevresini kapsayan "mikrosistem", bu çevrelerin birbiriyle olan ilişkisini ifade eden "mezosistem", bireyin doğrudan içinde olmadığı ancak medya veya sosyal politikalar gibi onu etkileyen ''ekzosistem'' ve toplumun genel kültürel değerlerini yansıtan ''makrosistem'' olarak ayrılmaktadır. Ayrıca zaman içinde meydana gelen değişimlerin ve tarihi olayların birey üzerindeki etkisini açıklayan ''kronosistem'' de bu sürecin önemli bir parçasını oluşturmaktadır.

3.4.Tüketim kültürü ve Postmodern Kimlik Kuramları

Günümüzde tüketim artık sadece bir şeyler satın almak değil, kişinin kim olduğunu dünyaya göstermek ve var olma çabası haline geldiği ortaya atılmaktadır. Satın alınan bir mal veya hizmetin yalnızca temel ihtiyaçlar doğrultusunda seçilmediği, o ürünün taşıdığı sembolik anlamlara da odaklanıldığı görülmektedir; bu doğrultuda tüketim alışkanlıkları aracılığıyla toplumsal bir kültür oluşturulmaktadır (Yanıklar, 2018). Postmodern kavramı da tam bu noktada, aklın ve pazarın tek tipleştirici etkisine karşı bir tepki olarak ortaya çıkmakta; duyguların, sembollerin ve kültürün toplumsal alanda yeniden önem kazanması ifade edilmektedir. Postmodern kimlik kuramları şunlardır;

Lyotard (2013), Postmodern dönemle birlikte artık tek bir doğru olduğu fikri geride kalmaktadır, hakikat kaybı ve anlam çoğulluğu yaşanmaya başlamıştır; bu durum bilginin herkes için farklı yorumlanmasına yol açmıştır. Bu süreçte toplumda çokkültürlülük ön plana çıkmış, eskiden dışlanan farklı kimlik ve gruplar artık seslerini daha gür duyurmaya başlamıştır. Funk (2015) yaklaşımına göre ise bireyler bencil olmadan kendi dünyalarına odaklanıp yeni bir dayanışma ruhuyla kendilerini inşa etmeye çalışmaktadır. Baudrillard'ın (2013) belirttiği gibi artık sanayi toplumu bitmiş, ideoloji olarak tüketim devri başlamıştır; bu sistemde sadece eşyaları değil, fikirleri ve kimlikleri de tüketir hale geldik. Son olarak Bauman (2010), bu yeni düzende haz, tüketim ve tabakalaşma kavramlarının merkeze oturduğunu vurgular. Bauman'a göre artık sadece birer ''tüketiciyiz'' ve en büyük derdimiz haz almaktır; bu yüzden ilişkilerimiz bile geçici hale gelmiş, ne kadar tüketirsek toplumda o kadar var olduğumuz bir sisteme hapsolduğumuzu ifade etmektedir (Özyurt, 2022). Baudrillard ve Bauman'ın vurguladığı bu 'tüketim odaklı var olma' hali, Erikson'un (1980) sağlıklı kimlik gelişimi için şart koştuğu 'içsel bütünlük' ilkesiyle çelişmektedir. Günümüz genci, içsel bir değer inşa etmek yerine, Baudrillard'ın belirttiği sembolleri tüketerek dışsal ve geçici bir kimlik arayışına hapsolmaktadır.

4.Influencer Kültürünün Çocukların Kimlik Gelişimine Etkileri

4.1.Rol Model alma ve özdeşim süreçleri

Ergenlik dönemi, çocukluktan gelen değerlerin sorgulandığı ve kişinin kendi kimliğini oluşturmaya çalıştığı çok önemli bir süreç olarak tanımlanmaktadır. Bu dönemde gençler kendilerine yeni modeller ararken genellikle güçlü veya "havalı" buldukları kişileri taklit etmeye başlamakta; ancak aile bağı zayıf olan gençler, bu boşluğu doldurmak için ünlü isimlere veya dış dünyadaki figürlere çok daha fazla bağlanabilirler ki bu durumun temelinde bir yere ait olma ihtiyacı yatmaktadır (Acer, 2025). Yapılan araştırmalar, gençlerin sadece günlük tercihlerini değil, gelecek hedeflerini ve hayat seçimlerini de bu medya karakterlerinden etkilenerek şekillendirdiklerini belirtmektedir (Talu, 2020). Gençlerin bu ''havalı'' figürlere yönelmesi, çalışmanın kuramsal kısmında değinilen Bandura'nın (2006) ''modelin statüsü'' ilkesini doğrular niteliktedir. Aile bağlarının zayıflığı, Bandura'nın sosyal öğrenme sürecindeki geleneksel modellerin (ebeveyn) etkisini yitirmesine ve dijital modellerin (influencer) kimlik inşasında ana otorite haline gelmesine zemin hazırlamaktadır.

4.2.Beden algısı ve benlik saygısı üzerindeki etkiler

Gelişim psikolojisinin en temel kuralı, gelişimin bir bütün olduğudur; yani bir alandaki değişim diğer her şeyi etkilemektedir. Örneğin, bir genç kendi dış görünüşünden memnun olduğunda, bu durum onun sosyal ve duygusal gelişimini de olumlu etkilemektedir. Özellikle ergenlik yıllarında sağlıklı bir kimlik kazanabilmek için kişinin kendi bedeniyle barışık olması çok kritik bir öneme sahiptir (Talu, 2020). Ancak günümüzde Instagram gibi platformlardaki influencerlar, sürekli ‘’kusursuz’’ ve estetik hayatlar paylaşarak tek tip bir güzellik anlayışını dayatmaktadırlar. Sosyal medyada karşımıza çıkan bu yapay standartlar, kişinin kendi gerçekliğinden uzaklaşmasına ve bedeniyle barışık olmadığı için öz güveninin düşmesine neden olmaktadır. Oysa hem psikolojik sağlığımızı korumak hem de kendimize olan saygımızı kaybetmemek için bedenimizi olduğu gibi kabul edebilmek hayati bir önem taşımaktadır (Bural, 2023). Instagram'ın dayattığı bu tek tip güzellik anlayışı, ergenin beden imajı ile benlik saygısı arasındaki bağı zedeleyerek, Erikson’un (1980) ergenlik dönemi için öngördüğü ‘’kimlik kazanımını’’ imkansızlaştırmakta ve bireyi kronik bir rol karmaşasına sürüklemektedir.

4.3.Tüketim odaklı kimlik inşası

Tüketim çağında mal ve hizmetlerin artmasıyla beraber alışveriş alışkanlıklarında da tamamen değişiklik yaşanmaktadır. Artık bir şeyler satın alırken sadece ihtiyacı karşılamak için değil, içinde bulunulan sosyal gruplara kendini kanıtlama çabasının olduğu belirtilmektedir. Bu durum, kimliğin kültürel köklerden koparak daha esnek ve değişken bir hale gelmesine neden olmaktadır. Kitle iletişim araçları aracılığıyla hayatın her alanına sızan tüketim toplumu, bireyi sürekli yeni arzular peşinde koşmaya itmektedir. Sonuç olarak bireyler, sırf başkalarına kendilerini kabul ettirmek veya tatmin olmak adına aslında ait olmadıkları dünyalara girmekte ve buralarda kendilerine yepyeni, yapay kimlikler inşa etmektedirler (Bayhan, 2022). ‘Yapay Kimlik’ inşası, çalışmanın kuramsal kısmında Özyurt (2022), aracılığıyla değinilen postmodern tüketim ideolojisiyle tam bir uyum içerisindedir. Özyurt’un (2022) vurguladığı 'eşyalarla beraber kimliklerin de tüketilmesi' süreci, günümüzde influencerların sunduğu yaşam tarzlarının taklit edilmesiyle somutlaşmaktadır. Bu durum, bireyin kendi gerçekliğinden koparak tamamen kurgulanmış dijital bir simülasyon içerisinde var olma çabasına dönüştüğünü kanıtlamaktadır.

4.4.Dijital onay/beğeni ve değer

Günümüzde sosyal medya, gençleri ve çocukları sürekli yeni bir şey görmeye zorlayarak ahlaki değerlere uymayan pek çok içerikle karşı karşıya bırakmaktadır. Bu platformlar her şeyin anında olup bitmesini ve hızla tüketilmesini desteklediği için, otokontrol kurulmasını zorlaştırmakta ve en büyük hedef kitlesi haline getirilmesi amaçlanmaktadır (Arıcı, 2025). Özellikle Instagram ve YouTube gibi yerlerde alınan her beğeni veya yorum, gençler için birer onaylanma mekanizmasına dönüşmekte; ancak bu durumun en riskli tarafı, sadece ‘’beğeni’’ almak uğruna doğal halinden vazgeçilip başkalarının istediği kalıplara girmeye çalışılmasıdır. Sonuç olarak, sosyal medyadaki onay arayışı yüzünden öz saygı ve kimlik algılarının tamamen dijitaldeki rakamlara, yani beğenilere bağlı hale geldiği sonucunu doğurmaktadır (Summak, 2024). Sonuç olarak, bu dijital onay arayışı, Bronfenbrenner’in (1979) mezosisteminde yer alan akran kabulü ihtiyacının dijital bir sapmasıdır. Beğeni sayılarına endeksli bu öz saygı algısı, sosyal hizmetin 'güçlendirme yaklaşımı' çerçevesinde ele alınması gereken temel bir risk alanı oluşturmaktadır.

4.5. Riskler

Gerçeklikten Kopma: Gerçek benlik, bireyin doğal ve özgün yönlerini ifade ederken; sahte benlik, toplumsal beklentilere uyum sağlamak amacıyla geliştirilen bir yapı olarak tanımlanmaktadır. Sosyal medya ortamında çocukların kimi zaman kendi duygu ve ihtiyaçlarından ziyade ebeveynleri tarafından oluşturulan temsiller üzerinden görünür hale geldiği görülmektedir. Bu durum, çocukların çevrimiçi ortamlarda idealize edilmiş kimlik sunumlarına maruz kalmalarına neden olabilmektedir (Avşar, 2020). Erik Erikson (1980) ’un kimlik gelişimi yaklaşımı açısından değerlendirildiğinde, dijital ortamlarda oluşturulan bu temsillerin çocukların özgün benlik algıları üzerinde etkili olabileceği düşünülmektedir.
İçerik Riskleri: İçerik riskleri, internet ortamında kullanıcıların karşılaşabileceği olumsuz yazılı, görsel ve işitsel içerikleri kapsamaktadır. Şiddet, nefret söylemi, ırkçı ifadeler ve yaşa uygun olmayan içerikler kışkırtıcı içerikler arasında değerlendirilirken; yanlış ya da zararlı bilgi paylaşımları yanıltıcı içerikler kapsamında ele alınabilmektedir (Güler vd., 2016).

Bu tür dijital risklerin çocukların sosyal ilişkileri ve çevrimiçi etkileşimleri üzerinde olumsuz etkiler oluşturabileceği, özellikle siber zorbalık gibi durumların aile, okul ve akran ilişkileriyle bağlantılı biçimde gelişebileceği belirtilmektedir (Dinç Kırlı, 2020).

Çevrimiçi Şiddet

Çevrimiçi ortamlarda çocukların şiddet içeriklerine ve olumsuz dil kullanımına maruz kalabildiği belirtilmektedir. Sosyal medya ve sanal oyun platformlarında küfür, hakaret ve saldırgan davranışların yaygın şekilde görünür olması, çocukların bu davranış örüntülerini normalleştirmelerine zemin hazırlayabilmektedir. Ayrıca yaşa uygun olmayan içeriklere maruz kalmanın çocukların duygu durumları ve sosyal davranışları üzerinde olumsuz etkiler oluşturabileceği ifade edilmektedir (Aydın & Çelik, 2019). Albert Bandura (2006) 'nın sosyal öğrenme yaklaşımı açısından değerlendirildiğinde, dijital ortamlarda tekrar eden şiddet içeriklerinin çocukların davranış biçimleri üzerinde etkili olabileceği düşünülmektedir.

Siber Zorbalık

Siber zorbalık, geleneksel akran zorbalığının bilgi ve iletişim teknolojileri aracılığıyla dijital ortamlara taşınmış biçimi olarak değerlendirilmektedir. Bu durumun gençlerin sosyal ilişkileri üzerinde çatışmalara yol açabildiği; depresyon, anksiyete, öfke ve stres gibi ruh sağlığı sorunlarıyla ilişkili olabileceği belirtilmektedir (Yaman & Sönmez, 2015). Facebook, Instagram, YouTube ve Twitter gibi etkileşim temelli sosyal medya platformlarının gençler arasında yoğun kullanılması, siber zorbalığın yaygınlaşmasını kolaylaştırabilmektedir. Sosyal medyanın denetimi zorlaştıran ve sürekli etkileşim sağlayan yapısı nedeniyle siber zorbalığın çok boyutlu bir risk alanı oluşturduğu ifade edilmektedir (Dinç Kırlı, 2020). Bu bağlamda Urie Bronfenbrenner (1979) 'in ekolojik sistem yaklaşımı doğrultusunda, siber zorbalığın yalnızca bireysel değil; aile, akran ilişkileri, okul ortamı ve dijital kültür gibi farklı çevresel sistemlerle ilişkili biçimde ele alınmasının önemli olduğu düşünülmektedir.

Dijital Bağımlılık

TÜİK verilerine göre Türkiye'de internet erişiminin yaygınlaşmasıyla birlikte dijital medya kullanımı günlük yaşamın önemli bir parçası haline gelmiştir (Aytekin, 2017). İnternet, iletişim ve bilgiye erişim açısından önemli kolaylıklar sağlasa da aşırı kullanımın bireylerin psikososyal yaşamı üzerinde olumsuz etkiler oluşturabileceği belirtilmektedir (Yıldırım, 2021). Problemli internet kullanımının; depresyon, sosyal kaygı, düşük benlik saygısı, stresle başa çıkmada güçlük ve dikkat sorunları gibi çeşitli psikolojik risklerle ilişkili olabileceği ifade edilmektedir (Durmuş & Eyüpoğlu, 2025). Bu durumun özellikle çocuk ve ergenlerin sosyal ilişkileri, benlik algıları ve kimlik gelişim süreçleri üzerinde olumsuz etkiler oluşturabileceği düşünülmektedir. Erik Erikson'un kimlik gelişimi yaklaşımı doğrultusunda değerlendirildiğinde, dijital ortamlarda yoğun geçirilen zamanın bireyin gerçek yaşam deneyimleriyle kurduğu sosyal etkileşimleri sınırlandırabileceği söylenebilir.

5.Pozitif Etkiler

5.1.Yaratıcılık ve Dijital Beceri Gelişimi

Dijital teknolojilerle büyüyen çocuk ve ergenlerin bilgiye erişim, medya kullanımı ve çoklu görev yürütme becerilerinin önceki kuşaklara göre farklılaştığı belirtilmektedir (Ardınç & Altun, 2017). Erken çocukluk döneminde dijital araç kullanımının yaygınlaşmasıyla birlikte bu araçların yaratıcılık, problem çözme, planlama ve gözlem gibi becerilerin gelişimini destekleyebildiği ifade edilmektedir. Ayrıca dijital oyunların çocukların eğlenerek öğrenme süreçlerine katkı sağlayabildiği vurgulanmaktadır (Eyinç, 2024). Bu durum, Albert Bandura (2006) 'nın öz yeterlilik kavramı kapsamında değerlendirildiğinde, çocukların dijital ortamlarda içerik üretme ve problem çözme deneyimleri aracılığıyla kendi becerilerine yönelik güven geliştirebildiklerini göstermektedir.

5.2.Sosyal Farkındalık ve Aktivizm

Sosyal medya, bireylerin toplumsal olaylara ilişkin görüşlerini paylaşabildiği ve kolektif farkındalık oluşturabildiği önemli dijital alanlardan biri haline gelmiştir. Dijital aktivizm olarak tanımlanan bu süreç, bireylerin benzer görüşlere sahip kişilerle etkileşim kurmalarına ve toplumsal konulara ilişkin içeriklerin geniş kitlelere hızlı biçimde ulaşmasına olanak sağlamaktadır (Tuna & Türkölmez, 2023). Sosyal medya platformlarının sağladığı bu iletişim ağı sayesinde farklı sosyal çevrelerden bireyler ortak dijital alanlarda bir araya gelebilmektedir (Turhan, 2017). Bu durum, Urie Bronfenbrenner (1979) 'in

ekolojik sistem yaklaşımı doğrultusunda değerlendirildiğinde, çocuk ve ergenlerin yalnızca yakın çevreleriyle değil, daha geniş toplumsal ve kültürel süreçlerle de etkileşim kurabilmelerini kolaylaştırmaktadır.

5.3.Eğitsel İçeriklerin Katkısı

Sosyal medya platformlarının öğrenciler tarafından yalnızca eğlence amacıyla değil, eğitim süreçlerini desteklemek amacıyla da kullanıldığı görülmektedir (Kuzhan, 2019). Araştırmalar, sosyal ağların öğrencilerin derslere katılımını artırabildiğini, arkadaşları ve okul çevresiyle iletişimlerini destekleyebildiğini ve bilgiye erişimi kolaylaştırabildiğini göstermektedir. Öğrencilerin bu platformları ders notlarını paylaşma, grup çalışmaları yürütme ve akademik bilgiye hızlı erişim sağlama amacıyla kullandıkları belirtilmektedir (Hançer & Mişe, 2019). Sosyal medyanın eğitim süreçlerinde işlevsel biçimde kullanılması, çocuk ve ergenlerin akademik yeterlilik algıları ile öğrenme motivasyonlarını destekleyebilmektedir. Bu durum, Erik Erikson'un okul çağı dönemine ilişkin ''çalışkanlık ve başarı'' duygusu kapsamında değerlendirildiğinde, dijital araçların bireyin kendini yeterli hissetme sürecine katkı sağlayabileceğini göstermektedir.

6.Sosyal Hizmetin Koruyucu ve Önleyici Rolü

(Birleşmiş Milletler [BM]) Çocuk Hakları Sözleşmesi'ne göre her çocuğun yaşama, gelişme ve korunma gibi temel hakları vardır. Çocukların sadece beslenme ve barınma gibi fiziksel ihtiyaçlarının karşılanması yetmez; aynı zamanda her türlü istismar, ihmal ve çocuk işçiliğinden de uzak tutulmaları gerekmektedir. Ayrıca çocukların kendi fikirlerini söyleyebilmesi ve büyüklerin de bu görüşleri dikkate alması en doğal haklarından biridir. İnternet dünyası çocuklar için her zaman güvenli bir alan teşkil etmediği görülmektedir; nitekim yapılan araştırmalar internet üzerinden çocuklara yönelik cinsel istismar vakalarının son yıllarda ciddi şekilde arttığını göstermektedir. Özellikle pandemi döneminde çocukların evde ve internette daha fazla vakit geçirmesi bu durumun tetiklendiğini belirtmiştir. Öyle ki, 2021 yılında yayınlanan raporlar, bir önceki yıla göre vaka sayısının neredeyse üç katına çıktığını ortaya koymaktadır (Internet Watch Foundation [IWF] 2021). Türkiye'de ise Adalet Bakanlığı, çocukları ihmal ve istismara karşı daha iyi korumak adına yasal düzenlemeler gerçekleştirmiştir. Birleşmiş Milletler Uluslararası Çocuklara Yardım Fonu (UNICEF, 2022), çocukların risklerden korunması için çeşitli öneriler sunmaktadır (Gedik, 2022).

Bu durum, Bronfenbrenner'in (1979) ekosistem kuramı çerçevesinde bütüncül bir sosyal hizmet müdahalesini zorunlu kılmaktadır. Çocuğun 'mikrosistem' (aile) düzeyinde dijital mahremiyetinin ve ebeveyn danışmanlığıyla korunması (mikro müdahale), okul ve topluluk gibi 'mezosistem' ağlarında dijital okuryazarlık mekanizmalarıyla desteklenmesi (mezo müdahale) ve nihayetinde 'makrosistem' (yasalar ve çocuk hakları sözleşmeleri) düzeyinde yasal savunuculukla güvence altına alınması, disiplinin koruyucu-önleyici rolünün temelini oluşturmaktadır.

6.1.Mikro Düzey Müdahaleler (Çocuk ve aile ile çalışma)

İnternet dünyasında "micro-celebrity" olarak bilinen fenomenler, takipçilerini çeşitli ürünlere yönlendirerek popülerlik kazandırmaktadır. Aileler çocuklarıyla ilgili paylaşımları genellikle iyi niyetle yapsalar da bu durum, çocukların kontrolü dışında gelişen ve silinmesi çok zor olan "dijital ayak izleri" oluşturarak ciddi hak ihlallerine zemin hazırlamaktadır. Çocuk Hakları Sözleşmesi'ne göre devletlerin çocukları her türlü ihmal ve istismardan koruması gerekmekte; ülkemizde de Millî Eğitim Bakanlığı 2017'de çıkardığı bir genelgeyle okul ortamındaki görüntülerin izinsiz paylaşılmasını yasaklamıştır. Sonuç olarak, çocukların mahremiyet sorumluluğu tamamen ebeveynlerdedir; ancak araştırmalar, pek çok ailenin çocuklarının ileride bu paylaşımlardan utanabileceğini bilmesine rağmen paylaşım yapmaya devam ettiğini göstermektedir (Çimke vd., 2018). Bu noktada, çocuk gelişimcilerin ve sosyal hizmet uzmanlarının mikro düzeydeki müdahalelerinin sadece ebeveynleri bilgilendirmekle sınırlı kalmaması gerektiği değerlendirilmektedir. Ebeveynlerin, çocuklarının dijital ayak izlerini oluştururken sergiledikleri *'sharenting'* davranışının, çocuğun gelecekteki özerkliği üzerindeki etkilerini 'çocuğun üstün yararı' ilkesi çerçevesinde yeniden analiz etmeleri sağlanmalıdır. Uzmanlar, aile görüşmelerinde ebeveynlerin dijital paylaşımlarını bir 'dijital miras' olarak değil, potansiyel bir 'kimlik ihlali' olarak görmelerine yardımcı olacak rehberlik modelleri üzerine yoğunlaşmalıdır. Böylece çocuk, henüz kendi rızasını beyan edemediği bir yaşta, ailesi tarafından inşa edilen bir dijital kimliğin pasif bir nesnesi olmaktan çıkarılıp, hakları korunan aktif bir birey konumuna taşınabilir.

6.2.Mezzo Düzey Müdahaleler (Okul ve toplum temelli çalışmalar)

Çocukları dijital ve fiziksel dünyadaki risklerden korumak için hazırlanan önleme programlarının hem ailelerin hem de öğretmenler gibi çocuklarla çalışan profesyonellerin eğitimini kapsayan çok yönlü bir süreç olduğu ifade edilmektedir. Dünya Sağlık Örgütü, çocuklara yönelik hazırlanan ve onlara kendi haklarını öğretip kendilerini koruma becerisi kazandıran bu eğitimlerin ne kadar etkili olduğunu vurgulamaktadır (Büyükbodur, 2024). Özellikle okul sosyal hizmet uzmanlarının, sorunlar daha ortaya çıkmadan önce okul yönetimi, öğrenciler ve aileler arasında bir köprü kurarak erken müdahale programları hazırladığı belirlenmiştir. Çocuk Haklarına Dair Sözleşme gereği, çocukların her türlü sömürüden uzak ve sağlıklı bir ortamda büyümesi yasal bir hak olduğu için, bu çalışmalar olumsuz faktörleri engelleyerek çocukların sağlıklı gelişimini desteklemektedir (Sağlık, 2021). Sosyal sistemler arasındaki bu etkileşimin güçlendirilmesi, çocuğun içinde bulunduğu 'mezosistem' ağını daha güvenli hale getirerek dijital risklere karşı toplumsal bir direnç oluşturmaktadır.

6.3.Makro Düzey Müdahaleler (Politika ve savunuculuk)

Çocuk haklarının korunması ve istismarın önlenmesi sürecinde, bireysel çalışmaların ötesine geçilerek toplumsal ve siyasi koşulların iyileştirilmesi gerektiğini, bu noktada sosyal hizmet uzmanlarının hem yerel hem de uluslararası politikalarda aktif savunuculuk rolü üstlenmesinin hayati olduğunu belirtmektedir. Türkiye'de bu alandaki en temel yasal dayanaklardan biri olan 1963 tarihli Türk Çocuk Hakları Bildirisi; çocukların sağlıklı bir ortamda büyümesi, eğitimde fırsat eşitliği ve engelli çocukların korunması gibi konularda devlete ve aileye büyük sorumluluklar yükleyerek makro düzeyde bir güvence sağlamaktadır (Özkan, 2022).

Güncel riskler, sosyal medyadaki "fenomen" olma arzusunun aileleri çocuklarını kontrolsüzce paylaşmaya *(sharenting)* ittiğini, bunun da çocukların mahremiyetini ihlal eden kalıcı dijital izler bıraktığını belirtmektedir (Öztürk, 2025).

Sosyal medya dünyasında ''Fenomen'' olma arzusu, ailelerin çocuklarını kontrolsüzce paylaşmasına ve çocukların ileride silinmesi zor ''Dijital ayak izleri'' bırakmasına neden oluyor. Bu durum, ebeveynlerin paylaşım özgürlüğü ile çocukların mahremiyet haklarını karşı karşıya getiriyor. Çocuk Hakları Sözleşmesi ve 1963 tarihli Türk Çocuk Hakları Bildirisi gibi belgeler, çocukları her türlü ihmal, sömürü ve istismardan koruma görevini hem devlete hem de aileye vermektedir. Çocuklukta yaşanan kötü tecrübeler ve hak ihlalleri, bireyin tüm geleceğini ve toplumla olan bağını olumsuz etkilemektedir. Bu noktada okul sosyal hizmet uzmanları devreye girerek; okullarda önleyici programlar hazırlar, çocuklara haklarını öğretir ve risk altındaki ailelere danışmanlık yapmaktadırlar. Özellikle ilkokul çağındaki çocuklara yönelik uygulanan "kendini koruma" eğitimleri, çocukların güvenliğini sağlamada çok başarılı olmaktadır. Sonuç olarak sosyal hizmet; hem okulda akran desteğiyle hem de ailelere verilen eğitimlerle çocukların haklarını savunan ve onların sağlıklı büyümesini destekleyen bir köprü görevi görmektedir (Tokaç & Duyan, 2021). Bu noktada sosyal hizmet uzmanlarının savunuculuk rolleri, Bronfenbrenner'in (1979) ''makrosistem'' olarak tanımladığı toplumsal ve yasal çerçeveyi, dijital dünyanın yeni risklerine karşı güncelleyerek çocuğun üstün yararını korumayı amaçlamaktadır.

6.4.Güçlendirme (Empowerment) Yaklaşımı

Koruyucu ve önleyici sosyal hizmet çalışmalarında en sık kullanılan yöntemlerden biri "güçlendirme yaklaşımı"dır. Bu yöntem; toplumda dışlanmış, baskı görmüş veya zor durumda kalmış kişilerin, grupların ve toplulukların kendi güçlü yanlarını fark etmelerini sağlamayı amaçlamaktadır. Böylece bu kişilerin, kendi ihtiyaçlarını ve haklarını çok daha iyi savunabilir hale gelmesi öngörülmektedir. Bu bakış açısıyla sosyal hizmet uzmanları, bireylerin sadece psikolojik olarak değil, sosyal ve fiziksel çevreleriyle olan bağlarını da kuvvetlendirerek onlara kendi hayatları üzerinde söz sahibi olma yeteneği kazandırmaktadır (Doğan & Yücer, 2025). Bu yaklaşım, Bandura'nın (2006) 'Öz yeterlilik' kuramıyla bütünleştiğinde; çocukların ve ailelerin sadece risklerden korunmasını değil, aynı zamanda dijital dünyada bilinçli ve yetkin birer özne olarak var olmalarını sağlayan bir kapasite gelişimini ifade etmektedir.

7.Sonuç ve Öneriler

Araştırma bulgularına göre kimlik gelişimi için kültür, tecrübe ve başkalarının davranış biçimi kimlik gelişimini etkilemektedir. Erikson'un (1980) vurguladığı ''Ben kimim?''sorusu, günümüzde sadece fiziksel çevrede değil, influencerların kurgulanmış yaşamları arasında yanıt aramaktadır. Bu durum, bireyin doğal gelişim sürecindeki kimlik arayışını, dijital onaya bağlı bir 'sahte benlik' inşasına dönüştürmektedir. Apak ve Aygül (2025); dijitalleşme ortamı ile beraber, çocuklar artık algılarını ve

düşüncelerini bulunduğu ortamın mecrasına göre hareket ettirmekte ve tüketim kültürüne göre kimliğini inşa etmektedir. Bu çalışma, influencer kültürünün yarattığı ‘’Mükemmel hayat’’ algısının, Erikson'un bahsettiği kimlik karmaşasını derinleştirerek gençlerde yetersizlik hissine yol açabileceğini destekler niteliktedir.

Albert Bandura’nın sosyal öğrenme kuramına göre çocuklar ve ergenler, çevrelerindeki kişileri gözlemleyerek rol model alma eğilimi göstermektedir. Günümüzde influencerların dijital ortamda görünürlük kazanması, bu öğrenme sürecinin çevrimiçi ortamlara taşınmasına neden olmuştur. Geleneksel rol model ilişkilerinden farklı olarak influencerlarla kurulan tek yönlü etkileşim biçiminin, gençlerin dijital araçlar üzerinden sosyalleşme biçimlerini değiştirdiği ve ebeveynleriyle olan duygusal bağlarını etkileyebildiği belirtilmektedir (Rasulay & Çalışır, 2025). Bununla birlikte influencerların yaşam tarzları ve tüketim alışkanlıklarının gençler tarafından model alınması, sosyal kimlik oluşum sürecini dolaylı pekiştirme mekanizmaları üzerinden etkileyebilmektedir.

7.1.Risk ve koruyucu faktörlerin bütüncül değerlendirilmesi

Dijital ekosistemde "kidfluencer" olgusunun yükselişi, çocukları maddi kazanç odaklı ticari birer özneye dönüştürmektedir. Özellikle ebeveynlerin çocuklarına ait özel anları ve görselleri dijital mecralarda paylaşması olarak tanımlanan ‘’sharenting’’ uygulamaları, çocuğun mahremiyet hakkını doğrudan ihlal etmektedir. Acar ve Koyuncu (2025), sosyal medya üzerinden yürütülen bu reklam içerikli paylaşımların, çocuğun henüz kavrayamadığı bir yaşta mahremiyetinin araçsallaştırılmasına yol açtığını belirtmektedir. Sosyal hizmet perspektifinden bu durum, sadece bir ebeveynlik tercihi değil, çocuğun emeğinin sömürüldüğü bir ‘’dijital çocuk işçiliği’’ riskidir. Sharenting yoluyla onay alınmadan yapılan paylaşımlar, çocuğun dijital kimlik inşasını manipüle ederek akran zorbalığı ve siber zorbalık gibi ikincil mağduriyetlere zemin hazırlamaktadır. Bu nedenle, koruyucu bir strateji olarak ebeveynlerin, anlık kazanımların ötesinde çocuğun gelecekteki "unutulma hakkını" ve psiko-sosyal iyilik halini gözeten bir sorumlulukla hareket etmesi elzemdir.

Sosyal hizmet uzmanları, influencer kültürünün çocuklar üzerindeki olumsuz etkilerini önlemek adına mikro düzeyde aile danışmanlığı, mezo düzeyde okul temelli dijital güvenlik eğitimleri ve makro düzeyde yasal düzenlemelerin takibi gibi üç farklı seviyede kritik bir görev üstlenmektedir (Selçuk, 2022). Bu mesleki çalışmalar yürütülürken, insanlara yardım etme sürecinde belirli etik değerlere göre hareket edilmesi ve bu doğrultuda doğru kararların alınması büyük önem taşımaktadır. Türkiye Cumhuriyeti Anayasası'na göre ülkemiz bir sosyal devlettir ve bu durum özellikle çocukların korunması noktasında devlete; onları her türlü şiddet ve istismardan koruma, eğitim ve güvenlik haklarını sağlama gibi büyük sorumluluklar yüklemektedir. Özetle sistemimiz, çocukları toplumun en özel ve korunması gereken grubu olarak kabul ederek onların tüm temel haklarını yasal güvence altına almaktadır (Geredeli vd., 2024).

Bu derleme çalışması, influencer kültürünün çocukların kimlik gelişimi üzerindeki derin etkilerini ve sosyal hizmetin bu süreçteki koruyucu rolünü ortaya koymaktadır. İnfluencerların paylaştığı içerikler, özellikle ergenlik dönemindeki çocukların düşünce yapısını ve karar verme süreçlerini doğrudan etkileyerek onları belirli kalıplara yönlendirmektedir. Bazı ailelerin maddi kazanç uğruna çocuklarını ‘’Kidfluencer’’ olarak yetiştirmesi, çocuğun mahremiyetine saygı gösterilmediğini ve çocukların henüz olgunlaşmamış zihinlerinden faydalanılarak sömürüldüğünü açıkça göstermektedir. Bu noktada sosyal hizmet uzmanlarının, çocuğun üstün yararını gözeterek hem aileye hem de topluma yönelik önleyici ve koruyucu müdahaleler geliştirmesi hayati bir önem taşımaktadır. Türkiye Cumhuriyeti Anayasası'na göre ülkemiz bir sosyal devlettir ve bu durum özellikle çocukların korunması noktasında devlete büyük sorumluluklar yüklemektedir. Dijital mecralarda çocukların ticari bir meta haline getirilmesi, mevcut yasal düzenlemelerin hızla değişen bu alanda yetersiz kalabildiğini göstermektedir. Dünya genelindeki uygulamalar incelendiğinde, Fransa tarafından 2020 yılında yürürlüğe konulan ‘’Çocuk Influencer Yasasının’’ bu alanda öncü bir model teşkil ettiği görülmektedir. Bu yasal düzenleme ile çocukların çalışma saatleri kontrol altına alınmış, elde edilen gelirlerin reşit olana dek korunması amacıyla yasal güvenceler oluşturulmuş ve platformlara, çocukların talebi doğrultusunda ‘’unutulma hakkını’’ tesis etme zorunluluğu getirilmiştir (Fransa yasası, 2020). Türkiye’deki sosyal hizmet uygulamaları açısından bu tür yasal düzenlemelerin savunuculuğunun yapılması, çocuk ihmal ve istismarının önlenmesinde stratejik ntnnnbir makro müdahale yöntemi olarak değerlendirilmektedir. Özetle; Bronfenbrenner’in ekosisteminde yer alan 'dijital mecralar', Bandura’nın sosyal öğrenme prensipleri aracılığıyla çocuğun rol modellerini değiştirmiş ve nihayetinde Erikson’un bahsettiği sağlıklı kimlik kazanımı sürecini bir

'onaylanma krizine' dönüştürmüştür. Bu noktada sosyal hizmet uzmanlarının, çocuğun üstün yararını gözeterek müdahaleler geliştirmesi hayati önem taşımaktadır.

Elde edilen tüm veriler ışığında, influencer kültürünün artık çocuk gelişimi için yalnızca dışsal bir değişken olarak değil, gelişimin bizzat içinde gerçekleştiği yeni bir ‘’Dijital ekosistem’’ olarak değerlendirilmesi gerektiği görülmektedir. Bu noktada sosyal hizmet disiplini açısından, dijitalleşmeyi reddeden bir tutum yerine; çocuğun dijital dünyadaki varlığının ‘’İnsan hakları’’ ve ‘’Çocuk işçiliği’’ temelinde yeniden tanımlanması zorunlu bir ihtiyaç olarak addedilmektedir. Sosyal hizmet uzmanının pozisyonu; teknolojiyi yasaklayan denetleyici bir rolden ziyade, çocuğun dijital kimliğini sömürüden uzak ve sağlıklı bir zeminde inşa etmesini sağlayan bir ‘’Dijital rehber’’ ve ‘’Hak savunucusu’’ olma yönünde evrilmelidir.

7.2.Uygulamaya Yönelik Öneriler

Bu derleme çalışması sonucunda, influencer kültürünün çocuk kimliği üzerindeki etkilerini minimize etmek ve sosyal hizmet müdahalesini güçlendirmek amacıyla şu öneriler sunulmaktadır:

7.3.Mikro ve Mezo Sistem Odaklı Müdahaleler

Bronfenbrenner’ın (1979) Ekolojik Sistemler Kuramı çerçevesinde; ebeveynlere yönelik sadece "bilinçlendirme" değil, ‘’Eleştirel Dijital Ebeveynlik Atölyeleri’’ düzenlenmelidir. Bu eğitimlerde, ebeveynlerin sharenting uygulamalarının çocuğun gelecekteki ‘’özerk kimlik inşası’’ üzerindeki riskleri (Erickson, 1968) somut vaka analizleriyle aktarılmalıdır. Okul sosyal hizmeti kapsamında ise; Bandura’nın (1977) Sosyal Öğrenme Kuramı bağlamında, çocukların dijital beğeni sayıları yerine içsel motivasyon ve gerçek yaşam becerilerine odaklanmalarını sağlayacak psiko-sosyal grup çalışmaları yürütülmelidir.

7.4.Makro Sistem ve Politika Önerileri

Çocuk haklarının dijital sahada korunması için yasal mevzuatta "Dijital Çocuk İşçiliği" tanımı yapılmalı; (Uluslararası Çalışma Örgütü [ILO]) standartları uyarınca çocukların ticari içeriklerde yer alması denetime tabi tutulmalıdır. Ayrıca, çocukların reşit olduklarında geçmişe dönük verilerini sildirebilmeleri için "Unutulma Hakkı" yasal güvenceye kavuşturulmalıdır. Aile ve Sosyal Hizmetler Bakanlığı bünyesinde, algoritma temelli hak ihlallerini izleyecek bir ‘’Dijital Çocuk Hakları İzleme Birimi’’ kurularak platform sorumluluğu denetlenmelidir (Tokaç ve Duyan, 2022).

7.5.Gelecek Araştırmalar İçin Öneriler

İlerleyen çalışmalarda, dijital dünyada büyüyen çocukların yetişkinlikteki öz saygı düzeylerini inceleyen boylamsal (longitudinal) araştırmalara odaklanılmalıdır. Ayrıca farklı sosyo-ekonomik düzeydeki ailelerin sharenting motivasyonları ile çocukların mahremiyet algısı arasındaki ilişki karşılaştırmalı olarak analiz edilmelidir.

Genel olarak bakıldığında sosyal hizmet disiplini, dijital ekosistemde ‘’pasif izleyici’’ rolünden sıyrılarak proaktif bir savunuculuk üstlenmelidir. Çocuğun yüksek yararı ilkesi, dijital dünyanın dinamiklerine göre yeniden yorumlanmalı ve teknoloji, müdahale süreçlerinin ayrılmaz bir parçası haline getirilmelidir.

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FEAR OF FALLING IN SURGICAL PATIENTS: A NARRATIVE REVIEW OF PREVALENCE, RISK FACTORS, CLINICAL OUTCOMES, AND NURSING INTERVENTIONS

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ABSTRACT

Aim

Fear of falling (FOF) is a common but often underrecognized concern among surgical patients, adversely affecting postoperative recovery, early mobilization, rehabilitation, and discharge readiness. This review aimed to synthesize current evidence regarding the prevalence, associated risk factors, clinical consequences, and interventions related to FOF in adult surgical populations.

Materials and Methods

A narrative literature review was conducted using recent peer-reviewed studies investigating FOF in surgical patients. Evidence from observational studies, quasi-experimental research, prospective cohort studies, systematic reviews, and meta-analyses involving orthopedic, spinal, neurosurgical, and cardiac surgery populations was examined. The review focused on FOF prevalence, predictive factors, long-term outcomes, and intervention strategies.

Results

The prevalence of postoperative FOF ranged from 56% to 99%, with the highest rates reported following fall-related orthopedic surgery and spinal procedures. A meta-analysis involving 3,088 patients reported a pooled prevalence of 66.9% after hip fracture surgery. Pain, anxiety, depression, previous falls, frailty, female sex, higher body mass index, and kinesiophobia consistently emerged as significant predictors of FOF across surgical populations. Kinesiophobia demonstrated one of the strongest associations with postoperative FOF and reduced mobilization. Elevated preoperative FOF was associated with poorer mobility and lower quality of life up to three years after hip fracture surgery. Emerging evidence also indicates that FOF follows distinct postoperative recovery trajectories influenced by demographic, psychological, and clinical factors. Educational interventions targeting fall prevention before surgery significantly reduced FOF following total knee arthroplasty, while qualitative findings emphasized that nursing support during first mobilization alleviated patients' fears. However, evidence from randomized controlled trials remains limited.

Conclusion

Fear of falling is a prevalent postoperative problem with important implications for functional recovery and rehabilitation. Early identification of high-risk patients and multidisciplinary interventions addressing modifiable factors, including pain, anxiety, frailty, and kinesiophobia, may improve postoperative outcomes. Further well-designed randomized controlled trials are needed to establish effective evidence-based interventions for reducing FOF in diverse surgical populations.

Keywords: Fear of falling; Postoperative care; Nursing care

INTRODUCTION

Fear of falling (FOF) is a common and clinically relevant concern among older adults and surgical patients, particularly during periods of impaired mobility and functional recovery. FOF refers to a persistent concern about falling that may lead individuals to restrict activities or avoid movement, and it has been associated with functional limitations and reduced quality of life. Although FOF has been extensively investigated in older adults, increasing evidence indicates that it is also an important concern across different surgical populations, including patients undergoing orthopedic, spinal, neurological, and cardiac procedures.[1,2] The postoperative period may be particularly important in the development or persistence of FOF because patients are required to mobilize despite pain, weakness, dizziness, balance impairment, and reduced physical confidence. During the first mobilization after surgery, patients may experience fear related to pain, dizziness, weakness, and the possibility of falling. Qualitative evidence from patients undergoing open-heart surgery indicates that these concerns may influence their experiences of early mobilization and that supportive communication and trust in nurses can facilitate

this process.[3] Similarly, FOF has been documented during the first mobilization following total knee and hip arthroplasty and among patients undergoing spinal and brain surgery.[4-7] FOF is clinically important because postoperative recovery depends substantially on safe and progressive mobilization. When patients perceive movement as threatening, they may reduce activity or become reluctant to participate fully in rehabilitation. Conversely, impaired mobility, pain, and previous experiences of falling may further reinforce fear. Thus, FOF may form part of a potentially self-perpetuating interaction between psychological distress and functional limitation during postoperative recovery.[8,9]

Aim and Scope of the Review

This narrative review aims to synthesize current evidence concerning the prevalence, associated factors, clinical consequences, temporal course, and nursing interventions related to FOF among adult surgical patients. The review focuses primarily on evidence from hip fracture surgery, total knee and hip arthroplasty, spinal surgery, brain surgery, open-heart surgery, and selected neurosurgical populations. The available literature includes cross-sectional studies, prospective cohort studies, quasi-experimental research, qualitative studies, scoping reviews, systematic reviews, and meta-analyses. Because the available evidence differs substantially in study design, patient characteristics, timing of assessment, and measurement instruments, findings should be interpreted within the context of the specific surgical population and postoperative phase.

Assessment of Fear of Falling

FOF has been assessed using several instruments and approaches across surgical populations. Commonly used measures include the Falls Efficacy Scale-International (FES-I), Short Falls Efficacy Scale-International (Short FES-I), Modified Falls Efficacy Scale, and Activities-specific Balance Confidence Scale. Some studies have additionally used single-item questions or evaluated FOF alongside functional measures such as the Timed Up and Go test.[5,6,10,11]

This heterogeneity in assessment methods is important when interpreting prevalence estimates. Differences in instruments, cut-off points, assessment timing, and clinical characteristics of participants may produce substantially different estimates of FOF. In particular, fear assessed during the first postoperative mobilization may reflect an acute response to surgery, whereas assessments conducted weeks or months later may capture persistent concerns related to functional recovery and activity participation.[4,7,9]

Prevalence of Fear of Falling in Surgical Populations

FOF appears to be highly prevalent in several surgical populations, particularly among older adults undergoing procedures associated with impaired mobility. A recent systematic review and meta-analysis of older adults after hip surgery estimated a pooled prevalence of FOF of 66.88% (95% CI, 64%–70%). The review also identified differences according to sex and geographic setting, emphasizing the heterogeneity of FOF across populations.[12]

High prevalence rates have also been reported in procedure-specific studies. Damar et al. [2021] reported FOF in 83.4% of older adults following spinal surgery, whereas Damar et al. [2023] reported FOF in 73.1% of patients after brain surgery.[5,6] During the first mobilization after total knee arthroplasty, FOF has also been reported as a common postoperative concern.[7] These findings indicate that FOF is not limited to patients with a history of falling but may also emerge as a postoperative concern in patients experiencing temporary or persistent functional limitations.

In patients undergoing total knee replacement, FOF may persist beyond the immediate postoperative period. Aljuhani et al. [2025] reported improvement in FOF during follow-up but found that fear remained clinically relevant in a proportion of patients three months after surgery.[11] Similarly, longitudinal evidence following total hip arthroplasty indicates that although FOF decreases during recovery, some patients continue to experience fear during specific daily activities.[9]

Risk Factors and Associated Factors

The available evidence suggests that FOF is multidimensional and associated with demographic, clinical, functional, and psychological factors. Previous falls, pain, impaired mobility, anxiety, depression, and fear-related responses to movement have repeatedly been identified as important correlates.

Previous Falls and Pain

Previous falls appear to be particularly important in the development of FOF. The recent meta-analysis by Ren et al. [2026] identified previous falls and postoperative pain among the factors associated with FOF after hip surgery.[12] These findings are consistent with the broader literature showing that previous experiences of falling may increase perceived vulnerability during subsequent mobility.[13] Pain may further contribute to FOF by increasing patients' expectations that movement will be difficult or unsafe. In patients undergoing spinal surgery, pain was associated with FOF together with kinesiophobia, anxiety, and depression.[5] Thus, postoperative pain management may have relevance not only for physical comfort but also for patients' confidence in mobilization.

Psychological Factors and Kinesiophobia

Psychological factors appear to play an important role in FOF. Anxiety and depression have been associated with FOF following spinal and brain surgery.[5,6] Kinesiophobia, defined as an excessive and debilitating fear of physical movement due to perceived vulnerability to injury or reinjury, may be particularly relevant because it can directly interfere with mobility and rehabilitation. In patients undergoing spinal surgery, kinesiophobia was among the factors most strongly associated with FOF.[5] In patients undergoing total joint arthroplasty, FOF and kinesiophobia were also associated with readiness for discharge, suggesting that psychological responses to movement may have implications for postoperative recovery.[8]

Functional and Demographic Factors

Age, sex, body mass index, previous falls, and postoperative functional status have also been associated with FOF in specific surgical populations. Among patients undergoing total knee arthroplasty, female sex, higher body mass index, and anxiety were identified as factors associated with FOF during early mobilization.[7] Following brain surgery, older age, fewer postoperative mobilizations, previous falls, poorer Timed Up and Go performance, and anxiety were associated with FOF.[6] These findings indicate that FOF should be understood within a broader biopsychosocial framework rather than as an isolated psychological symptom.

Clinical Consequences of Fear of Falling

FOF may have important consequences for postoperative functional recovery. In frail older adults with hip fracture, greater FOF was associated with poorer activities of daily living and functional outcomes, indicating that fear may remain relevant even when patients are already receiving surgical and rehabilitative care.[14] Evidence from total hip arthroplasty also suggests that FOF may restrict specific daily activities. In a one-year longitudinal study, FOF decreased following surgery but continued to restrict activities such as stair climbing, floor transfers, and walking in the neighborhood among some patients.[9] These findings suggest that overall improvement in FOF does not necessarily indicate complete restoration of activity confidence. FOF may also influence discharge readiness. Dalkilic et al. [2025] found that FOF and kinesiophobia were associated with older patients' readiness for discharge after total joint arthroplasty.[8] Because discharge readiness reflects a combination of physical, psychological, and functional preparedness, this finding highlights the potential relevance of FOF to broader postoperative outcomes. Long-term consequences may extend beyond the immediate recovery period. A recent post-hoc analysis of a prospective cohort reported that preoperative FOF was associated with poorer mobility and quality of life three years after hip fracture surgery.[15] Although such observational associations do not establish causality, they suggest that FOF may identify patients at increased risk of prolonged functional limitations.

Fear of Falling as a Dynamic Postoperative Phenomenon

FOF should not be regarded as a static condition. Longitudinal studies indicate that its intensity may change substantially during postoperative recovery. Following total knee arthroplasty, Xia et al. [2026] identified distinct trajectories of FOF, including patients with persistently high fear, patients with consistently low fear, and patients whose fear changed over time.[16] Similarly, FOF generally decreases following total knee and hip arthroplasty, but this improvement is not uniform among all patients.[9,11] In patients with shunted idiopathic normal pressure hydrocephalus, both falls and FOF improved after surgery, although they did not necessarily return to levels observed in comparison groups.[17] These findings have important implications for nursing assessment. A single assessment during hospitalization may not adequately capture the patient's subsequent trajectory.

Repeated assessment may therefore help identify patients whose fear persists or increases during recovery and who may benefit from additional support.

Nursing Interventions

Despite the high prevalence of FOF, evidence regarding interventions specifically designed to reduce FOF in surgical patients remains limited. Among the available studies, preoperative fall-prevention education provides direct evidence of a potentially modifiable nursing target. Kaya and Bilik [2022] conducted a quasi-experimental study among patients scheduled for total knee arthroplasty and reported that patients who received fall-prevention education consisting of written material and face-to-face education had lower FES-I scores during postoperative follow-up than those receiving usual care.[10] These findings suggest that initiating education before surgery may help patients develop greater awareness and confidence regarding safe postoperative mobility. Support provided during the first mobilization may also be important. In a qualitative study of patients undergoing open-heart surgery, participants described fears related to pain, dizziness, weakness, and falling during their first out-of-bed mobilization. Trust in nurses, reassurance, and supportive communication were identified as factors that helped patients manage these concerns.[3] From a nursing perspective, these findings support an individualized approach that incorporates FOF assessment into postoperative mobility care. Patients with elevated FOF may benefit from clear explanations before mobilization, reassurance, appropriate pain management, environmental safety measures, progressive assistance, and encouragement of active participation. However, evidence for broader perioperative fall-prevention interventions is less consistent. Fritz et al. [2022] evaluated a multicomponent perioperative fall-prevention intervention among patients undergoing elective inpatient surgery.[18] Although the intervention was associated with improved quality of life, it did not significantly reduce falls at one year. This finding illustrates that interventions designed to prevent falls may not necessarily reduce FOF or improve all dimensions of postoperative recovery.

Gaps in the Evidence

Several limitations characterize the current evidence base. First, many studies are cross-sectional or single-center investigations, limiting causal inference. Consequently, it remains unclear whether FOF directly contributes to poorer recovery or primarily reflects underlying physical and psychological vulnerability. Second, the literature is concentrated in older orthopedic populations, particularly patients undergoing hip and knee arthroplasty or hip fracture surgery. Comparatively less is known about FOF among patients undergoing abdominal, thoracic, vascular, or other major surgical procedures. Expanding research beyond orthopedic populations would help determine whether the mechanisms and clinical significance of FOF are consistent across surgical specialties. Third, considerable heterogeneity exists in the assessment of FOF. Differences in measurement instruments, timing of assessment, and operational definitions make comparisons between studies difficult. Future research should consider standardized assessment strategies and clearly defined clinically meaningful thresholds. Fourth, intervention evidence remains limited. The available quasi-experimental evidence supports preoperative education, but robust randomized controlled trials evaluating comprehensive interventions specifically targeting FOF are scarce.[10] Future interventions should consider the multidimensional nature of FOF and potentially combine education, pain management, anxiety reduction, graded mobilization, balance training, and psychological support. Finally, more research is needed to determine whether reducing FOF produces improvements in clinically important outcomes such as mobilization, rehabilitation adherence, functional independence, length of stay, discharge readiness, falls, and long-term quality of life. Longitudinal studies such as those examining FOF trajectories and long-term mobility outcomes provide an important foundation for this work.[15,16]

Implications for Nursing Practice

FOF should be incorporated into the assessment of postoperative mobility, particularly among older adults and patients undergoing orthopedic, spinal, neurological, and other procedures associated with functional impairment. Nurses should assess not only the patient's physical risk of falling but also their perceived confidence and fear related to mobilization. Patients reporting substantial FOF may require individualized mobilization plans that combine education, reassurance, symptom management, environmental safety, and progressive assistance. Particular attention should be given to patients with previous falls, significant pain, anxiety, kinesiophobia, impaired mobility, or persistent fear during repeated mobilization.

Because FOF may change throughout recovery, assessment should not be limited to the immediate postoperative period. Repeated assessment during hospitalization and follow-up may help identify patients whose fear persists and may interfere with rehabilitation or activities of daily living.

Conclusion

Fear of falling is a common and clinically meaningful concern across several surgical populations, particularly among older adults undergoing hip fracture surgery, spinal surgery, brain surgery, and joint arthroplasty. Current evidence indicates that FOF is associated with previous falls, pain, anxiety, depression, kinesiophobia, impaired mobility, and other indicators of functional vulnerability.[5,6,12] FOF may have consequences extending beyond psychological distress, including restricted daily activities, reduced functional independence, lower discharge readiness, and poorer long-term mobility and quality of life.[8,14,15] Importantly, FOF appears to change over the course of recovery, with some patients demonstrating persistent or unfavorable trajectories despite overall postoperative improvement.[16] Nurses are well positioned to identify FOF, address modifiable contributing factors, and support safe and confident mobilization. Preliminary evidence suggests that preoperative education and supportive nursing communication may reduce or alleviate FOF; however, evidence from rigorous intervention studies remains insufficient. Future research should therefore focus on longitudinal and multicenter studies and randomized controlled trials evaluating procedure-specific, multidimensional nursing interventions. Such research may help clarify whether targeted reduction of FOF can translate into improved mobilization, functional recovery, rehabilitation participation, and quality of life among surgical patients.

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OTİZM SPEKTRUM BOZUKLUĞUNDA KISITLI VE YİNELEYİCİ DAVRANIŞLARIN GENETİK VE EPİGENETİK MEKANİZMALARI: DUYGU DÜZENLEME GÜÇLÜKLERİ İLE İLİŞKİSİ

GENETIC AND EPIGENETIC MECHANISMS OF RESTRICTED AND REPETITIVE BEHAVIORS IN AUTISM SPECTRUM DISORDER: THEIR RELATIONSHIP WITH EMOTION REGULATION AND EMOTION DYSREGULATION

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ÖZET

Kısıtlı ve yineleyici davranışlar (KYD), otizm spektrum bozukluğunun (OSB) temel tanı alanlarından biri olmakla birlikte motor stereotipiler, duyusal yineleyici davranışlar, aynılıkta ısrar ve sınırlı ilgi alanları gibi farklı alt boyutlardan oluşan heterojen bir davranış kümesini temsil etmektedir. Bu derlemenin amacı, OSB'de görülen kısıtlı ve yineleyici davranışların altında yer alan genetik ve epigenetik mekanizmaları güncel kanıtlar doğrultusunda incelemek ve bu mekanizmaların duygu düzenleme ile duygu düzenleme güçlükleri (emotion dysregulation) arasındaki ilişkisini değerlendirmektir. Bu çalışma, 2000–2026 yılları arasında yayımlanan hakemli insan araştırmalarını kapsayan yapılandırılmış bir anlatı derlemesidir. PubMed/MEDLINE başta olmak üzere uluslararası veri tabanlarında yer alan sistematik derlemeler, meta-analizler, genom çapında ilişkilendirme çalışmaları (GWAS), ekzom dizileme araştırmaları, epigenom çalışmaları, kohort araştırmaları, uzunlamasına çalışmalar ve kontrollü klinik araştırmalar öncelikli olarak değerlendirilmiştir. Güncel genomik araştırmalar, kısıtlı ve yineleyici davranışların tek bir gen tarafından açıklanamayacağını; yaygın poligenik varyantlar, nadir kalıtsal varyantlar, de novo mutasyonlar ve gelişimsel gen düzenlenmesinin birlikte rol oynadığı heterojen bir biyolojik mimariye işaret etmektedir. Epigenetik çalışmalar ise DNA metilasyonu ve kromatin düzenlenmesindeki değişikliklerin nörogelişimsel süreçleri etkileyebileceğini, ancak davranış alt tiplerine özgü biyobelirteçlerin henüz yeterince ortaya konulamadığını göstermektedir. Bulgular ayrıca motor stereotipiler ile aynılıkta ısrar davranışlarının farklı sinir ağları ve gelişimsel süreçlerle ilişkili olduğunu; özellikle aynılıkta ısrarın kaygı, belirsizliğe tahammülsüzlük ve duygu düzenleme güçlükleriyle daha güçlü ilişki gösterdiğini ortaya koymaktadır. Buna karşın motor stereotipiler bazı bireylerde fizyolojik ve duyusal öz düzenleme işlevi görebilmektedir. Kısıtlı ve yineleyici davranışlar tek bir genetik ya da epigenetik mekanizmanın sonucu olarak değerlendirilemez. Mevcut kanıtlar, genetik yatkınlık, epigenetik düzenleme, kortikostriatal ağ gelişimi, duyusal işlemleme ve duygusal düzenleme süreçlerinin dinamik etkileşimi sonucunda farklı davranış fenotiplerinin ortaya çıktığını göstermektedir. Klinik değerlendirme ve müdahalelerde davranışın yalnızca görünümüne değil, işlevine, bireyin düzenlenmesine katkısına ve günlük yaşamdaki etkilerine odaklanan bütüncül bir yaklaşım benimsenmelidir.

Anahtar Kelimeler: Otizm spektrum bozukluğu, kısıtlı ve yineleyici davranışlar, stereotipi, genetik, epigenetik, duygu düzenleme, duygu düzenleme güçlüğü.

ABSTRACT

Restricted and repetitive behaviors (RRBs) constitute one of the two core diagnostic domains of autism spectrum disorder (ASD) and encompass a heterogeneous range of behavioral phenotypes, including motor stereotypies, repetitive sensory-motor behaviors, insistence on sameness, and restricted interests. This review aimed to examine the current evidence regarding the genetic and epigenetic mechanisms underlying RRBs and to explore their relationship with emotion regulation and emotion dysregulation. A structured narrative review was conducted using peer-reviewed human studies published between 2000 and 2026. Priority was given to systematic reviews, meta-analyses, genome-wide association studies, large-scale exome sequencing studies, epigenome-wide investigations, longitudinal cohort

studies, neuroimaging research, and controlled clinical studies retrieved primarily from PubMed/MEDLINE and related biomedical databases. Current evidence indicates that RRBs cannot be explained by a single genetic determinant. Instead, they arise from the interaction of common polygenic variants, rare inherited variants, de novo mutations, and developmental gene regulatory mechanisms. Epigenetic studies suggest that alterations in DNA methylation and chromatin regulation may contribute to neurodevelopmental pathways associated with ASD; however, robust epigenetic biomarkers specific to RRB subtypes remain lacking. Neuroimaging and developmental studies further demonstrate that motor stereotypies and insistence on sameness are associated with partially distinct neural circuits and developmental trajectories. Insistence on sameness is consistently linked to anxiety, intolerance of uncertainty, and emotion dysregulation, whereas motor stereotypies may function as adaptive mechanisms for sensory and physiological self-regulation in some individuals. Restricted and repetitive behaviors should not be conceptualized as the consequence of a single biological pathway. Rather, they represent heterogeneous developmental phenotypes emerging from the interaction between genetic susceptibility, epigenetic regulation, neural circuit maturation, sensory processing, and emotional regulation processes. Future research should integrate multi-omics approaches with longitudinal developmental phenotyping to better clarify the biological diversity underlying RRBs and to support individualized intervention strategies.

Keywords: Autism spectrum disorder, restricted and repetitive behaviors, motor stereotypies, genetics, epigenetics, emotion regulation, emotion dysregulation.

1. Giriş

Otizm spektrum bozukluğu (OSB), sosyal iletişim ve sosyal etkileşimde süreğen farklılıkların yanı sıra kısıtlı ve yineleyici davranış, ilgi veya etkinlik örüntüleriyle tanımlanan nörogelişimsel bir durumdur. DSM-5 sınıflamasında bu ikinci alan; stereotipik ya da yineleyici motor hareketler, nesne kullanımı veya konuşma; aynılıkta ısrar ve rutinlere katı bağlılık; yoğunluğu ya da odağı olağandışı sınırlı ilgiler; duyusal girdiye aşırı veya düşük tepki ve duyusal uyaranlara olağandışı ilgi olmak üzere dört görünüm altında ele alınır (American Psychiatric Association [APA], 2013). Bununla birlikte bu sınıflama, aynı başlık altında toplanan davranışların gelişimsel seyir, işlev ve öznel deneyim bakımından eşdeğer olduğu anlamına gelmez.

Kısıtlı ve yineleyici davranışlar (KYD), literatürde sıklıkla toplam puan ya da tek bir belirti kümesi gibi incelenmiştir. Oysa motor stereotipiler, değişikliğe direnç, yoğun ilgi alanları ve duyusal arayış; farklı tetikleyiciler, pekiştireçler ve nörobiyolojik süreçlerle ilişkili olabilir (Leekam ve ark., 2011; Uljarević ve ark., 2023). Aynı davranış bir bağlamda dikkati sürdürmeyi veya uyarılmayı dengelemeyi kolaylaştırırken başka bir bağlamda ağrı, sıkıntı ya da katılım kaybının göstergesi olabilir. Bu nedenle gözlenen biçim, davranışın işlevini tek başına açıklamaz.

Son yıllarda moleküler genetik, epigenetik ve işlevsel görüntüleme çalışmalarından elde edilen bulgular, KYD'lerin biyolojik altyapısına ilişkin çok düzeyli modelleri desteklemiştir. Buna paralel olarak otistik bireylerin yaşantısına dayanan çalışmalar, özellikle stimming olarak adlandırılan yineleyici hareket ve seslerin öz-düzenleme, iletişim ve ifade işlevlerini görünür kılmıştır (Kapp ve ark., 2019). Bu iki bilgi alanını karşı karşıya koymak yerine birlikte değerlendirmek gerekir: biyolojik bir ilişkinin gösterilmesi davranışın kişi için taşıdığı işlevi geçersiz kılmaz; öz-düzenleyici bir işlevin bulunması da güvenlik veya işlev kaybı yaratan durumlarda desteğe duyulan gereksinimi ortadan kaldırmaz.

Bu derlemenin amacı, KYD'lere ilişkin seçilmiş genetik, epigenetik, nöral devre ve yaşantısal bulguları duygu düzenleme ve işlevsel değerlendirme perspektifiyle bir araya getirmektir. Temel soru, belirli bir biyolojik belirtecin KYD'leri 'açıklayıp açıklamadığı' değil; farklı kanıt düzeylerinin neyi desteklediği, neyi desteklemediği ve klinik yorumun bu sınırlar içinde nasıl kurulabileceğidir. Bu nedenle çalışma, genetik veya epigenetik etkenlerden duygu düzenleme üzerinden KYD'lere uzanan bütünleşik bir mekanizmanın kanıtlandığını varsaymamakta; doğrudan ve dolaylı bulguları birbirinden ayırmayı amaçlamaktadır.

2. Yöntem

Bu çalışma, konu odaklı bir anlatı derlemesidir. Literatür taraması 14 Eylül 2026 tarihinde güncellenmiş; PubMed üzerinde 2007-Eylül 2026 tarih aralığı için 'autism' veya 'autism spectrum disorder' terimleri, 'restricted repetitive behavior', 'stimming' ya da 'circumscribed interest' terimleriyle ve 'genetic', 'epigenetic', 'DNA methylation', 'SHANK3', 'corticostriatal' veya 'emotion regulation' terimleriyle çeşitli birleşimler hâlinde aranmıştır. Seçilen çalışmaların kaynakçaları geriye doğru taranmış; tanısal çerçeve

ve klinik öneriler için DSM-5 ile NICE kılavuzuna başvurulmuştur. Türkçe veya İngilizce tam metnine ya da yeterli yapılandırılmış özetine erişilebilen; KYD tanımı ve faktör yapısı, SHANK3 ve sinaptik organizasyon, prenatal stres-HPA aksı ve DNA metilasyonu, kortiko-striatal bağlantısallık, kişisel yoğun ilgi alanlarının nöral işlenmesi veya stimmingin işleviyle doğrudan ilişkili hakemli çalışmalar amaçlı olarak seçilmiştir.

Tarama sistematik derleme veya meta-analiz olarak tasarlanmamış; önceden kaydedilmiş bir protokol, çift araştırmacılı tarama, standartlaştırılmış kalite puanlaması ya da PRISMA akış şeması kullanılmamıştır. Bu nedenle arama terimleri ve tarih aralığı bildirilmiş olsa da çalışma seçimi kanıtın tümünü kapsayıcı biçimde temsil etmez ve seçilim yanlılığına açıktır. Sentez moleküler/sinaptik, epigenetik, nöral devre ve davranışsal/yaşantısal düzeylerde yapılmış; her bulgu çalışma tasarımı, örneklem, ölçüm dokusu ve nedensel çıkarım kapasitesi dikkate alınarak yorumlanmıştır.

3. Bulgular ve Tartışma

3.1. Heterojen Bir Tanı Alanı ve Davranışın İşlevi

KYD'lerin faktör yapısını inceleyen çalışmalar, düşük düzeyli motor/duyusal yineleyicilik ile yüksek düzeyli aynılıkta ısrar ve sınırlı ilgilerin bütünüyle tek bir boyuta indirgenemeyeceğini göstermektedir. Uljarević ve arkadaşlarının (2023) faktör analizi çalışmalarını inceleyen sistematik derlemesi de alanın ölçüm araçları, yaş grupları ve klinik özellikler bakımından önemli heterojenlik taşıdığını ortaya koymaktadır. Bu heterojenlik, toplam puanı klinik açıdan yararlı kılmakla birlikte, mekanizma ve müdahale araştırmalarında alt boyutların ayrı incelenmesini gerekli kılar.

İşlevsel yaklaşım, yineleyici davranışı yalnızca sıklığı azaltılacak bir belirti olarak değil, belirli bir çevresel ve içsel bağlamda ortaya çıkan bir düzenleme stratejisi olarak ele alır. İşlev odaklı bir kapsam derlemesinde, KYD'lerin duyusal deneyimi düzenleme, kaygıyla baş etme, kesinlik ve kontrol oluşturma ve çevreyi anlamlandırma işlevleri bildirilmiştir (Lock Man Lung ve ark., 2024). Buradaki kritik nokta, bütün KYD'lerin yararlı olduğu ya da bütün davranışların aynı işlevi gördüğü değildir. İşlev hipotezi, doğrudan gözlem, bireyin anlatısı, bakım veren bilgisi ve davranış öncesi-sonrası koşulların birlikte incelenmesiyle sınanmalıdır.

KYD benzeri örüntüler yalnızca OSB'ye özgü değildir. Motor stereotipiler gelişimsel yetersizliklerde, ritüel ve tekrarlama örüntüleri obsesif-kompulsif bozuklukta, tekrarlayıcı öz-düzenleme davranışları ise dikkat eksikliği hiperaktivite bozukluğu ve kaygı durumlarında görülebilir. OSB ile obsesif-kompulsif bozukluktaki yineleyici davranışları karşılaştıran derleme; kaygı, yürütücü işlevler ve duyusal süreçler açısından hem örtüşen hem ayrışan ilişkiler bulunduğunu göstermektedir (Jiujias ve ark., 2017). Dışarıdan benzer görünen bir davranışın öznel sıkıntı, direnç veya algılanan zorunluluk bakımından nasıl yaşandığı birey düzeyinde ayrıca değerlendirilmelidir. Bu nedenle davranışın tanısal anlamı yalnızca biçiminden değil, gelişimsel öykü, bağlam ve öznel yaşantıdan türetilmelidir.

3.2. SHANK3: Sinaptik Organizasyondan Davranış Fenotipine

SHANK3, eksitatör sinapsların postsinaptik yoğunluğunda glutamat reseptörlerini, sinyal proteinlerini ve aktin hücre iskeletini bir araya getiren bir iskele proteinini kodlar. SHANK3 işlev kaybına yol açan patojenik varyantlar ile 22q13.3 bölgesini kapsayan delesyonlar Phelan-McDermid sendromunun başlıca moleküler nedenleri arasındadır; SHANK3 varyantları bazı sendromik olmayan OSB olgularında da bildirilmiştir (Kolevzon ve ark., 2014; Moessner ve ark., 2007). Bununla birlikte bu nadir varyantlar OSB'nin ve KYD'lerin yalnızca küçük bir bölümünü açıklayabilir. Dolayısıyla SHANK3, bütün KYD'ler için ortak bir neden değil, sinaptik organizasyonun davranışsal yineleyicilikle nasıl ilişkilendirilebileceğini incelemek için güçlü fakat özgül bir modeldir.

İnsan Q321R varyantını taşıyan knock-in farelerde artmış kendini tımar etme davranışı, elektroensefalografik değişiklikler ve azalmış nöronal uyarılabilirlik bildirilmiştir (Yoo ve ark., 2019). Bu sonuç, belirli bir SHANK3 değişikliğinin sinaptik ve davranışsal fenotipleri birlikte etkileyebileceğini destekler. Bununla birlikte farede kendini tımar etme, insanlarda stimming, aynılıkta ısrar veya yoğun ilginin doğrudan karşılığı değildir. Hayvan modeli; hücresel mekanizmayı ve devre duyarlılığını sınamak için değerlidir, fakat insan davranışının iletişimsel, duygusal ve kültürel anlamını modellemez.

Bu ayrım, molekülden davranışa uzanan şemaların yorumunda oldukça önemli bir belirleyicidir. Genetik varyasyon sinaptik düzeni, sinaptik düzen devre dinamiklerini ve devre dinamikleri de davranış olasılıklarını etkileyebilir; ancak gelişim, öğrenme, çevresel uyaranlar ve kişinin stratejileri her aşamada

bu ilişkiyi değiştirebilir. Kanıt, tek yönlü ve kaçınılmaz bir zincirden çok karşılıklı etkileşimli bir duyarlılık modeliyle uyumludur.

3.3. Prenatal Stres, HPA Aksı ve Epigenetik Düzenleme

Prenatal dönemdeki psikososyal stresin maternal HPA aksı ve glukokortikoid sinyalizasyonu üzerinden fetüsün gelişimsel ortamını etkileyebileceği; stres yanıtıyla ilişkili genlerde DNA metilasyonu ve diğer epigenetik değişikliklere katkıda bulunabileceği öne sürülmektedir. Güncel bir anlatı derlemesi, 2020-2025 dönemindeki çalışmaların bu biyolojik olasılığı desteklemekle birlikte insan çalışmalarında ölçüm zamanı, stresin tanımlanması, karıştırıcı değişkenler ve doku özgüllüğü nedeniyle nedensel yolun henüz kurulamadığını vurgulamaktadır (Kelaidoni ve Kotsis, 2026). Bununla birlikte bu derleme genel OSB etiyolojisine odaklanmakta; prenatal stres veya HPA aksıyla ilişkili epigenetik değişikliklerin KYD'lere ya da duygu düzenleme güçlüklerine özgü bir mekanizma oluşturduğunu göstermemektedir.

Epigenetik, çevresel etkinin doğrudan ve kalıcı biçimde "gene yazılması" şeklinde anlaşılmamalıdır. Metilasyon dokular arasında değişir; hücre bileşimi, yaş, ilaçlar, beslenme ve eşlik eden sağlık durumlarından etkilenebilir. Ayrıca metilasyon farkı her zaman gen ekspresyonunda beklenen yönde bir değişiklik yaratmaz. Prenatal stres ile OSB arasında doğrusal bir anlatı kurmak, bilimsel belirsizliği örter ve annelere yönelik temelsiz suçlayıcı yorumlar doğurabilir. Mevcut kanıt, risk ve dayanıklılık etmenlerinin birlikte işlediği olasılıksal bir gelişim modelini destekler.

3.4. NR3C1, FOXO3 ve ASCL1 Metilasyonu: Kore Kardeş Çalışması

Oh ve arkadaşları (2024), OSB tanılı çocuklar ve etkilenmemiş kardeşlerini içeren 54 aileden toplam 117 katılımcıda periferik kan örneklerini incelemiştir. Metilasyona duyarlı kantitatif polimeraz zincir reaksiyonu ile aday genlerin promotör bölgeleri değerlendirilmiştir. OSB grubunda NR3C1 metilasyonu daha yüksek (ortalama fark = 0,806; p = ,002), FOXO3 metilasyonu daha düşük (ortalama fark = −0,392; p = ,034) ve ASCL1 metilasyonu daha yüksek (ortalama fark = 0,543; p = ,048) bulunmuştur. Kardeş karşılaştırması ortak ailevi ve çevresel etmenlerin bir bölümünü denetleme avantajı sağlasa da bu tasarım, tanı sonrasında ölçülen epigenetik farkın ne zaman veya neden oluştuğunu göstermez.

Araştırmada FOXO3 metilasyonu ile Social Quotient puanı arasında pozitif ilişki (β = 8,711; p = ,037), ASCL1 metilasyonu ile ADI-R sözel olmayan iletişim güçlüğü arasında pozitif ilişki (β = 0,793; p = ,049) ve Vineland günlük yaşam becerileri arasında negatif ilişki (β = −4,247; p = ,014) bildirilmiştir. Baba yaşı ile ASCL1 metilasyonu arasında da bir ilişki sinyali gözlenmiştir. Ancak yaş, tam ölçek zekâ puanı ve cinsiyet aynı modelde birlikte denetlendiğinde fenotipik ilişkilerin hiçbiri anlamlılığını korumamıştır. Bu sonuç, ham ilişki katsayılarının doğrulanmış bir klinik belirteç gibi sunulmaması gerektiğini açıkça göstermektedir.

Çalışmanın en önemli yorum sınırı doku ve ölçüm düzeyidir. Periferik kandaki promotör metilasyonu, beyindeki özgül hücre tiplerinin metilasyonunu veya gen ekspresyonunu doğrudan göstermez. Ayrıca çalışma, bu metilasyon farklılıklarının KYD'lere ya da duygu düzenleme güçlüklerine özgü olduğunu göstermemektedir; bulgular OSB fenotipi düzeyinde keşifsel aday gen ilişkileri olarak değerlendirilmelidir. Üç aday gen için bulunan yön farklılıkları mekanistik hipotez üretmeye uygundur; tanı, prognoz veya tedavi seçimi için geçerli bir biyobelirteç oluşturmaz. Bulguların hücre bileşimi denetlenmiş epigenom çapında analizler, bağımsız örneklemler ve boylamsal tasarımlarla yinelenmesi gerekir.

3.5. Kortiko-Striatal Sevreler ve Ağ Bağlantısallığı

Bazal gangliyonlar ve kortiko-striatal döngüler eylem seçimi, alışkanlık oluşumu, ödül öğrenmesi ve bilişsel esneklikle ilişkilidir; bu nedenle motor yineleyicilik ve aynılıkta ısrar için öne çıkan aday devre düzeylerinden biridir (Lewis ve Kim, 2009). Abbott ve arkadaşları (2018), 8-17 yaşlarındaki 50 OSB ve 52 nörotipik katılımcıda dinlenim durumu bağlantısallığını incelemiş; limbik ve frontoparietal tohumlarla göreli aşırı, motor tohumlarla göreli düşük kortiko-striatal bağlantısallık örüntüleri bildirmiştir. Bağlantısallık dengesizliğinin KYD düzeyiyle ilişkisi, tek bir bölgedeki 'fazla' veya 'az' etkinlikten çok devreler arasındaki organizasyonun önemine işaret eder.

Kişisel yoğun ilgi alanlarına odaklanan işlevsel manyetik rezonans görüntüleme çalışmasında Antezana ve arkadaşları (2022), 15 otistik ve 16 nörotipik yetişkini kişiye özgü ilgi görsellerini pasif izleme ve bilişsel yeniden değerlendirme koşullarında karşılaştırmıştır. Otistik grupta yeniden değerlendirme sırasında posterior singulat korteks (PCC) etkinliğinin daha az modüle edildiği ve PCC bağlantısallığında grup farklılıkları olduğu bildirilmiştir. Otistik grupta düzenleme öncesinden düzenleme koşuluna değişim ile ADOS-G yineleyici davranış puanı arasındaki ilişkiler sağ kaudat

çekirdekte ρ = ,65 (p = ,009), sol putamende ρ = ,67 (p = ,007) düzeyindedir. Bulgular, kişisel olarak belirgin ilgilerin öz-referanslı işlemleme ve kortiko-striatal düzenleme süreçleriyle ilişkili olabileceğini düşündürür.

Bu sonuçların sınırları güçlüdür: örneklem küçüktür, ağırlıklı olarak erkek ve zihinsel yetersizliği olmayan yetişkinlerden oluşur; kişisel ilgi uyaranları bireyler arasında içerik ve duygusal değer bakımından değişir. Korelasyonlar hem görüntüleme hem klinik ölçüm hatasına açıktır ve kullanılan istatistiksel eşikler keşifsel bulguların bağımsız örneklemde yinelenmesini gerektirir. Dolayısıyla PCC, kaudat veya putamen "KYD merkezi" olarak adlandırılamaz; çalışma belirli bir görev bağlamında ağ düzeyinde ilişki göstermektedir.

3.6. Yoğun İlgi Alanları ve Duygu Düzenleme

Yoğun ve sınırlı ilgi alanları dışarıdan dar odaklı görünse de birey için bilgi edinme, yeterlik geliştirme, sosyal bağ kurma ve olumlu duygulanım kaynağı olabilir. Cascio ve arkadaşları (2014), kişiye özgü yoğun ilgi görsellerinin OSB'de ödül ve duygusal belirginlikle ilişkili bölgelerde yanıt oluşturduğunu göstermiştir. Antezana ve arkadaşlarının (2022) bulguları ise bu uyaranların bilişsel yeniden değerlendirme sırasında frontal kontrol ve PCC temelli öz-referans süreçleriyle farklı biçimde etkileşebileceğini düşündürmektedir.

Bu veriler iki uç yorumdan kaçınmayı gerektirir. Yoğun ilgi alanı ne başlı başına patolojik bir saplantıdır ne de her durumda koruyucu bir güçtür. İlginin işlevsel değeri; kişinin seçimi, olumlu duygulanım, öğrenme ve toplumsal katılımı desteklemesiyle birlikte zaman kullanımı, esneklik, sıkıntı ve zorunluluk deneyimi üzerinden değerlendirilmelidir. Duygu düzenleme açısından odaklanmış bir ilgi, uyarılmayı azaltan öngörülebilir bir alan sağlayabilir; buna karşılık erişimin kesilmesi veya katılığın artması bazı kişilerde sıkıntıyı yoğunlaştırabilir.

3.7. Stimming: Bedensel Öz-Düzenleme ve İfade

Stimming; el çırpma, sallanma, dönme, nesneleri yineleyici biçimde kullanma, ses çıkarma veya sözcükleri yineleme gibi ritmik davranışları kapsayan topluluk kökenli bir terimdir. Kapp ve arkadaşlarının (2019) 32 otistik yetişkinle yürüttüğü görüşme ve odak grup çalışmasında katılımcılar stimmingi aşırı duyusal/duygusal uyarılmayı azaltma, düşük uyarılmayı artırma, yoğun duyguyu dışa vurma ve öznel dengeyi sürdürme aracı olarak tanımlamıştır. Katılımcılar, yararlı ve zarar vermeyen davranışları bastırmaya yönelik toplumsal baskının sıkıntı ve utanç yaratabileceğini de belirtmiştir.

Bu bulgular nitel ve öz-bildirime dayalıdır; tüm otistik bireylere veya bütün stimming biçimlerine genellenemez. Buna rağmen klinik değerlendirmede sıklıkla eksik kalan öznel işlevi doğrudan görünür kılar. Aynı sallanma davranışı bir kişide sakinleşmeye, diğerinde uyanıklığı artırmaya; aynı kişide ise farklı zamanlarda farklı amaçlara hizmet edebilir. Davranışın dış görünümünden işlev çıkarmak yerine, "öncesinde ne oldu, kişi ne hissetti, davranış sırasında ve sonrasında ne değişti?" sorularının yanıtı aranmalıdır.

Duygu düzenleme bu nedenle yalnızca üstten aşağı bilişsel yeniden değerlendirmeyle sınırlı değildir. Duyusal girdiyi değiştirmek, hareket aracılığıyla bedensel uyarılmayı ayarlamak, öngörülebilir bir ritim oluşturmak ve ilgi alanına yönelmek de düzenleme repertuvarının parçaları olabilir. Bu stratejilerin toplumsal olarak alışılmadık görünmesi, otomatik olarak işlevsiz olduklarını göstermez.

3.8. Kanıt düzeylerinin birlikte okunması

Tablo 1, derlemenin çok düzeyli çerçevesinde her kanıt türünün sağladığı katkıyı ve aşılmaması gereken yorum sınırını özetlemektedir.

Tablo 1. KYD'lere ilişkin çok düzeyli kanıtların yorumlanması

Düzey	Temsilci kanıt	Desteklediği çıkarım	Yorum sınırı
Genetik/sinaptik	SHANK3 insan varyantları ve Q321R fare modeli	Eksitatör postsinaptik organizasyonun yineleyici davranış yatkınlığına katkısı	Nadir varyant; hayvan davranışı insan deneyiminin doğrudan eşdeğeri değildir.
Epigenetik	NR3C1, FOXO3 ve ASCL1 periferik kan metilasyonu	OSB grubunda aday gen düzeyinde farklılık sinyali	Doku özgüllüğü; küçük örneklem; çok değişkenli denetimde klinik ilişkiler korunmamış ve KYD'ye özgü ilişki sınanmamıştır.

Düzey	Temsilci kanıt	Desteklediği çıkarım	Yorum sınırı
Nöral devre	Kortiko-striatal bağlantısallık ve kişisel ilgi fMRI görevleri	Eylem seçimi, esneklik ve öz-referanslı düzenlemeyle ilişkili ağ farklılıkları	Korelasyonel, göreve bağımlı ve seçilmiş örneklemler; tek bir "KYD merkezi" yoktur.
Davranış/yaşantı	Otistik yetişkin görüşmeleri ve işlev odaklı derlemeler	Stimmingin duyusal ve duygusal öz-düzenleme, ifade ve öngörülebilirlik işlevleri	İşlev kişiye ve bağlama özgüdür; öz-bildirim örneklemleri tüm spektrumu temsil etmeyebilir.
Klinik sentez	Gözlem, öz-bildirim, bakım veren bilgisi ve işlevsel analiz	Güvenlik, sıkıntı, katılım ve yaşam kalitesine dayalı bireyselleştirilmiş destek	Biyobelirteçler günümüzde tanı veya müdahale seçimi için doğrulanmış değildir.

4. Klinik ve Araştırmaya Yönelik Çıkarımlar

Mevcut kanıt, KYD'lerin otomatik olarak ortadan kaldırılmasını değil, işlevsel ve kişi merkezli değerlendirilmesini desteklemektedir. İlk adım davranışın güvenlik riski, ağrı veya tıbbi sorunla ilişkisi, duyusal çevresi, tetikleyicileri, iletişimsel işlevi, kişinin davranışa ilişkin görüşü ve seçtiği etkinliklere katılım üzerindeki etkisini belirlemektir. Özellikle çocuk ve ergenlerde yeni başlayan veya hızla artan kendine zarar verici ya da zorlayıcı davranışlarda diş, gastrointestinal, nörolojik veya diğer ağrı kaynakları; iletişim güçlükleri; rutin değişiklikleri ve ışık-gürültü gibi çevresel etmenler sistematik olarak değerlendirilmelidir (National Institute for Health and Care Excellence [NICE], 2013).

Zarar vermeyen ve öz-düzenlemeyi destekleyen stimming için temel hedef baskılama değil, toplumsal kabul ve güvenli kullanım olmalıdır. Gürültü ve ışık yükünü azaltmak, hareket molaları sağlamak, geçişleri öngörülebilir kılmak, alternatif iletişim yolları sunmak ve kişinin tercih ettiği duyusal araçlara erişimini kolaylaştırmak davranışın çevresel yükünü azaltabilir. Destek planı, davranışın öncüllerini, örüntüsünü, sonuçlarını ve kişi için taşıdığı işlevi içeren işlevsel bir değerlendirmeye dayanmalıdır (NICE, 2013). Klinik müdahale; yaralanma, belirgin ağrı veya sıkıntı, kişinin seçtiği yaşama katılımda ciddi engel ya da işlev kaybı bulunduğunda gündeme gelmeli; en az kısıtlayıcı ve davranışın düzenleyici işlevini koruyan seçenekler tercih edilmelidir.

Biyobelirteç araştırmalarında aday gen yaklaşımından bağımsız doğrulamaya, hücre tipi ve doku özgüllüğüne, boylamsal örneklemeye ve çoğul test denetimine geçiş gereklidir. Görüntüleme çalışmalarında daha büyük, cinsiyet ve bilişsel özellikler bakımından kapsayıcı örneklemler; görevlerin doğal yaşam işlevleriyle ilişkilendirilmesi; öznel duygu düzenleme ölçümlerinin görüntüleme verisine eklenmesi önemlidir. En önemlisi, biyolojik bulguların klinik ölçeklerle ilişkilendirilmesi kadar otistik bireylerin davranışın anlamına ilişkin bildirimlerinin de araştırma sonuçlarına dâhil edilmesidir.

5. Sınırlılıklar

Bu metin konu odaklı bir anlatı derlemesidir; önceden kaydedilmiş sistematik bir protokol, çift araştırmacılı tarama ve çalışma kalitesi puanlaması yapılmadığından seçilim yanlılığı olasılığı vardır. Ele alınan literatür aday gen, periferik epigenetik ölçüm, kesitsel bağlantısallık, küçük görüntüleme örneklemleri ve hayvan modelleri gibi birbirinden farklı kanıt türlerini içerir. Bu tasarımlar aynı nedensel zincirin ardışık basamaklarını doğrudan test etmemekte; özellikle genetik veya epigenetik değişikliklerden duygu düzenleme üzerinden KYD'lere uzanan bir mekanizmayı göstermemektedir. Çocuk, ergen ve yetişkin örneklemlerinin; zihinsel yetersizlik durumu, dil düzeyi ve cinsiyet dağılımlarının farklılığı sentezin genellenebilirliğini ayrıca sınırlar.

İncelenen çalışmaların önemli bir bölümü KYD toplam puanına dayanmakta, alt davranışların işlevini veya öznel anlamını ayrıntılı ölçmemektedir. Otistik yetişkinlerin yaşantılarını inceleyen nitel çalışmalar ise klinik örneklemlere göre işlevi doğrudan ele alsa da konuşma ve öz-bildirim kapasitesi farklı bireyleri yeterince temsil etmeyebilir. Bu nedenle moleküler, devresel ve yaşantısal bulgular arasındaki bütünleştirme, kanıtlanmış bir mekanizma değil, gelecekte sınanması gereken bir çerçevedir.

6. Sonuç

Mevcut literatür, genetik veya epigenetik değişikliklerden duygu düzenleme üzerinden KYD'lere uzanan tek ve bütünleşik bir mekanizmayı doğrudan göstermemektedir. Bunun yerine OSB'de KYD'lerin;

genetik duyarlılıklar, epigenetik düzenleme, sinaptik organizasyon, kortiko-striatal ve geniş ölçekli ağ dinamikleri, gelişimsel öğrenme ve çevresel bağlamın karşılıklı etkileşimi içinde ortaya çıkan heterojen örüntüler olduğu yönünde çok düzeyli fakat parçalı kanıtlar vardır. SHANK3 ve aday metilasyon bulguları biyolojik hipotez üretir; klinik tanı veya tedavi seçimini yönlendiren doğrulanmış belirteçler değildir. Görüntüleme sonuçları kişisel ilgi alanları ile duygu düzenleme sırasında PCC ve striatal bölgelerin olası katkısını gösterir, fakat küçük örneklemler nedensel ve genellenebilir sonuçlara izin vermez.

Davranışın biyolojik mekanizması ile kişi için taşıdığı anlam aynı analiz düzeyi değildir ve birbirinin yerine kullanılamaz. Stimming ve yoğun ilgi alanları bazı bireylerde öz-düzenleme, olumlu duygulanım ve katılımı destekleyebilir; bazı durumlarda ise sıkıntı, yaralanma veya işlev kaybıyla ilişkili olabilir. Bu nedenle klinik yaklaşımın merkezinde davranışın biçimi değil; güvenlik, bağlam, işlev, kişinin tercihi ve yaşam kalitesi bulunmalıdır. Molekülden davranışa geçerli bir açıklama, ancak mekanizmayı deneyimle ve biyolojik olasılığı nedensel belirsizlikle birlikte okuyabildiğinde kurulabilir.

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PHYSIOLOGICAL EFFECTS OF MORTALITY SALIENCE: AUTONOMIC NERVOUS SYSTEM RESPONSES AND NEUROENDOCRINE FINDINGS

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ABSTRACT

Objective: Mortality salience, defined as heightened awareness of one's own mortality, has been studied extensively for its psychological and behavioral effects, but its physiological consequences remain uncertain. This review evaluated whether mortality salience produces immediate autonomic, cardiovascular, or endocrine responses and whether it modifies physiological responses during subsequent performance tasks or laboratory stressors.

Materials and Methods

A PubMed search through July 2026 was supplemented by screening relevant records indexed in Scopus and Web of Science, reference lists of potentially eligible publications, and citing articles. Peer-reviewed human experiments were included if they used a mortality-salience or death-related manipulation, included a comparison condition, and reported at least one objective physiological outcome relevant to autonomic, cardiovascular, or endocrine function. Eleven original articles met the eligibility criteria and were synthesized narratively.

Results

Conventional mortality-salience procedures generally did not produce acute physiological activation exceeding relevant comparison conditions. A virtual-reality cemetery paradigm produced differences in selected heart rate variability indices without a heart-rate difference. Two performance-task studies showed task-dependent cardiovascular response patterns involving systolic blood pressure and pre-ejection period, although not all direct comparisons were statistically significant. Studies of later stress exposure showed heterogeneous hormonal and autonomic findings. No direct mortality-salience effect on testosterone was demonstrated in the available study. One investigation found reduced cortisol responsivity to a subsequent psychosocial stressor among men with low early-life adversity, whereas a later study in women did not demonstrate a corresponding mortality-salience effect on cortisol as a function of perceived maternal care. Across existential-threat conditions, negative affective responses could occur without parallel condition-specific physiological activation.

Conclusion: Current evidence does not support mortality salience as a uniform acute physiological stressor. Its physiological effects appear context-dependent and may emerge during subsequent performance or stress exposure rather than immediately after mortality-related cognition.

Keywords: Autonomic nervous system; Cardiovascular responses; Mortality salience; Neuroendocrine responses; Stress physiology

1. INTRODUCTION

Mortality salience refers to heightened awareness of one's own mortality and is most commonly studied within terror management theory. Experimental paradigms typically increase accessibility of death-related thoughts by asking participants to reflect on their own death or by exposing them to death-related cues.

Rosenblatt et al.[1] provided early experimental evidence for mortality-salience effects and also tested whether these effects could be explained by increased physiological arousal. The physiological consequences of mortality salience remain less clear than its psychological and behavioral effects. Cardiac, vascular, electrodermal, respiratory, and endocrine measures do not necessarily change in parallel, and subjective arousal may diverge from peripheral physiological activation. Klackl and Jonas[2] emphasized that direct physiological evidence was limited and inconsistent, while Poppelaars et al.[3] later showed that existential-threat reflection could increase negative affect without a corresponding condition-specific increase in objective physiological activation.

The timing of measurement may be critical. Mortality-related cognition may produce little immediate autonomic or endocrine activation yet modify responses during a later performance task or laboratory stressor. The review examined experimental human evidence for (1) immediate autonomic and physiological responses, (2) cardiovascular responses during subsequent performance tasks, and (3) neuroendocrine or autonomic responses to later stressors.

2. Methods

A PubMed search through July 2026 was supplemented by screening relevant records indexed in Scopus and Web of Science, reference lists of potentially eligible publications, and citing articles. Peer-reviewed human experiments were eligible if they used a mortality-salience or death-related manipulation, included a comparison condition, and reported at least one objective physiological outcome relevant to autonomic, cardiovascular, or endocrine function. Eligible outcomes included cardiac and vascular measures, heart rate variability, electrodermal and respiratory measures, and salivary biomarkers relevant to stress-related or endocrine physiology. Studies reporting only behavioral, self-reported, facial electromyographic, neural, or neuroimaging outcomes were outside the core scope.

Review articles were used only for orientation and citation tracking. Eleven original peer-reviewed articles met the criteria. For each article, participant characteristics, manipulation, comparison condition, timing, physiological outcomes, subsequent tasks or stressors, and relevant findings were extracted. When reported, sex, stressor type, early-life adversity, and perceived maternal care were also recorded. Because procedures, outcomes, and timing differed substantially, findings were not quantitatively pooled but were synthesized narratively. The synthesis kept original study findings and the authors' interpretations separate from conclusions drawn across studies.

3. Results

3.1. Overall Characteristics of the Evidence

Across the 11 included articles, five examined physiological activity during or shortly after mortality-salience induction,[1-5] two examined cardiovascular responses during a subsequent performance task,[6,7] and four examined neuroendocrine or autonomic responses to a later stressor.[8-11] Endpoints spanned pulse-based measures, blood pressure, heart rate, heart rate variability, pre-ejection period, electrodermal and respiratory measures, cortisol, salivary alpha-amylase, and testosterone. Comparison conditions ranged from neutral or non-death topics to aversive controls such as dental pain. A null between-condition difference does not necessarily imply an absence of physiological change, because an active comparator may evoke a similar response. Measurement timing ranged from the mortality manipulation itself to later tasks or stressors. These differences separate two questions: whether mortality-related cognition itself evokes acute activation and whether it modifies physiological responding to a subsequent challenge.

3.2. Immediate Autonomic and Physiological Responses

In Experiment 5 of Rosenblatt et al.,[1] pulse rate, pulse volume, and skin resistance were measured after mortality-salience, eating-related, or no-questionnaire conditions. After adjustment for premanipulation values, none differed significantly across conditions, indicating no mortality-specific physiological arousal pattern.

Chittaro et al.[4] compared an immersive virtual cemetery with a public park. The cemetery increased accessibility of death-related themes and produced significant differences in heart rate variability (HRV) low-frequency (LF) power and in the LF/HF ratio, whereas heart rate did not differ. These selected HRV differences should not be interpreted as evidence of generalized sympathetic activation.

Klackl and Jonas[2] measured cardiac, respiratory, and electrodermal activity before, during, and after reflection on mortality or dental pain in a final physiological sample of 108 participants. Physiological activity changed during and after reflection, but for most signals and periods mortality salience did not produce greater arousal than dental pain. The physiological response was largely not specific to mortality.

Poppelaars et al.[3] studied 171 participants across four existential-threat conditions, social-evaluative threat, and a television-salience control. The existential-threat composite showed increases in skin conductance and respiratory rate and decreases in respiratory sinus arrhythmia (RSA) during parts of the reflection period, but these physiological changes were not reliably greater than those observed in

the control condition. At the composite level, existential-threat reflection nevertheless produced larger increases in self-reported negative affect than the control condition.

Buttlar et al.[5] compared mortality salience with a neutral control and a laboratory stress manipulation using salivary cortisol and salivary alpha-amylase. Cortisol increased in the laboratory stress condition, whereas mortality salience did not produce greater cortisol or salivary alpha-amylase responses than the neutral control. Considered with the preceding studies, this finding does not show a consistent mortality-specific acute autonomic or endocrine response.

3.3. Cardiovascular Responses During Subsequent Performance Tasks

Schuler et al.[6] studied 62 participants performing an identity-relevant mouse-clicking task after high or low mortality salience. Task difficulty was either fixed at a low level or unfixed. The prespecified systolic blood pressure contrast supported the authors' predicted overall response pattern. Responses remained low across salience conditions when difficulty was fixed at a low level. In the unfixed condition, the high-salience group had a descriptively higher response than the low-salience group, but the direct comparison did not reach conventional statistical significance ($p = 0.072$). Heart rate, diastolic pressure, and mean arterial pressure showed broadly parallel patterns.

Mlynski et al.[7] extended this design using a bar-pressing task with low, high, or unfixed difficulty. The prespecified contrast for pre-ejection period (PEP) was significant. At high task difficulty, PEP responses were stronger under high than low mortality salience ($p < 0.001$); in the unfixed condition the corresponding difference was only a trend ($p < 0.059$), and no salience-related difference occurred at low difficulty. Primary analyses of blood pressure and heart rate showed no corresponding significant effects. These studies suggest a task-dependent rather than generalized cardiovascular pattern.

3.4. Neuroendocrine and Autonomic Responses to Subsequent Stressors

Byrd-Craven et al.[8] examined 142 undergraduates exposed to mortality salience or a dental-pain control before either crying-infant or out-group-threat videos. Cortisol showed a significant mortality-salience × stressor × sex interaction. In men exposed to out-group threat, the cortisol response observed in the control condition was suppressed after mortality salience, contrary to the authors' prediction of an intensified response.

A related study of 155 participants measured cortisol and testosterone.[9] Mortality salience was not a significant main predictor of cortisol percentage change among responders, although a significant three-way interaction with stressor type and sex was observed. In follow-up analyses, the mortality-salience versus control contrast under out-group threat was not significant ($p = 0.85$), while the corresponding crying-infant comparison was only marginal ($p = 0.07$). Mortality salience also did not significantly predict testosterone. Among testosterone responders, responses differed by sex and stressor, with higher average responses to out-group threat in males and to crying infants in females.

Zakreski et al.[10] studied 128 healthy young men classified as having relatively high or low early-life adversity. Death thoughts did not increase cortisol or subjective stress before the psychosocial stressor. However, among men with low early-life adversity, prior death thoughts significantly reduced cortisol area under the curve with respect to ground (AUC_G; $p = 0.024$), whereas no significant effect occurred in the high-adversity group ($p = 0.279$).

Bentele et al.[11] studied 73 healthy young women reporting low or high early-life maternal care who contemplated death or sleep before the Trier Social Stress Test for Groups. In the primary cortisol model, low maternal care was associated with a flatter cortisol response, but adding mortality-salience × maternal-care × time terms did not improve model fit. Salivary alpha-amylase increased during the stress task, but adding maternal care, mortality salience, or their interactions did not improve model fit. A maternal-care × mortality-salience interaction was observed for RSA recovery, although pairwise comparisons were not significant, and a corresponding interaction was found for subjective stress. The later-response findings varied with experimental and individual context.

4. Discussion

Across the available experiments, mortality salience did not reliably behave like a conventional acute physiological stressor. Rosenblatt et al.,[1] Klackl and Jonas,[2] Poppelaars et al.,[3] and Buttlar et al.[5] point to the same distinction: mortality-related reflection may produce psychological or within-person physiological changes, yet these changes generally do not exceed relevant comparison conditions in a

consistent mortality-specific manner. Chittaro et al.[4] provided a partial exception in selected HRV indices during immersive cemetery exposure, but heart rate was unchanged and the findings do not establish generalized sympathetic activation.

Variability across physiological endpoints is not necessarily contradictory because the measured variables do not represent a single unitary stress output. Klackl and Jonas[2] emphasized that physiological arousal indicators can behave differently and should be considered together. In Mlynski et al.,[7] pre-ejection period was used as a relatively proximal index of cardiac contractile activation under beta-adrenergic influence, whereas heart rate and blood pressure are additionally shaped by parasympathetic input and peripheral vascular factors. A pre-ejection period effect without parallel heart-rate or blood-pressure effects is therefore physiologically plausible. Conversely, the LF and LF/HF differences reported by Chittaro et al.[4] occurred without a heart-rate difference and should remain confined to those measured HRV indices rather than being generalized to the autonomic system as a whole.

The endocrine findings make the timing distinction equally important. Buttlar et al.[5] found no greater acute cortisol or alpha-amylase response to mortality salience than to a neutral control, whereas Zakreski et al.[10] found no acute cortisol increase after death thoughts but did observe modification of the cortisol response to a later psychosocial stressor. Activation by a mortality cue and modulation of a later stress response should therefore be treated as separate outcomes.

A different temporal pattern emerged in the performance-task studies. Schuler et al.[6] and Mlynski et al.[7] found cardiovascular response patterns that depended on task demands after mortality salience. The evidence was strongest for a prespecified systolic blood pressure pattern in Schuler et al. and for PEP under high task difficulty in Mlynski et al.; some direct comparisons, however, were not statistically significant. The original authors interpreted these findings within an effort-related framework. The pattern suggests that mortality-related cognition may influence cardiovascular responding during later goal-directed activity rather than simply increasing cardiovascular activity immediately.

The subsequent-stressor studies were likewise not uniform in direction. Byrd-Craven et al.[8,9] reported sex- and stressor-dependent hormonal patterns, with no direct mortality-salience effect on testosterone in the 2016 study. Zakreski et al.[10] found reduced cortisol responsivity after death thoughts specifically among men with low early-life adversity, whereas Bentele et al.[11] did not find evidence that mortality salience modified cortisol responsivity as a function of perceived maternal care in women. These studies differ in sex, stressor, and operationalization of early-life experience and should not be treated as direct replications or contradictions.

Subjective and physiological responses also diverged. Poppelaars et al.[3] showed greater negative affect for the existential-threat composite than for the control condition without greater condition-specific physiological activation. Subjective distress alone should therefore not be taken as evidence of autonomic or endocrine stress.

The evidence base is small and heterogeneous. Mortality-salience manipulations, comparison conditions, timing, physiological outcomes, subsequent tasks, statistical methods, and participant populations vary markedly. A neutral control and an aversive control such as dental pain answer different questions; similar responses in mortality-salience and aversive-control conditions cannot be interpreted as evidence that neither condition changed physiology. Measurements obtained during the manipulation, immediately afterward, and during a later task also characterize different phases of responding. Several studies assessed multiple signals across repeated time points, so isolated significant findings should be interpreted within the broader response pattern.

Samples were often young adults, and some investigations included only men or only women. Early-life adversity in Zakreski et al.[10] and retrospectively perceived maternal care in Bentele et al.[11] are not equivalent constructs. In Bentele et al., some results were also sensitive to covariate adjustment. The literature search itself was centered on PubMed and supplemented by indexed-record, reference-list, and citation screening rather than fully replicated systematic searches of every database. These limitations warrant cautious interpretation and make a pooled physiological effect estimate difficult to defend.

Future studies would benefit from prespecifying a primary physiological endpoint and measurement window while retaining complementary measures across systems. When feasible, including both neutral and aversive non-death comparisons would help distinguish mortality-specific effects from responses to unpleasant reflection more generally. Baseline, during-induction, immediate post-induction, and delayed task or stressor measurements should be separated clearly. Adequately powered samples including both sexes, transparent reporting of effect sizes and nonsignificant findings, and replication

of the same mortality-salience procedure across laboratories would help identify reproducible moderators. Individual-difference variables such as early-life experience should also be defined prospectively, with distinct constructs kept separate.

Across studies, the evidence points to a context-dependent pattern. Mortality reminders do not consistently produce a generalized acute autonomic or hypothalamic-pituitary-adrenal (HPA) axis stress response. When physiological effects are observed, they appear more likely during subsequent performance demands or stress exposure and may depend on task characteristics and individual history.

5. Conclusion

Current experimental evidence does not support mortality salience as a uniform acute physiological stressor. Immediate autonomic, cardiovascular, respiratory, electrodermal, and endocrine responses do not consistently exceed relevant comparison conditions. Physiological effects may instead emerge during subsequent tasks or stressors and vary with task demands, sex, stressor type, and early-life experience. Future studies should use clearly defined comparison conditions, repeated physiological measurements, and designs that separate immediate from later responses.

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SAĞLIK HİZMETLERİNDE ALARM YORGUNLUĞU VE HASTA GÜVENLİĞİ

ALARM FATIGUE AND PATIENT SAFETY IN HEALTHCARE

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Abstract
Clinical alarms play an important role in patient safety by enabling the early recognition of changes in patients' physiological condition. However, frequent exposure to repetitive and clinically nonactionable alarms, particularly in technology-intensive settings such as intensive care units, may contribute to alarm fatigue among healthcare professionals. This review examines the implications of alarm fatigue for patient safety and current approaches to its reduction. This study was structured as a narrative review of current literature. Research articles and reviews concerning alarm fatigue, clinical alarms, nursing, intensive care, and patient safety were examined. Findings were synthesised in relation to contributing factors, safety implications, and alarm management approaches. The literature indicates that alarm fatigue remains an important problem, especially in intensive care units. Frequent clinically insignificant alarms, false alarms, inappropriate thresholds, simultaneous use of multiple medical devices, and demanding work environments contribute to alarm burden. Repeated exposure is associated with desensitisation, reduced attention, cognitive workload, and stress, potentially delaying responses or allowing critical alarms to be overlooked. Current studies report positive associations with nurses' stress and negative associations with perceptions of safety climate and teamwork. Alarm management approaches include individualised parameters, reduction of unnecessary alarms, staff education, technological filtering, standardised protocols, reminders, and multicomponent intervention bundles. Alarm fatigue extends beyond staff discomfort and represents a system-level risk that may threaten patient safety. Alarm management should be supported by institutional policies, patient-specific settings, education, and technological improvements, with clearly defined responsibilities across the healthcare team. These measures should be implemented together, while preserving the detection of clinically important events and monitoring whether meaningful safety outcomes improve.
Keywords: Alarm fatigue, patient safety, clinical alarm, nursing, intensive care.

Özet
Klinik alarmlar, hastaların fizyolojik durumundaki değişikliklerin erken fark edilmesini sağlayarak hasta güvenliğinde önemli rol oynamaktadır. Bununla birlikte özellikle yoğun bakım gibi yüksek teknolojili bakım ortamlarında sık, tekrarlayan ve klinik olarak eylem gerektirmeyen alarmlara maruz kalmak sağlık profesyonellerinde alarm yorgunluğuna yol açabilmektedir. Bu derlemenin amacı, alarm yorgunluğunun hasta güvenliği üzerindeki etkilerini ve alarm yorgunluğunun azaltılmasına yönelik güncel yaklaşımları incelemektir. Bu çalışma güncel literatürün anlatı derlemesi olarak yapılandırılmıştır. Alarm yorgunluğu, klinik alarm, hemşirelik, yoğun bakım ve hasta güvenliği kavramları çerçevesinde yayımlanan güncel araştırma ve derlemeler değerlendirilmiştir. Güncel literatür, alarm yorgunluğunun özellikle yoğun bakım ünitelerinde önemli bir sorun olmaya devam ettiğini göstermektedir. Sık ve klinik açıdan önemsiz alarmlar, yanlış alarm oranlarının yüksekliği, uygun olmayan alarm eşikleri, çok sayıda monitör ve tıbbi cihazın eş zamanlı kullanımı ile yoğun çalışma ortamı alarm yükünü artıran başlıca faktörlerdir. Tekrarlayan alarm maruziyeti; hemşirelerde duyarsızlaşma, dikkat azalması, bilişsel yük ve stresle ilişkilendirilmekte, bu durum alarm yanıtlarının gecikmesine veya kritik bir alarmın gözden kaçırılmasına zemin hazırlayabilmektedir. Güncel çalışmalar alarm yorgunluğunun hemşirelerin stres düzeyleriyle pozitif; güvenlik iklimi ve ekip çalışması algılarıyla ise olumsuz ilişkili olduğunu göstermektedir. Alarm yönetimine ilişkin güncel girişimler; alarm parametrelerinin hastaya özgü bireyselleştirilmesi, gereksiz alarmların azaltılması, alarm yönetimi eğitimleri, teknolojik filtreleme sistemleri, standart protokoller, hatırlatıcı sistemler ve çok bileşenli alarm yönetim paketlerini kapsamaktadır. Alarm yorgunluğu yalnızca sağlık çalışanlarının çalışma konforunu etkileyen bir sorun değil, hasta güvenliğini doğrudan tehdit edebilen sistem düzeyinde bir risk faktörüdür. Alarm yönetiminin bireysel hemşire sorumluluğuna bırakılmaması; hasta

özelliklerine göre bireyselleştirilmiş alarm ayarları, eğitim, teknolojik iyileştirmeler ve kurum düzeyinde standart alarm yönetimi politikalarının birlikte uygulanması önerilmektedir.

Anahtar Kelimeler: Alarm yorgunluğu, hasta güvenliği, klinik alarm, hemşirelik, yoğun bakım

GİRİŞ

Klinik alarmlar, hastanın fizyolojik durumundaki değişiklikleri ve tıbbi cihazlarla ilgili sorunları sağlık ekibine bildirerek erken değerlendirmeyi desteklemektedir. Bununla birlikte bir alarmın üretilmesi, uyarının doğru yorumlandığı ve zamanında karşılık bulduğu anlamına gelmemektedir. Alarm güvenliği; sinyalin doğruluğu, klinik önemi, ilgili çalışana ulaşması ve uygun yanıtın verilmesiyle birlikte değerlendirilmelidir. Joint Commission, tıbbi cihaz alarm güvenliğine ilişkin uyarısında benzer alarm seslerine, hastaya göre değiştirilmemiş varsayılan ayarlara ve alarm sinyallerine yanıt verilmemesine dikkat çekmiştir.[1]

Özellikle yoğun bakım ünitelerinde tekrarlayan ve klinik eylem gerektirmeyen uyarılar, sağlık çalışanlarının alarm sistemlerine duyduğu güveni ve alarmlara yanıt verme biçimini etkileyebilmektedir. Michels ve arkadaşlarının kapsam derlemesi, alarm yorgunluğunu tekrarlayan alarm maruziyetiyle ilişkili duyusal yüklenme, duygusal zorlanma ve giderek azalan yanıtlılık üzerinden ele almaktadır.[2] Hemşirelerin hastanın yanında sürekli bulunması ve farklı cihazlardan gelen uyarıları bakımın diğer gereksinimleriyle birlikte değerlendirmesi, bu konuyu hemşirelik bakımının niteliği açısından önemli kılmaktadır.

Bu anlatı derlemesinin amacı, alarm yorgunluğunun hasta güvenliğiyle ilişkisini ve azaltılmasına yönelik yaklaşımları incelemektir. Çalışmada fizyolojik monitör ve ventilatör alarmlarına ağırlık verilerek kavramsal ayrımlar, çalışan ve bakım ortamıyla ilişkili etmenler, ölçüm yaklaşımları ve girişimlerin kanıtları tartışılmaktadır. Alarm sayısındaki değişim, öz bildirime dayalı alarm yorgunluğu ve hasta güvenliği sonuçları ayrı değerlendirilerek hemşirelik uygulamalarına yönelik öneriler geliştirilmektedir.

GELİŞME

Alarm yorgunluğu ve klinik alarm türleri

Alarm yorgunluğu, alarm sayısıyla eş anlamlı değildir. Alarm yükü belirli bir sürede üretilen ya da çalışanın maruz kaldığı uyarıların yoğunluğunu ifade ederken alarm yorgunluğu bu maruziyetle ilişkili algısal, duygusal ve davranışsal değişimleri kapsamaktadır. Bu ayrım, aynı alarm ortamındaki çalışanların farklı deneyimler bildirebilmesini ve cihaz kayıtlarıyla öz bildirim ölçümlerinin birbirinin yerine kullanılamamasını açıklamaktadır.[2]

Yanlış pozitif alarm, uyarının işaret ettiği fizyolojik olayın gerçekte bulunmadığı durumdur. Eylem gerektirmeyen alarm ise yanlış pozitif bir sinyal olabileceği gibi doğru algılanmış ancak mevcut klinik bağlamda müdahale gerektirmeyen bir değişikliği de gösterebilir. Dolayısıyla doğru alarm ile eylem gerektiren alarm aynı kategori değildir. Bu sınıflandırma yapılmadan yalnızca "gereksiz alarm" ifadesinin kullanılması, sorunun teknik doğrulukta mı yoksa klinik eşiklerin uygunluğunda mı olduğunu belirsizleştirmektedir.[3,4]

Drew ve arkadaşlarının 461 yetişkin yoğun bakım hastasını kapsayan 31 günlük gözlemsel çalışmasında 2.558.760 alarm kaydedilmiş; sesli alarm yükü yatak başına günde 187 olarak hesaplanmıştır. Ayrıntılı olarak değerlendirilen 12.671 aritmi alarmının %88,8'i yanlış pozitif bulunmuştur.[3] Bu oran, çalışmadaki bütün alarm türlerinin yanlış pozitiflik oranı değildir. Çalışmanın gösterdiği temel sorun, yüksek alarm yükünün hasta özellikleri, ayarlar ve algılama algoritmalarındaki sınırlılıkların birlikte etkisiyle oluşabilmesidir.

Alarm yorgunluğuyla ilişkili etmenler

Alarm yorgunluğunun gelişimi, yalnızca bireyin sese alışmasıyla açıklanamaz. Xu ve arkadaşlarının yapmış olduğu meta-sentez çalışmasında sık alarmlar, alarm sistemlerine güven kaybı, cihaz kullanımındaki güçlükler ve birime özgü çalışma koşulları birlikte ele alınmıştır.[5] Bu bulgular, çalışanların tepkilerini değerlendirirken klinik bağlamın dikkate alınması gerektiğini göstermektedir. Aynı anda farklı hastalara bakım verme, birden fazla cihazın uyarısını ayırt etme ve aciliyet sıralaması yapma gereksinimi, alarm yönetiminin bilişsel boyutunu oluşturmaktadır.

Ong ve arkadaşlarının Singapur'da 110 yoğun bakım çalışanıyla yürüttüğü kesitsel çalışmada bilişsel iş yükü ve algılanan çevresel gürültü alarm yorgunluğuyla ilişkili bulunmuştur. Hemşire, hekim ve solunum terapistlerini kapsayan bu araştırma, planlanan çevresel girişimden önceki başlangıç

değerlendirmesidir; sessiz yoğun bakım uygulamasının etkililiğini göstermemektedir.[6] Araştırma, iş yükünün alarm yönetimiyle birlikte incelenmesini desteklemekle birlikte ilişkinin yönü ve zaman içindeki gelişimi için izlem çalışmalarına gereksinim vardır.

Bireysel özelliklere ilişkin bulgular ise tutarlı değildir. Zhu ve arkadaşlarının 6.908 yoğun bakım hemşiresini içeren 28 araştırmalık sistematik derleme ve meta-analiz çalışmasında çalışmalar arası heterojenlik çok yüksek bulunmuştur. Kullanılan başlıca ölçüm aracına ilişkin birleşik analizde I^2 yaklaşık %98'dir. İlişkili etmenlerin önemli bölümünde sonuçlar tutarsız veya istatistiksel olarak anlamsızdır.[7] Bu nedenle yaş, cinsiyet, deneyim veya eğitim düzeyine dayanarak bütün kurumlar için geçerli bir "yüksek riskli hemşire profili" tanımlamak uygun değildir. Yerel değerlendirme, değiştirilebilir iş ve cihaz özelliklerine odaklanmalıdır.

Alarm yanıtı ve hasta güvenliği

Alarm yorgunluğunun hasta güvenliği açısından en önemli olası sonucu, klinik olarak anlamlı uyarının gecikmeli değerlendirilmesi veya gözden kaçırılmasıdır. Bonafide ve arkadaşlarının 36 hemşireyi 210 saat boyunca gözlemlediği çalışmada, önceki iki saatte eylem gerektirmeyen alarmlara maruziyet arttıkça sonraki alarmlara yanıt süresinin uzadığı bulunmuştur. Araştırmacılar bu bulgunun alarm yorgunluğuyla açıklanabileceğini belirtmiş, iş yükü gibi diğer etmenlerin de incelenmesini önermiştir.[8]

Aynı araştırma grubunun daha sonraki çalışması, ilişkinin her ortamda aynı olmadığını göstermektedir. Çocuk servisinde 38 hemşire ve 100 hastayı kapsayan video analizinde, önceki iki saatteki eylem gerektirmeyen alarm sayısı yanıt süresiyle ilişkili bulunmamıştır. Buna karşılık hemşire başına düşen hasta sayısı, vardiyada geçen süre ve alarmın niteliği yanıt süresiyle ilişkili bulunmuştur.[9] Birlikte değerlendirildiğinde bu çalışmalar, her gecikmenin doğrudan alarm yorgunluğuna bağlanamayacağını; hastanın durumu ve bakım organizasyonunun da açıklayıcı olabileceğini ortaya koymaktadır.

Alarm yorgunluğuyla stres ve güvenlik algısı arasındaki ilişkiyi inceleyen güncel çalışmalar da bulunmaktadır. Al-Dossary'nin yedi hastanede 190 kritik bakım hemşiresiyle yürüttüğü kesitsel araştırma çalışmasında alarm yorgunluğu ile algılanan stres arasında pozitif ilişki bildirilmiştir. Yayının özetinde güvenlik iklimi ve ekip çalışması iklimiyle olumsuz ilişkiler de belirtilmektedir.[10] Er ve Gül'ün 268 cerrahi yoğun bakım ve ameliyathane hemşiresini kapsayan araştırmasında ise alarm yorgunluğu, ahlaki cesaret ve hasta güvenliği iklimi arasında ilişkiler saptanmıştır.[11] Her iki çalışmanın öz bildirim ve kesitsel tasarıma dayanması, bulguların gerçekleşmiş hasta zararını veya nedensel etkiyi doğrudan göstermesini sınırlandırmaktadır.

Türkiye'den Gülşen ve Arslan'ın 201 cerrahi yoğun bakım hemşiresiyle yürüttüğü araştırmada alarm yorgunluğu ile Hemşirelikte Tıbbi Hataya Eğilim Ölçeği puanları arasında negatif ilişki bulunmuştur. Bu ölçekte düşük puanın daha yüksek hata eğilimini göstermesi nedeniyle sonuç, artan alarm yorgunluğunun daha yüksek hata eğilimiyle ilişkili olduğu biçiminde yorumlanmıştır.[12] Burada ölçülen değişken, kayıtlarla doğrulanmış tıbbi hata sayısı değildir. Ölçek puanındaki ilişkiyi doğrudan hata sıklığındaki artış olarak sunmak, bulgunun anlamını aşmaktadır.

Alarm yorgunluğunun değerlendirilmesi

Değerlendirme sürecinde cihaz kayıtları ve çalışan deneyimi birlikte kullanılmalıdır. Alarm sayısı, alarmın türü ve önceliği, eylem gerektirip gerektirmediği ve yanıt süresi farklı soruları yanıtlamaktadır. Paine ve arkadaşlarının sistematik derlemesi, alarm özelliklerinin ve girişimlerin değerlendirilmesinde yöntem farklılıklarına ve olası istenmeyen sonuçların izlenmesine dikkat çekmektedir.[4] Alarm sayıları karşılaştırılırken izlenen hasta sayısı ve izlem süresinin dikkate alınması, dönemler arasındaki klinik yoğunluk farklarının yanlış yorumlanmasını azaltabilir.

Öz bildirim araçlarından Charité Alarm Fatigue Questionnaire, hemşire ve hekimler için geliştirilen dokuz maddeli bir araçtır; alarm stresi ve alarmlarla baş etme olmak üzere iki boyut içermektedir.[13] Daha sonraki doğrulayıcı faktör analizi çalışması bu yapıya ilişkin kanıt sağlamıştır.[14]

Erbay-Dallı ve Bağcı-Derinpınar'ın Türkçeye uyarladığı Alarm Fatigue Assessment Questionnaire'ın son formu 21 maddeli ve beş faktörlüdür; toplam iç tutarlılık katsayısı 0,85 olarak bildirilmiştir.[15] Benzer ad taşıyan araçların madde sayıları ve boyutları birbirinden farklı olabilir. Araştırmalarda aracın tam adı, kullanılan sürüm ve puan yönü açıkça belirtilmeli; farklı ölçeklerin ham puanları doğrudan karşılaştırılmamalıdır. Ayrıca öz bildirimde azalan alarm yorgunluğu, kritik alarmlara yanıtın nesnel olarak iyileştiği anlamına gelmediğinden davranışsal ölçümlerle desteklenmelidir.

Hastaya özgü ayarlar ve teknik iyileştirmeler

Alarm yönetiminin ilk basamağı, izlem endikasyonunun ve ölçüm kalitesinin değerlendirilmesidir. American Association of Critical-Care Nurses'ın uygulama önerileri; elektrot yerleştirmeden önce uygun cilt hazırlığını, doğru oksijen satürasyonu probu kullanımını ve alarm ayarlarının vardiya başlangıcında, hastanın durumu değiştiğinde ve bakım veren değiştiğinde kontrol edilmesini içermektedir. Parametrelerin hastaya göre düzenlenmesi, birim veya hastane politikasına uygun yürütülmelidir.[16] Böylece artefakt kaynaklı uyarılar ile uygun olmayan eşiklere bağlı uyarılar farklı müdahalelerle ele alınabilir.

Hastaya özgü ayarlama, alarm eşiklerinin yalnızca ses sayısını azaltmak amacıyla genişletilmesi şeklinde anlaşılmamalıdır. Sınırlar hastanın klinik durumu, izlem amacı ve ilgili cihazın özellikleriyle birlikte belirlenmeli; kritik değişikliklerin algılanması korunmalıdır. Paine ve arkadaşları alarm gecikmelerinin, eşik düzenlemelerinin ve elektrot bakımının alarm sıklığını azaltma potansiyelini bildirirken güvenlik sonuçlarının da izlenmesini önermektedir.[4] Bu nedenle bütün hastalar için tek bir sayısal eşik veya gecikme süresi önermek yerine, kurumsal sorumluluğu tanımlanmış bir değerlendirme süreci kurulmalıdır.

Ruppel ve arkadaşlarının 56 yataklı bir dahili yoğun bakım ünitesindeki ön test–son test çalışmasında, alarm sınırlarını özelleştirmeyi destekleyen yazılım ve eğitim birlikte uygulanmıştır. Orta öncelikli kalp hızı, solunum sayısı ve arteriyel basınç alarmlarında sırasıyla %9,3, %11,8 ve %15,9 azalma görülmüş; oksijen satürasyonu alarmlarında anlamlı azalma saptanmamıştır.[17] Bulgular, karar desteğinin bazı alarm türlerinde yarar sağlayabileceğini, ancak etkisinin bütün parametrelere genellenemeyeceğini göstermektedir. Ayrıca yazılım ve eğitim birlikte kullanıldığından değişimin tek bir bileşene bağlanması mümkün değildir.

Eğitim ve hatırlatıcı uygulamalar

Alarm yönetimi eğitimi; uyarının klinik nedenini değerlendirme, cihazın teknik özelliklerini kullanma ve uygun yanıtı seçme becerilerini içermelidir. Bi ve arkadaşlarının 93 yoğun bakım hemşiresiyle yürüttüğü randomize kontrollü çalışmada, planlı davranış teorisine dayalı 12 haftalık eğitim sonrasında müdahale grubunun alarm yorgunluğu, toplam alarm ve eylem gerektirmeyen alarm sonuçları kontrol grubuna göre daha düşük bulunmuştur. Gerçek kriz alarmlarında gruplar arasında anlamlı fark bildirilmemiştir.[18] Bu sonuçlar eğitimi desteklemekle birlikte, tek bir çalışmanın nadir hasta güvenliği olayları bakımından kesin güvence sağlaması beklenmemelidir.

Kibar ve Özsaban'ın 19 yoğun bakım hemşiresiyle gerçekleştirdiği tek gruplu yarı deneysel araştırmada sunumlar, olgu çalışmaları ve hatırlatıcı kartlardan oluşan eğitim kullanılmıştır. Eğitim sonrasında bilgi ve alarm yönetimi davranışlarında iyileşme, alarm yorgunluğunda ve yanıt süresinde azalma bildirilmiştir.[19] Küçük örneklem, kontrol grubunun bulunmaması, gözlemin davranışları etkileyebilmesi ve uzun dönem izlemin yapılmaması sonuçların yorumunu sınırlandırmaktadır. Hatırlatıcı kartların bağımsız etkisi de bu tasarımla belirlenemez.

Nasirmoghadas ve arkadaşlarının 75 hemşireyi kapsayan çalışmasında iki yoğun bakım ünitesi müdahale ve kontrol grubu olarak atanmıştır. Ventilatör alarmlarının nedenleri ve yönetimine yönelik eğitim; cihazlara yerleştirilen rehberler ve bir aylık eğitim desteğiyle birleştirilmiştir. Müdahale grubunda alarm yorgunluğunun ve incelenen yaygın ventilatör alarmlarının azaldığı bildirilmiştir.[20] Yalnızca iki birimin kümeler olarak kullanılması, birim özellikleriyle müdahale etkisinin ayrıştırılmasını güçleştirmektedir. Bulguların farklı yoğun bakımlarda doğrulanması gerekir.

Çok bileşenli programların kanıtları

Ding ve arkadaşlarının 2026 tarihli kanıt haritalamasına 18 girişim çalışması alınmış; bunların ikisinin randomize kontrollü, 16'sının yarı deneysel olduğu bildirilmiştir. Eğitim ve alarmların özelleştirilmesi öne çıkan yaklaşımlar olmakla birlikte çalışmaların tamamı orta veya yüksek yanlılık riskiyle değerlendirilmiştir.[21] Bu dağılım, tek bir girişim paketinin bütün klinikler için en etkili seçenek olarak kabul edilmesini güçleştirmektedir.

Program başarısını yalnızca toplam alarm sayısıyla değerlendirmek de yanıltıcı olabilir. Lewandowska ve arkadaşlarının eğitim ile teknik düzenlemeleri birleştirdiği araştırmada toplam alarm sayısı artarken kırmızı teknik alarmlarda azalma görülmüştür.[22] Arkilic ve arkadaşlarının kalite geliştirme çalışmasında ise alarm sıklığı beklenenin aksine artmış; hasta yoğunluğu, hemşire istihdamı ve cihazlardan gelen veri miktarındaki değişimlerin sonuçları etkilediği anlaşılmıştır.[23]

Bu çalışmalar, alarm türlerini ve uygulama bağlamını izlemeyen bir değerlendirmede hem başarının hem başarısızlığın yanlış sınıflandırılabileceğini göstermektedir.
Hemşirelerin karar verme yetkisinin desteklenmesi de ayrı bir müdahale alanıdır. Ron ve arkadaşlarının iki yoğun bakımda yürüttüğü ön test–son test araştırmasında, eğitimle desteklenen alarm eşiği belirleme yetkisinin hemşirelere devredilmesi öz yeterlik ve güven bakımından olumlu bildirimlerle sonuçlanmıştır. Buna karşılık gözlenen alarm yanıt oranı çocuk yoğun bakımda %65'ten %69'a yükselmiş, yetişkin yoğun bakımda %50 olarak değişmeden kalmıştır.[24] Bu sonuç, çalışanların kendini daha yetkin hissetmesi ile gözlenen bakım davranışının aynı hızda değişmeyebileceğini göstermektedir.

Çalışan desteği ve kurumsal uygulama
Çalışanların stresle baş etmesini destekleyen yaklaşımlar, teknik ve örgütsel girişimlerin tamamlayıcısı olarak ele alınabilir. Pourkhajoei ve arkadaşlarının 50 yoğun bakım hemşiresiyle yürüttüğü yarı deneysel çalışmada dört haftalık diyafragmatik solunum eğitimi sonrasında alarm yorgunluğu ve hasta güvenliği kültürü ölçeklerinde olumlu değişiklikler bildirilmiştir.[25] Sonuçlar öz bildirime ve kısa süreli değerlendirmeye dayanmaktadır; gerçek alarm yanıtı, alarm sayısı veya hasta zararında azalma gösterilmemiştir. Bu tür uygulamalar, gereksiz alarm üreten koşulların düzeltilmesinin yerine geçmemelidir.
Kurumsal düzeyde hemşirelik yönetimi, hekimler ve biyomedikal biriminin birlikte çalışması; alarm önceliklerinin, ayar değişikliği yetkilerinin ve yanıt sorumluluklarının belirlenmesini kolaylaştırabilir. AACN, birime özgü varsayılan parametreleri, disiplinler arası ekibi ve süreklilik gösteren eğitimi önermektedir.[16] Xu ve arkadaşlarının sentezi de çalışanların teknik destek, uygun çevre koşulları ve psikolojik desteğe duyduğu gereksinimi ortaya koymaktadır.[5] Bu doğrultuda alarm yönetimi, yalnızca çalışanlara "daha dikkatli olma" çağrısı yapılan bir uygulama olmaktan çıkarılmalı ve bakım işleyişinin ölçülebilir bir parçası olarak düzenlenmelidir.

Tablo 1 Alarm yönetiminde uygulama alanları ve izlenecek göstergeler

Uygulama alanı	Temel uygulama	İzlenecek gösterge
Ölçüm kalitesi	Elektrot, prob ve bağlantıları kontrol etme	Teknik alarm ve artefakt sıklığı
Hastaya özgü ayarlar	Klinik duruma uygun sınırları yetki ve politika çerçevesinde gözden geçirme	Alarm türlerine göre sıklık ve kritik olayların algılanması
Eğitim	Klinik neden, cihaz kullanımı ve uygun yanıtı uygulamayla öğretme	Bilgi, gözlenen davranış ve alarm yorgunluğu
Hatırlatıcı desteği	Kart veya yazılım desteğini iş akışına uygun kullanma	Ayarlama uygulamaları ve çalışanların kullanım deneyimi
Ekip sorumluluğu	Alarmı değerlendirecek kişiyi ve destek sürecini belirleme	Yanıtsız alarm ve kritik uyarıya yanıt süresi
Program değerlendirmesi	Cihaz kayıtlarını çalışan ve hasta göstergeleriyle birlikte inceleme	İzlem süresine göre alarm yükü ve istenmeyen güvenlik olayları

*Literatür doğrultusunda oluşturulmuştur.[16,17,21,23]

Tartışma ve araştırma gereksinimleri
Literatürün birlikte değerlendirilmesi, alarm yorgunluğunun cihaz tasarımı, bakım gereksinimleri ve çalışan deneyiminin kesişiminde oluştuğunu göstermektedir. Hemşirelerin alarmı fark etme ve yorumlama becerileri önemlidir; ancak uygun olmayan ayarlar, zayıf sinyal kalitesi veya belirsiz sorumluluklar sürdüğünde yalnızca eğitime dayalı iyileştirme sınırlı kalabilir. Eğitim ve teknik düzenlemelerin birlikte uygulanması gerekçelendirilebilir; hangi bileşenin hangi sonuç üzerinde etkili olduğu ise ayrı değerlendirilmelidir.[21,22]
Gelecek araştırmalarda alarm yükü, yorgunluk ölçekleri, kritik alarmlara yanıt ve hasta güvenliği olaylarının aynı çalışma içinde fakat ayrı sonuçlar olarak izlenmesi önerilmektedir. Çok merkezli tasarımlar, yeterli sayıda birim içeren küme randomizasyonu ve uzun dönem değerlendirme, mevcut

çalışmaların sınırlarını azaltabilir. Hasta profili, vardiya, hemşire başına düşen hasta sayısı ve cihaz güncellemelerinin kaydedilmesi; gözlenen değişimin müdahaleden mi yoksa bakım ortamından mı kaynaklandığının yorumlanmasına yardımcı olacaktır.[9,23] Çok bileşenli programlarda uygulamaya uyumun ayrıca izlenmesi, etkisiz görünen bir müdahalenin aslında yetersiz uygulanmış olabileceğinin değerlendirilmesini sağlayabilir.

Bu derlemenin sınırları, kaynak seçiminin hedefli yapılması, bazı yayınların yalnızca özetlerine erişilebilmesi ve biçimsel yanlılık değerlendirmesinin uygulanmamasıdır. Dayanak çalışmaların önemli bölümü tek merkezli, kesitsel veya kısa süreli girişim araştırmalarıdır. Bu nedenle sonuçlar, bütün sağlık kurumlarına genellenebilecek etki büyüklükleri sunmamaktadır. Bununla birlikte gerçek yayınlardan hareketle kavramları ve ölçülen sonuçları ayrıştırması, hemşirelik uygulamalarında kullanılabilecek dengeli bir değerlendirme çerçevesi sağlamaktadır.

SONUÇ

Alarm yorgunluğu, sağlık çalışanlarının iyilik hâlini ve klinik uyarılara yanıtını etkileyebilen, hasta güvenliği açısından dikkate alınması gereken bir sorundur. Bulgular, sık ve eylem gerektirmeyen alarmların azaltılmasını; ölçüm kalitesinin iyileştirilmesini, hastaya özgü alarm ayarlarını ve uygulamayla desteklenen eğitimi öne çıkarmaktadır. Hemşirelerin klinik değerlendirmesi bu sürecin merkezindedir; güvenli uygulama ise açık sorumluluklar, teknik destek ve kurumsal izlem gerektirmektedir.

Alarm yönetimi programlarının başarısı, yalnızca daha az alarm veya daha düşük yorgunluk puanıyla tanımlanmamalıdır. Klinik olarak önemli uyarıların algılanması ve uygun karşılık bulması korunmalıdır. Bu nedenle kurumlara, yerel alarm sorunlarını belirlemeleri, eğitim ile teknik düzenlemeleri birlikte planlamaları ve çalışan deneyimini nesnel bakım göstergeleriyle birlikte izlemeleri önerilmektedir. Mevcut kanıtlar iyileştirmeye yönelik uygulanabilir seçenekler sunmakla birlikte, hasta zararını azaltma ve etkinin sürdürülebilirliği konularında daha güçlü araştırmalara ihtiyaç vardır.

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HEMŞİRELERİN TIBBİ HATALARI FARK ETME, DURDURMA VE DÜZELTMEDEKİ ROLÜ

THE ROLE OF NURSES IN IDENTIFYING INTERRUPTING AND CORRECTING MEDICAL ERRORS

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Abstract
Medical errors are an important cause of preventable patient harm. Nurses, who ensure continuity of care and closely monitor patients, are also a safety barrier against errors reaching patients. Medical error recovery involves identifying, interrupting, and correcting errors to prevent patient harm. This review examines nurses' roles in these stages and the factors influencing the recovery process in light of current literature. This study was structured as a narrative review of current literature. Studies examining nurses' roles in medical error recovery were considered. Findings were synthesised according to the identification, interruption, and correction of errors, together with individual and organisational factors influencing these processes. This synthesis focused on the nursing contribution throughout the recovery process. The literature indicates that nurses have a distinctive, yet often invisible, role in preventing medical errors from reaching patients. Knowing the patient, care plan, and clinical environment; recognising unexpected changes in the patient's condition; and clinical reasoning are prominent in error identification. Once an error is recognised, questioning orders, communicating with team members, voicing safety concerns, and interrupting an intervention when necessary are key nursing behaviours. Near-miss events are considered opportunities to identify system vulnerabilities and prevent future errors, rather than merely events without harm. Nurses constitute a critical safety barrier against patient harm from medical errors. Improving patient safety requires strengthening nurses' capacity to identify, question, interrupt, and correct errors, alongside efforts to reduce error rates. Healthcare organisations should develop a non-punitive safety culture that supports learning from near misses and enables nurses to raise safety concerns without hesitation.
Keywords: Medical error, patient safety, nursing, near miss.

Özet
Tıbbi hatalar, sağlık hizmetlerinde önlenebilir hasta zararının önemli nedenlerindendir. Hasta bakımının sürekliliğini sağlayan ve klinik durumu yakından izleyen hemşireler, yalnızca hata riski taşıyan sağlık profesyonelleri değil, aynı zamanda hataların hastaya ulaşmasını engelleyen önemli bir güvenlik bariyeridir. Tıbbi hata kurtarma; hatanın fark edilmesi, durdurulması ve hasta zararını önlemek amacıyla düzeltilmesini içeren bir süreçtir. Bu derlemenin amacı, hemşirelerin tıbbi hataları fark etme, durdurma ve düzeltmedeki rollerini ve bu süreci etkileyen faktörleri güncel literatür doğrultusunda incelemektir. Bu çalışma, güncel literatürün anlatı derlemesi olarak yapılandırılmıştır. Hemşirelerin tıbbi hata kurtarma sürecindeki rolünü inceleyen çalışmalar değerlendirilmiştir. Bulgular; hatanın fark edilmesi, durdurulması ve düzeltilmesi aşamaları ile bu süreçleri etkileyen bireysel ve örgütsel faktörler doğrultusunda sentezlenmiştir. Literatür, hemşirelerin tıbbi hataların hastaya ulaşmasını önlemede özgün ancak çoğu zaman görünmeyen bir role sahip olduğunu göstermektedir. Hata kurtarma sürecinin ilk aşamasında hastayı, bakım planını ve klinik çevreyi yakından tanıma; hastanın durumundaki beklenmedik değişiklikleri fark etme ve klinik muhakeme becerisi ön plana çıkmaktadır. Hata fark edildiğinde istemi sorgulama, ekip üyeleriyle iletişim kurma, güvenlik endişesini dile getirme ve gerektiğinde uygulamayı durdurma, hatanın hastaya ulaşmasını engelleyen temel hemşirelik davranışlarıdır. Güncel literatürde ramak kala olaylar, yalnızca zarar oluşmayan olaylar olarak değil, sistemdeki güvenlik açıklarının belirlenmesi ve gelecekteki hataların önlenmesi açısından önemli öğrenme fırsatları olarak değerlendirilmektedir. Hemşireler, tıbbi hataların hasta zararına dönüşmesini önleyen kritik bir güvenlik bariyeridir. Hasta güvenliğinin geliştirilmesinde yalnızca hata oranlarının azaltılmasına değil, hemşirelerin hataları fark etme, sorgulama, durdurma ve düzeltme kapasitelerinin güçlendirilmesine de odaklanılmalıdır. Sağlık kurumlarında ramak kala olaylardan öğrenmeyi destekleyen, cezalandırıcı olmayan ve hemşirelerin güvenlik endişelerini çekinmeden dile getirebildiği bir güvenlik kültürünün oluşturulması önerilmektedir.
Anahtar Kelimeler: Tıbbi hata, hasta güvenliği, hemşirelik, ramak kala olay.

GİRİŞ

Hasta güvenliği, sağlık hizmeti sırasında ortaya çıkabilecek önlenebilir zararın azaltılmasını ve güvenli bakımın sürdürülebilmesini gerektirir. Dünya Sağlık Örgütü (DSÖ), hasta zararını bireysel davranışların yanı sıra iş süreçleri, kaynaklar, iletişim ve teknolojiyle ilişkili bir sistem sorunu olarak ele almaktadır. Bu yaklaşım, güvenliğin yalnızca sağlık çalışanlarının dikkatli olmasına bağlanamayacağını; bakımın sunulduğu koşulların da değerlendirilmesi gerektiğini göstermektedir.[1]

Reason'ın insan hatasına ilişkin sistem yaklaşımında, istenmeyen sonuçların ortaya çıkmasında savunma katmanlarındaki zayıflıkların bir araya gelmesi önem taşır. Hata yapan kişiyi belirlemek, olayın nedenlerini açıklamak ve tekrarını önlemek için tek başına yeterli değildir. İş yükü, araçların tasarımı ve örgütsel kararlar gibi koşulların incelenmesi, hataya elverişli süreçlerin anlaşılmasını sağlar.[2]

Hemşirelerin hasta güvenliğine katkısının önemli bir boyutu, bakım sırasında ortaya çıkan hataları fark ederek hastaya ulaşmasını veya daha ağır sonuçlar doğurmasını engellemeleridir. Gaffney ve arkadaşlarının yaptığı çalışmada, hata kurtarmanın hatayı fark etme, durdurma ve düzeltme aşamalarından oluştuğunu ve hemşirelerin bu süreçteki katkısının çoğu zaman görünür olmadığını ortaya koymaktadır. Bu nedenle yalnızca gerçekleşen hataların sayılması, hemşirelik bakımının güvenliğe katkısını bütünüyle açıklamaz.[3]

Uluslararası Hemşireler Konseyi'nin etik kodları, hemşirelerin güvenli bakımı tehdit eden durumları tanımasını ve uygun koruyucu girişimlerde bulunmasını mesleki sorumlulukları arasında tanımlamaktadır.[4] Bu derlemenin amacı, hemşirelerin tıbbi hataları fark etme, durdurma ve düzeltmedeki rollerini; bu rolleri etkileyen bireysel, ekip ve örgüt düzeyindeki etmenlerle birlikte incelemektir. Ayrıca hata kurtarma deneyimlerinin eğitim, klinik uygulama ve kurumsal öğrenme süreçlerine nasıl yansıtılabileceği tartışılmaktadır.

GELİŞME

Tıbbi hata kurtarmanın kavramsal çerçevesi

Tıbbi hata, planlanan bir eylemin amaçlandığı biçimde gerçekleştirilememesi veya amaca ulaşmak için yanlış bir planın kullanılmasıyla ilişkilidir. Hata ile zarar aynı kavram değildir: Bir hata hastaya ulaşmadan durdurulabilir; hastaya ulaşsa bile fark edilebilir bir zarar oluşturmayabilir. Uluslararası Hasta Güvenliği Sınıflandırması çerçevesinde ramak kala olay, hastaya ulaşmayan olaydır. Zarar oluşturmayan olay ise hastaya ulaşmış olmasına rağmen fark edilebilir bir zararla sonuçlanmamıştır. Zarar veren olay, hastada zarara yol açan hasta güvenliği olayıdır. Bu ayrımlar, olayları yalnızca sonuca göre adlandırmanın yaratabileceği karışıklığı azaltır.[5]

Hata kurtarma, hatanın ilerleyişine müdahale eden bir süreçtir; ramak kala ise bu sürecin başarıyla tamamlanmasıyla ilişkili olabilecek olay sonuçlarından biridir. Bununla birlikte hata kurtarma, yalnızca hastaya ulaşmadan önce gerçekleşmez. Rothschild ve arkadaşlarının bir koroner yoğun bakım ünitesinde yürüttüğü araştırmada, kurtarılan 142 tıbbi hatanın %69'u hastaya ulaşmadan durdurulmuş; %13'ünde hastaya ulaşan hatanın zarar oluşturması, %18'inde ise daha ağır zarar gelişmesi engellenmiştir.[6]

Literatürde kavramların kullanımında farklılıklar bulunmaktadır. Zhou ve arkadaşlarının kavram analizi, hemşirelikte ramak kala olayların tanınması ve bildirilmesinde tanımsal değişkenliğe dikkat çekmektedir.[7] Bu derlemede kavramsal tutarlılık için ramak kala olayın hastaya ulaşmama özelliği esas alınmıştır. Ayrıca klinik kötüleşmenin fark edilmesi her durumda tıbbi bir hatanın saptandığı anlamına gelmez. Hata kurtarma değerlendirmesinde, belirli bir yanlışlığın veya bakım sürecindeki sapmanın ne olduğu ve hangi girişimle düzeltildiği açıklanmalıdır.

Hatanın fark edilmesi

Hata kurtarmanın ilk aşaması, mevcut durum ile beklenen bakım süreci arasındaki uyumsuzluğun tanınmasıdır. Henneman ve arkadaşlarının 20 yoğun bakım hemşiresiyle gerçekleştirdiği odak grup çalışmasında; hastayı, bakım planını ve ekip üyelerini tanıma, klinik gözetim, politika ve prosedür bilgisi, çift kontrol, sistematik süreçler ve sorgulama, hata saptamada kullanılan stratejiler arasında belirlenmiştir. Bulgular, hemşirelerin yalnızca bir istemi yerine getirmekle kalmayıp farklı bilgi kaynakları arasındaki tutarlılığı da değerlendirdiğini göstermektedir.[8]

Klinik gözetim, monitör değerlerini izlemekten daha geniş bir süreçtir. Hasta verilerinin amaçlı ve sürekli olarak toplanmasını, yorumlanmasını ve klinik karar için bir araya getirilmesini içerir. Henneman, Gawlinski ve Giuliano, izlemenin gözetimin önemli bir parçası olduğunu, ancak tek başına

yeterli olmadığını vurgulamaktadır.[9] Örneğin bir laboratuvar sonucunun hastanın önceki değerleri ve klinik görünümüyle uyuşmaması, veri veya süreç doğrulaması gerektirebilir. Böyle bir uyumsuzluk doğrudan hata kanıtı değildir, yeniden değerlendirmeyi başlatan bir işarettir.

Çift kontrol, hata saptamada sık kullanılan uygulamalardan biri olmakla birlikte etkililiği koşullara bağlıdır. Koyama ve arkadaşlarının sistematik derlemesi, çift kontrolün tek kontrole göre ilaç uygulama hatalarını veya hasta zararını azalttığını göstermek için kanıtların yetersiz olduğunu bildirmiştir.[10] Westbrook ve arkadaşlarının 2026 yılında yayımlanan, 82 hemşirenin katıldığı randomize simülasyon araştırmasında bağımsız çift kontrolün hata saptama performansına katkısı deneyimli hemşirelerde görülmüş, mesleğinin ilk yıllarındaki hemşirelerde aynı yarar gösterilememiştir. Ayrıca çift kontrol daha fazla zaman gerektirmiştir.[11] Bu bulgular, kontrolün niteliğinin ve çalışanların yetkinliğinin değerlendirilmesini destekler, simülasyondaki hata saptama başarısı gerçek hastalarda zarar azalmasıyla eş tutulmamalıdır.

Hatanın durdurulması

Hata fark edildiğinde, sıradaki gereksinim hatalı eylemin ilerleyişini kesmektir. Henneman ve arkadaşlarının acil servis araştırmasında hemşireler; hasta savunuculuğu, yardım teklif etme, açıklığa kavuşturma, sözel olarak araya girme ve doğrulama için gecikme oluşturma gibi stratejiler bildirmiştir.[12] Güvenlik gerekçesiyle bir uygulamanın doğrulanana kadar bekletilmesi, ilgili klinik durumun aciliyeti ve kurumsal süreçler dikkate alınarak yürütülmelidir. Buradaki amaç gerekli bakımın gecikmesi değil, şüpheli uygulamanın güvenli biçimde değerlendirilmesidir.

Güvenlik endişesini dile getirme, uluslararası literatürde "speaking up" olarak adlandırılmaktadır. Lee ve arkadaşlarının 15 nitel araştırmayı birleştiren metasentezi, hemşirelerin konuşma kararında olası olumsuz tepkileri değerlendirdiğini; hiyerarşik yapı ve olumsuz çalışma ortamının engel, mesleki sorumluluk ve destekleyici atmosferin ise kolaylaştırıcı olduğunu göstermektedir.[13] Dolayısıyla hatayı fark etmek, kendiliğinden etkili bir müdahaleye dönüşmeyebilir. Hemşirenin kime, nasıl ve ne kadar hızlı ulaşabildiği de belirleyicidir.

AHRQ'nun TeamSTEPPS kapsamında sunduğu CUS aracı; endişenin, rahatsızlık nedeninin ve hasta güvenliği sorununun açıkça ifade edilmesini, sorun dikkate alınmadığında sorumlu yöneticiye bildirilmesini önerir.[14] SBAR ise durum, ilgili geçmiş, değerlendirme ve öneri veya talep bileşenleriyle iletişimin yapılandırılmasını sağlar.[15] Bu araçlar, güvenlik kaygısının belirsiz bir uyarı olarak kalmasını önleyebilecek iletişim çerçeveleridir. Kullanımları, ekip üyelerinin bu dili tanıması ve uyarıyı değerlendirecek bir yanıt mekanizmasının bulunmasıyla anlam kazanır.

Hatanın düzeltilmesi ve güvenli bakımın sürdürülmesi

Düzeltme aşamasında, hatalı sürecin durdurulmasının ardından güvenli bakımın yeniden kurulması amaçlanır. Yoğun bakım hemşireleriyle yapılan araştırmada, bakım planının gözden geçirilmesi veya doğrulanması, uygun seçeneklerin sunulması, standartlara ya da uzman görüşüne başvurulması ve başka bir hemşire veya hekimin sürece katılması düzeltme stratejileri olarak tanımlanmıştır.[8] Acil servis araştırmasında ise ekibin bir araya getirilmesi ve liderliğin sürece dahil edilmesi öne çıkmıştır.[12] Böylece hata kurtarma, tek kişinin gerçekleştirdiği bir işlemden ekip içinde tamamlanan bir bakım sürecine dönüşür.

Hemşirenin düzeltmedeki rolü, mesleki yetkinliği ve sorumluluk alanıyla uyumlu olmalıdır. Klinik değerlendirme, ilgili profesyonelle istemin açıklığa kavuşturulması, doğrulanan planın uygulanması ve hastanın yanıtının izlenmesi bu kapsamda ele alınabilir. Uluslararası Hemşireler Konseyi, güvenliğin tehlikeye girdiği durumlarda uygun girişimde bulunma ve güvenli uygulama için gerekli mesleki sorumluluğu üstlenme yükümlülüğünü vurgulamaktadır.[4] Hatanın düzeltildiğinin varsayılması yerine, düzeltmenin ilgili bakım sürecine gerçekten yansıdığının kontrol edilmesi gerekir.

Üç aşamanın ilişkisini açıklamak için oluşturulan aşağıdaki örnek, gerçek bir olgu veya araştırma bulgusu değildir. İlaç hazırlığı sırasında istem ile hazırlanan ürün arasında uyumsuzluk saptayan bir hemşire, uygulamayı doğrulama tamamlanana kadar bekletir, ilgili ekip üyesiyle bilgileri karşılaştırır ve doğrulanan uygulama planının izlenmesini sağlar. Burada uyumsuzluğu tanıma fark etme, şüpheli uygulamanın ilerlemesini engelleme durdurma, güvenli planı oluşturup izleme ise düzeltme aşamasını örneklemektedir. Tablo 1, bu aşamaların karşılaştırmalı bir özetini sunmaktadır.

Tablo 1 Hata kurtarma aşamaları ve hemşirelik davranışları

Aşama	Hemşirelik davranışı	Sürecin odağı
Fark etme	Hasta ve bakım planındaki bilgileri karşılaştırma; uyumsuzluğu sorgulama	Hatanın veya şüpheli durumun belirlenmesi
Durdurma	Güvenlik endişesini iletme; açıklama isteme; hatalı eylemin ilerleyişini kesme	Hatanın hastaya ulaşmasının veya sürmesinin engellenmesi
Düzeltme	Ekiple planı doğrulama; uygun girişimi yürütme; sonucu izleme	Güvenli bakımın yeniden kurulması

*Literatür doğrultusunda oluşturulmuştur.[8,12]

Bireysel yetkinlik ve çalışma koşulları

Hata kurtarma kapasitesinin değerlendirilmesinde eğitim, klinik uzmanlık ve bakım bağlamı birlikte ele alınmalıdır. Gaffney ve arkadaşlarının 184 dahiliye ve cerrahi hemşiresiyle yaptığı kesitsel araştırmada, eğitim düzeyi ve algılanan uzmanlık ile bildirilen hata kurtarma arasında pozitif ilişkiler saptanmıştır. Buna karşılık yaş veya çalışma süresi gibi değişkenler aynı örüntüyü göstermemiştir.[16] Bu bulgu, kıdemin tek başına yeterli bir yetkinlik göstergesi olmadığını düşündürür. Araştırmanın öz bildirime dayalı ve kesitsel yapısı nedeniyle, eğitimin hata kurtarmayı doğrudan artırdığı sonucuna varılamaz.

Örgütsel koşullar, bireysel yetkinliğin kullanılabileceği alanı belirler. Dall'Ora ve arkadaşlarının boylamsal araştırmaları inceleyen sistematik derlemesi, daha yüksek hemşire istihdamı ile daha iyi hasta sonuçları, özellikle mortalite açısından tutarlı bir ilişki bulunduğunu bildirmektedir.[17] Bu kanıt doğrudan hata kurtarmanın bütün aşamalarını ölçmemektedir; ancak hemşirelerin klinik gözetim ve bakım için yeterli zamana sahip olmasının önemini desteklemektedir. Hata kurtarmayı güçlendirmek için eğitim kadar işin nasıl düzenlendiğinin de değerlendirilmesi gerekir.

İş akışındaki kesintiler de önemlidir. Westbrook ve arkadaşlarının iki hastanede 98 hemşirenin ilaç uygulamalarını gözlediği çalışmada, kesintilerin sıklığı ile işlem eksiklikleri ve klinik hatalar arasında ilişki belirlenmiştir.[18] Bununla birlikte her kesinti aynı anlamı taşımaz: Hatalı uygulamayı durdurmak amacıyla yapılan güvenlik uyarısı, korunması gereken bir iletişimdir. Bu nedenle uygulama alanı için çıkarım, bütün iletişimi engellemek değil; gereksiz bölünmeleri azaltırken acil güvenlik uyarılarının iletilebildiği bir düzen kurmaktır.

Flynn ve arkadaşlarının araştırmasında destekleyici çalışma ortamı ile hemşirelerin hataları yakalama uygulamaları arasında pozitif, hata yakalama uygulamaları ile ilaç hatası oranları arasında ise negatif ilişki bulunmuştur.[19] Hemşireye danışılabilen, destek alınabilen ve bakım kararlarına katılımın mümkün olduğu bir ortamın oluşturulması, hata kurtarmanın yalnızca kişisel cesarete bırakılmaması açısından önemlidir. Kurumsal iyileştirmede, hemşirelerin hangi hataları yakaladığı kadar hangi koşullarda müdahale edemediği de araştırılmalıdır.

Teknolojinin sağladığı olanaklar ve sınırlılıklar

Elektronik ilaç uygulama kayıtları ve barkod doğrulama sistemleri, hemşirelerin hata saptamasını destekleyebilir. Poon ve arkadaşlarının bir akademik tıp merkezindeki önce ve sonra karşılaştırmalı araştırmasında, barkod destekli elektronik ilaç uygulama kaydı kullanılan birimlerde zamanlama dışı ilaç uygulama hataları %11,5'ten %6,8'e düşmüştür. Bununla birlikte hatalar tamamen ortadan kalkmamıştır.[20] Bulgular, belirli bir teknoloji ve uygulama bağlamına aittir; her bilgi sisteminin aynı sonucu sağlayacağını göstermez. Ayrıca araştırmada değerlendirilen potansiyel zarar, gerçekleşmiş hasta zararıyla karıştırılmamalıdır.

Du ve arkadaşlarının 2025 yılında yayımlanan, Çin'de 12 hastaneden 1311 hemşireyi kapsayan kesitsel araştırmasında, hemşirelik bilgi sistemi görevlerindeki öz bildirime dayalı ramak kala deneyimleri; bilişim yetkinliği, sistemin özellikleri ve iş ortamındaki kesintilerle ilişkili bulunmuştur.[21] Bu sonuçlar, dijitalleşmenin güvenlik için tek başına yeterli olmadığını göstermektedir. Hemşirenin ekran bilgisini hasta ve bakım planıyla karşılaştırabilmesi; sistemin yanlış veya eksik bilgiyi fark etmeye olanak vermesi önem taşır.

Teknolojik desteğe ilişkin uygulama önerisi, doğrulama araçlarını klinik değerlendirmeyle birlikte kullanmaktır. Bir uyarının neden ortaya çıktığı açıklığa kavuşturulmalı; arayüz, erişim veya iş akışı

sorunları güvenli bakımın önünde tekrarlayan engeller oluşturuyorsa kurumsal düzeyde değerlendirilmelidir. Teknolojinin güvenliği ve insan ilişkilerini desteklemesi gerektiği, hemşirelik etiği çerçevesinde de vurgulanmaktadır.[4]

Ramak kala olaylardan kurumsal öğrenme

Hatanın hasta başında düzeltilmesi, benzer bir hatanın yeniden oluşmasını kendiliğinden engellemez. Jeffs ve arkadaşlarının nitel araştırması, ekip üyelerinin hatalarını başkalarının yakalayacağına güvenmesinin bireysel mesleki sorumluluğu zayıflatabileceğine dikkat çekmektedir.[22] Bu bulgu, ortak gözetimin kişisel doğrulama sorumluluğunun yerine geçmemesi gerektiğini düşündürür. Hem hatayı üreten koşulların hem de hatayı durdurmayı mümkün kılan uygulamaların görünür olması, bakım süreçlerinin anlaşılmasına katkı sağlayabilir. Başarılı müdahale, tekrarlayan bir süreç sorununun olağan karşılanmasına yol açmamalıdır.

DSÖ'nün olay bildirim ve öğrenme sistemlerine ilişkin rehberi, bildirim verilerinin dikkatli yorumlanması gerektiğini vurgulamaktadır. Bildirim sisteminden öğrenme üretilebilmesi, kayıtların analize ve iyileştirmeye dönüşmesine bağlıdır.[23] Buradan hareketle, bildirim sayısındaki bir artışın tek başına güvenliğin kötüleştiği şeklinde yorumlanması uygun değildir; artış, olayların daha iyi tanınması veya bildirim için daha destekleyici bir ortam oluşmasıyla da ilişkili olabilir. Benzer biçimde, az bildirim olması hataların az olduğunu kanıtlamaz.

Klinik uygulama için olay kayıtlarında yalnızca hatanın türü değil; nasıl fark edildiği, hangi aşamada durdurulduğu, hangi düzeltmenin yapıldığı ve hastanın etkilenip etkilenmediği de yer almalıdır. Bu derlemeden çıkarılan bir uygulama önerisi olarak, kayıtların ilgili ekip tarafından değerlendirilmesi, iyileştirme sorumlusunun ve zamanının belirlenmesi ve sonucun çalışanlara geri bildirilmesi önerilebilir. Böylece bildirim, tamamlanmış bir form olmanın ötesinde izlenebilir bir öğrenme sürecine dönüşebilir.

Öğrenmeyi destekleyen yaklaşım, çalışanların dürüstçe bildirdikleri olaylar nedeniyle otomatik olarak suçlanmadıkları bir ortamı gerektirir. Bununla birlikte sistem yaklaşımı, mesleki sorumluluğun veya kasıtlı güvensiz davranışların değerlendirilmesini ortadan kaldırmaz. DSÖ, sistem nedenlerinin anlaşılması ile ihmal ya da uygunsuz davranışların göz ardı edilmemesi arasında bu ayrımı korumaktadır.[1] Hemşirelerin hata kurtarma kapasitesi, çalışan güvenliği ve adil değerlendirme süreçleriyle birlikte güçlendirilmelidir.

Hemşirelik eğitimi ve yönetime yönelik çıkarımlar

Eğitimde yalnızca hata türlerinin anlatılması yeterli değildir; öğrencilerin ve hemşirelerin şüpheli bir durumu nasıl sorgulayacağını, güvenlik endişesini nasıl ileteceğini ve düzeltmenin tamamlandığını nasıl doğrulayacağını uygulaması gerekir. Jeong ve Kim'in beş hastaneden 12 hemşireyle yürüttüğü nitel çalışma, güvenlik için konuşmayı destekleyen ortamın ve özellikle öğrenciler ile yeni hemşirelere yönelik eğitimin gerekliliğine işaret etmektedir.[24] Eğitim senaryolarında hiyerarşi, bilgi eksikliği ve ilk uyarının dikkate alınmaması gibi klinik güçlüklerin ele alınması, bu bulgulardan çıkarılabilecek bir öneridir.

Lee ve arkadaşlarının konuşma eğitimlerine ilişkin kapsam derlemesinde, 21 çalışma incelenmiş; çalışmaların çoğunun öğrenme düzeyindeki sonuçlara odaklandığı, yalnızca ikisinin klinik davranış düzeyindeki etkiyi değerlendirdiği ve hiçbirinin hasta düzeyindeki sonuçları ölçmediği bildirilmiştir.[25] Bu nedenle eğitim sonrasında özgüven veya iletişim puanının yükselmesi, hasta zararının azaldığı şeklinde sunulmamalıdır. Eğitimlerin değerlendirilmesinde bilgi ve tutumun yanında gözlenen davranış ve klinik süreç göstergelerine de yer verilmesi gerekir.

Bu derleme doğrultusunda eğitim değerlendirmesi için; doğru hata saptama, uygun zamanda güvenlik endişesini dile getirme, ilgili ekip üyesine ulaşma ve düzeltmenin tamamlandığını doğrulama gibi ölçütler önerilebilir. Yönetim düzeyinde ise yeni hemşirelere erişilebilir danışmanlık, güvenlik uyarıları için açık başvuru yolları ve olaylardan öğrenmenin düzenli ekip toplantılarına taşınması önceliklendirilebilir. Bunlar tek başına etkinliği kanıtlanmış bir müdahale paketi olarak değil, mevcut kanıtlar temelinde yerel olarak geliştirilip değerlendirilmesi gereken uygulamalar olarak ele alınmalıdır.

Derlemenin sınırlılıkları ve araştırma gereksinimleri

Bu anlatı derlemesinde kaynak seçimi sistematik derlemelerdeki kapsamlı ve bağımsız seçim sürecine dayanmamaktadır. Bazı yayınların yalnızca özetlerine erişilebilmiştir. İncelenen çalışmaların bir bölümünün küçük nitel örneklemlerle veya öz bildirime dayalı kesitsel tasarımlarla yürütülmüş olması, bağlamlar arasında genellemeyi ve nedensel çıkarımı sınırlandırmaktadır.

Ayrıca ramak kala olay, hata yakalama ve hata kurtarma kavramlarının farklı biçimlerde kullanılması, sonuçların doğrudan karşılaştırılmasını güçleştirmektedir.
Gelecek araştırmalarda hata kurtarmanın üç aşamasını birlikte değerlendiren, doğrudan gözlem ve olay kayıtlarını birleştiren çok merkezli çalışmalar yararlı olacaktır. Yalnızca kurtarılan hata sayısına odaklanmak, hemşirelerin maruz kaldığı hata fırsatları arasındaki farklılıkları gözden kaçırabilir. Bu nedenle hata türü, bakım ortamı, iş yükü ve olası zarar düzeyiyle birlikte değerlendirme yapılması önerilmektedir. Eğitim veya teknoloji girişimlerinin etkisi araştırılırken, simülasyon başarısı ile gerçek klinik sonuçlar ayrı olarak raporlanmalıdır.

SONUÇ

Hemşirelerin tıbbi hataları fark etme, durdurma ve düzeltmedeki rolü, hasta güvenliğinin klinik bakım içinde sürdürülebilmesi açısından önemlidir. Hata kurtarma; hastayı ve bakım planını tanıma, farklı bilgileri karşılaştırma, güvenlik endişesini ifade etme ve ekip içinde güvenli bakımın yeniden kurulmasını sağlama süreçlerini içerir. Bu katkının görünür hale getirilmesi, hemşirelik bakımının yalnızca gerçekleştirilen işlemlerle değil, önlenen veya sınırlandırılan zarar açısından da değerlendirilmesine olanak sağlayabilir.
Mevcut kanıtlar, hata kurtarma kapasitesinin bireysel dikkat veya kıdemle açıklanamayacağını; eğitim, çalışma koşulları, ekip iletişimi ve teknolojik süreçlerle birlikte ele alınması gerektiğini göstermektedir. Kurumların hemşirelerin uyarılarını değerlendiren, ramak kala olaylardan öğrenen ve iyileştirmelerin sonucunu izleyen süreçler geliştirmesi önerilmektedir. Bununla birlikte farklı stratejilerin hasta sonuçlarına etkisini ortaya koymak için daha güçlü ve klinik uygulamaya dayalı araştırmalara gereksinim vardır.

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IN VITRO EVALUATION OF THE ANTIPROLIFERATIVE EFFECT OF A SYNTHESIZED BENZIMIDAZOLE DERIVATIVE ON THE HUMAN BREAST CANCER MCF-7 CELL LINE

SENTEZLENEN BİR BENZİMİDAZOL TÜREVİNİN İNSAN MEME KANSERİ MCF-7 HÜCRE HATTI ÜZERİNDEKİ ANTİPROLİFERATİF ETKİSİNİN İN VİTRO OLARAK DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Breast cancer is one of the most common malignancies among women and represents a major public health problem due to its high mortality rates. The limitations of current chemotherapeutic agents, including systemic toxicity and drug resistance, necessitate the development of novel anticancer compounds with greater selectivity and efficacy. This study aimed to investigate the *in vitro* cytotoxic and antiproliferative effects of a synthesized benzimidazole derivative, compound 4, on the MCF-7 human breast cancer cell line.

Materials and Methods

Compound 4 was synthesized and characterized as a benzimidazolium salt derivative. MCF-7 cells were cultured under standard cell culture conditions (37°C, 5% CO_2). After seeding into 96-well plates, the cells were incubated with various concentrations of compound 4 (12.5–500 µM) for 24 and 48 h. Cell viability was assessed using the MTT assay, and absorbance values were measured with a microplate reader. Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test in SPSS version 22, and $p < 0.05$ was considered statistically significant.

Results

The MTT assay demonstrated that compound 4 significantly reduced the viability of MCF-7 cells in a dose- and time-dependent manner. Marked decreases in cell viability were observed at concentrations of 50 µM and above after 24 h of treatment, whereas cytotoxic activity was further enhanced after 48 h, with cell viability decreasing to approximately 39% at 500 µM ($p < 0.001$). These findings indicate that compound **4** exerts a potent cytotoxic effect at higher concentrations and that its activity increases with prolonged incubation time.

Conclusion

The synthesized benzimidazole derivative compound 4 exhibited pronounced dose- and time-dependent cytotoxic and antiproliferative effects on MCF-7 human breast cancer cells. The obtained results suggest that this compound may represent a promising candidate for further investigation as a potential therapeutic agent for breast cancer and warrants additional cellular and molecular studies.

Keywords: Antiproliferative effect; benzimidazole; breast cancer; MCF-7; cytotoxic activity.

ÖZET

Amaç: Meme kanseri, kadınlarda en sık görülen malignitelerden biri olup yüksek mortalite oranları nedeniyle önemli bir halk sağlığı sorunudur. Mevcut kemoterapötik ajanların sistemik toksisite ve ilaç direnci gibi sınırlılıkları, daha seçici ve etkili yeni antikanser bileşiklerin geliştirilmesini gerekli kılmaktadır. Bu çalışmada, sentezlenen benzimidazol türevi bileşik 4'ün MCF-7 insan meme kanseri hücre hattı üzerindeki sitotoksik ve antiproliferatif etkileri *in vitro* koşullarda araştırılmıştır.

Materyal ve Yöntem

Bileşik 4, benzimidazolyum tuzu yapısında sentezlenmiş ve karakterize edilmiştir. MCF-7 hücreleri standart hücre kültürü koşullarında (%5 CO_2, 37°C) çoğaltılmıştır. Hücreler 96 kuyucuklu plakalara ekildikten sonra 12,5–500 µM aralığındaki farklı bileşik 4 konsantrasyonları ile 24 ve 48 saat süreyle inkübe edilmiştir. Hücre canlılığı MTT yöntemi ile değerlendirilmiş, absorbans değerleri mikroplaka okuyucuda ölçülmüştür. Veriler SPSS 22 programında tek yönlü ANOVA ve Tukey testi kullanılarak analiz edilmiş, $p < 0,05$ anlamlı kabul edilmiştir.

Bulgular

MTT analizi sonuçları bileşik 4'ün MCF-7 hücre canlılığını doza ve zamana bağlı olarak anlamlı şekilde azalttığını göstermiştir. 24 saatlik uygulamada 50 µM ve üzerindeki konsantrasyonlarda belirgin düşüşler saptanırken, 48 saatlik uygulamada sitotoksik etkinin daha da arttığı ve 500 µM konsantrasyonda canlılığın yaklaşık %39'a kadar düştüğü belirlenmiştir ($p<0,001$). Bulgular, bileşiğin yüksek dozlarda güçlü sitotoksik etki oluşturduğunu ve etkinliğinin inkübasyon süresi uzadıkça arttığını ortaya koymuştur.

Sonuç

Yeni sentezlenen benzimidazol türevi bileşik 4, MCF-7 insan meme kanseri hücreleri üzerinde belirgin doza ve zamana bağlı sitotoksik ve antiproliferatif etki göstermiştir. Elde edilen sonuçlar, bu bileşiğin meme kanseri tedavisinde potansiyel terapötik ajan adayı veya hücresel ve moleküler düzeyde araştırılmaya değer olduğunu düşündürmektedir.

Anahtar kelimeler: Antiproliferatif etki; benzimidazol; meme kanseri; MCF-7; sitotoksik aktivite.

INTRODUCTION

Cancer is a complex disease resulting from the disruption of mechanisms that regulate normal cellular growth and division, characterized by the uncontrolled proliferation of abnormal cells and the potential to disseminate to other parts of the body.[1–3] As the second leading cause of mortality worldwide following cardiovascular diseases, cancer represents an increasingly significant public health challenge driven by factors such as extended life expectancy, environmental exposures, lifestyle changes, and genetic susceptibility.[1] Particularly in breast cancer, its high degree of heterogeneity at the molecular and cellular levels necessitates cancer-specific diagnostic and therapeutic strategies, thereby complicating the treatment process. Furthermore, the capacity for invasive spread and metastasis poses additional hurdles to effective clinical management.[1,3–5]

Breast cancer is the most prevalent malignancy among women and constitutes one of the primary causes of cancer-related mortality in the female population.[6] Worldwide, it represents the most frequently diagnosed cancer in women; although rarer, it can also occur in men. Breast cancer accounts for 31% of all newly diagnosed female cancer cases and 15% of total cancer-attributable deaths in women.[7] According to World Health Organization (WHO) data,[8] approximately 2.4 million women were diagnosed with breast cancer globally in 2024, and nearly 694,000 women succumbed to the disease. Furthermore, based on WHO statistics,[8] breast cancer ranks first in incidence among women in Turkey, with 25,080 absolute cases reported in 2024. As a heterogeneous group of diseases characterized by high malignancy and mortality, breast cancer is managed through diverse therapeutic modalities, including surgery, chemotherapy, radiotherapy, and hormone therapy.[9,10] Despite extensive research dedicated to its management, the desired level of success in reducing these high mortality and morbidity rates has not yet been fully achieved.[7]

Chemotherapy remains one of the most widely utilized bedrock treatment modalities alongside surgical intervention, radiotherapy, and immunotherapy in cancer management. However, because chemotherapeutic agents can also affect rapidly dividing healthy cells, they give rise to severe side

effects such as myelosuppression, gastrointestinal mucosal damage, nausea, vomiting, alopecia, and drug resistance.[1,2] Furthermore, the heterogeneous architecture of breast tumors and the development of multidrug resistance represent major impediments that constrain the efficacy of current therapeutic regimes. Consequently, the development of novel therapeutic agents that selectively target cancer cells while minimizing damage to healthy tissues is of paramount importance.[10] In recent years, research on targeted therapies and small-molecule inhibitors aimed at achieving this objective has gained considerable momentum; in particular, benzimidazole derivatives have been reported to exert antitumor effects through mechanisms such as cell cycle arrest, induction of apoptosis, and modulation of signal transduction pathways.[1,10]

The objective of this study was to evaluate the anticancer potential of compound **4**, a synthesized benzimidazole derivative, against the MCF-7 human breast cancer cell line. In this context, the cytotoxic and antiproliferative effects of the compound were investigated *in vitro* at various concentrations and incubation periods (24 and 48 hours). The obtained findings are intended to establish a foundation for future studies directed toward the development of novel therapeutic agents with potential utility in breast cancer treatment.

MATERIALS AND METHODS

Synthesis of a Benzimidazolium Salt

The synthesis of a benzimidazolium salt was carried out based on previously published procedures.[11,12] In the first step, benzimidazole (1 mmol) was dissolved in 20–40 mL of ethanol, and potassium hydroxide (KOH, 1.5 mmol) was added slowly. The reaction mixture was stirred at room temperature (25°C) for 1 h. Subsequently, the appropriate alkyl halide or *N*-(bromomethyl)phthalimide (1 mmol) was introduced into the reaction medium, and the mixture was refluxed for 6 h. Upon completion of the reaction, the precipitated potassium chloride was removed by filtration. Following the evaporation of the solvent under reduced pressure, the resulting *N*-alkylbenzimidazole intermediate was crystallized from ethanol and purified by washing several times with diethyl ether. In the second step, the synthesized *N*-alkylbenzimidazole (1 mmol) was dissolved in anhydrous dimethylformamide (DMF, 4 mL), and the appropriate alkyl halide (1 mmol) was added dropwise. The reaction mixture was stirred in a Schlenk tube at 80 °C for 24 h (Figure 1). After the completion of the reaction, DMF was evaporated under reduced pressure. The crude benzimidazolium salts were purified by recrystallization using suitable solvents or solvent mixtures (ethanol–diethyl ether). Utilizing this procedure, a benzimidazolium salt was synthesized in high yield and isolated in pure form.[11,13]

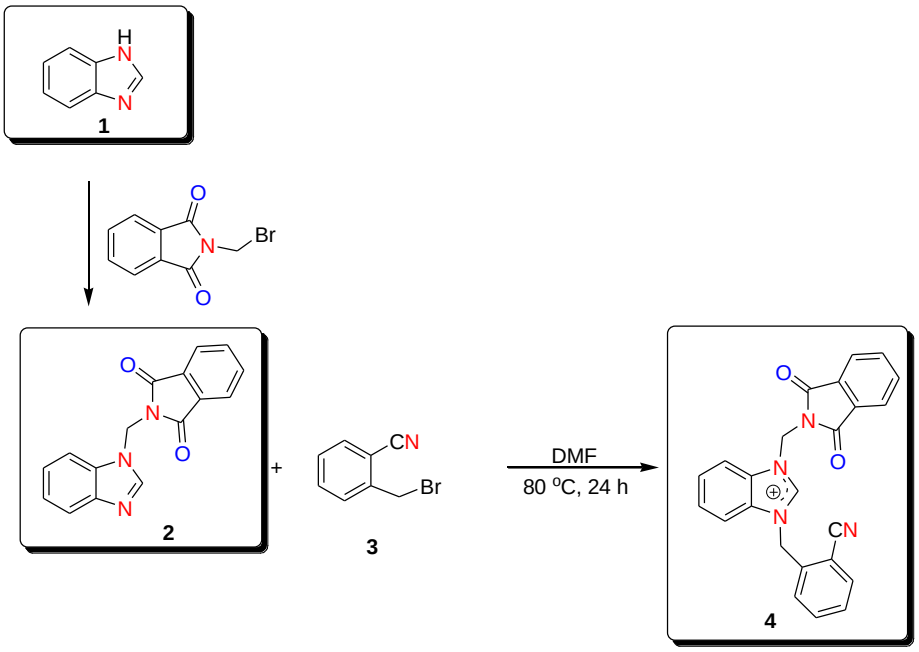


Figure 1. Synthesis of compound 4.

Synthesis of a Benzimidazole-Based Compound 4

Compound **4** was synthesized from **1** (1 g, 1 mmol) and 2- (bromomethyl) benzonitrile (0.708 g, 1 mmol) in DMF for 24 h at 80 ºC. Yield: 87%, m.p.: 275 ºC, color: white. IR: 1566.1 (CN); 1722.3 cm^{-1} (C=O). ^{1}H NMR (400.13 MHz, DMSO-d_6, 298 K), δ: 6.10 (s, 2 H, H20); 6.41 (s, 2 H, H10); 7.35 (d, 1 H, H26, *J*= 7.7 Hz); 7.59 (t, 1 H, H24, *J*= 7.7 Hz); 7.67 (t, 1 H, H5, *J*= 7.4 Hz); 7.70 (t, 1 H, H25, *J*= 7.7 Hz); 7.79 (t, 1 H, H6, *J*= 8.4 Hz); 7.84 (d, 1 H, H4, *J*= 8.4 Hz); 7.91-7.98 (m, 5 H, H13-16 and H23); 8.26 (d, 1 H, H7, *J*= 7.4 Hz); 10.04 (s, 1 H, H2). ^{13}C NMR (100.13 MHz, DMSO-d_6, 298 K), δ: 47.2 (C10); 48.3 (C20); 110.5 (C22); 113.4 (C7); 114.1 (C4); 116.7 (*C* ≡ N); 123.6 (C13 and C16); 127.0 (C5); 127.1 (C6); 128.2 (C26); 129.3 (C24); 130.7 (C8 and C9); 131.3 (C17 and C18); 133.6 (C23); 133.8 (C25); 135.0 (C14 and C15); 136.8 (C21); 144.8 (C2); 166.7 (C12 and C19). HRMS $[L\text{-}Br]^+$ calcd for $C_{24}H_{17}N_4O_2$: 393.42, found m/z: 393.14. % Elemental analysis for $C_{24}H_{17}N_4O_2Br$ (473.32 g/mol): Found C: 60.41; H: 3.71; N: 11.68. Anal. Calc. C: 60.90; H: 3.62; N: 11.84.[11]

MCF-7 Cell Culture

The human breast cancer cell line (MCF-7) (ATCC® HTB-22™) utilized in this study was commercially obtained from the American Type Culture Collection (ATCC, USA). Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM with 4,500 mg/L D-glucose; Serox, Germany) supplemented with 10% fetal bovine serum (FBS; Sigma, F7524, Brazil) and 1% L-glutamine (Sigma, G7513, Brazil) in a humidified incubator at 37°C in an atmosphere of 5% CO_2.

Upon thawing from cryovials, the cells were seeded into culture flasks and subcultured every 2–3 days when they reached approximately 80–90% confluence. Cells reaching adequate confluence were detached using trypsin-EDTA (Serox, Germany), collected by centrifugation, resuspended in fresh culture medium, and seeded into 96-well plates suitable for experimental assays.

Cytotoxic Activity

Cells were seeded into sterile 96-well plates at a density of 5×10^3 cells/well and incubated for 24 h to allow adherence. Subsequently, the culture medium in each well was discarded, and the cells were treated with compound **4** at varying concentrations (12.5, 25, 50, 100, 200 and 500 µM). The 96-well plates were then incubated for 24 and 48 h. Following the incubation period, the medium was carefully aspirated, and 50 µL of MTT stock solution (5 mg/mL; SERVA-298-93-1, Germany) was added to each well. The plates were further incubated for 4 h. At the end of this period, the culture medium was gently removed, and 100 µL of DMSO was added to each well. To dissolve the resulting formazan crystals, the plates were agitated on an orbital shaker for 10 min in the dark. The absorbance values were measured at 590 nm using a microplate spectrophotometer (Thermo Scientific Multiskan GO). Compound **4** was evaluated in quadruplicate biological replicates across three independent experiments. The cell viability of the untreated control group (0 µM compound **4**) was defined as 100% for all incubation periods. Half-maximal inhibitory concentration (IC_{50}) values were calculated using GraphPad Prism version 9.3 (GraphPad Software, La Jolla, CA, USA).

Statistical analysis

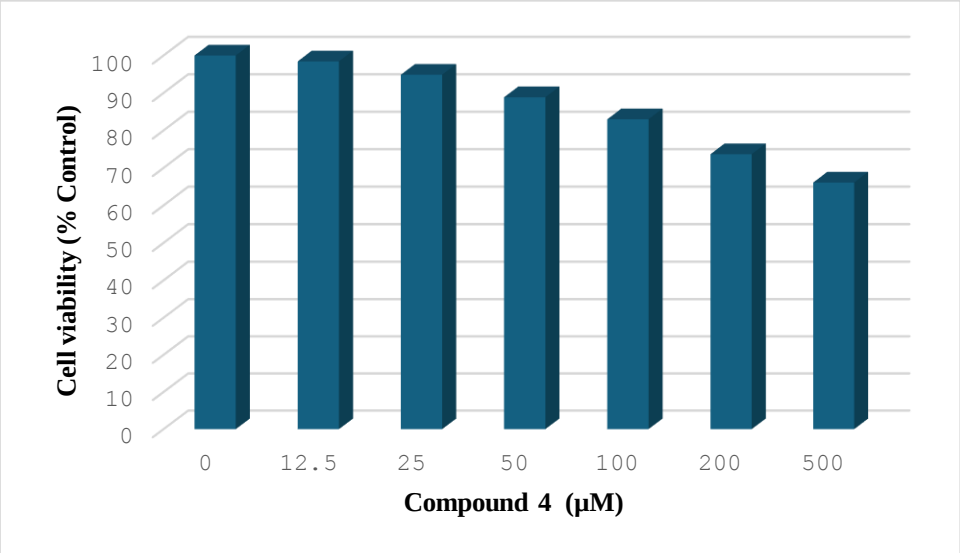
Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0. In descriptive analyses, mean and standard deviation values were utilized for variables exhibiting both normal and non-normal distributions. The conformity of continuous variables to a normal distribution was evaluated visually using histograms and probability plots, and analytically using the Kolmogorov–Smirnov and Shapiro–Wilk tests, stratified by both overall and categorical parameters. Descriptive statistics were presented as mean ± standard error (SE) values.

To investigate the effects of compound treatment on the cells, one-way analysis of variance (ANOVA) was performed to determine whether differences among parameters were statistically significant. Homogeneity of variances was assessed using Levene's test. When significant differences were detected among groups via ANOVA, Tukey's *post-hoc* test was applied for multiple comparisons. The threshold for statistical significance was defined as $p < 0.05$.

RESULT

SA cell viability graph was generated using the results of the MTT assay obtained following the treatment of MCF-7 cells with compound **4** at concentrations ranging from 12.5 to 500 µM for 24 and 48 hours of incubation (Figure 2).

A.



B.

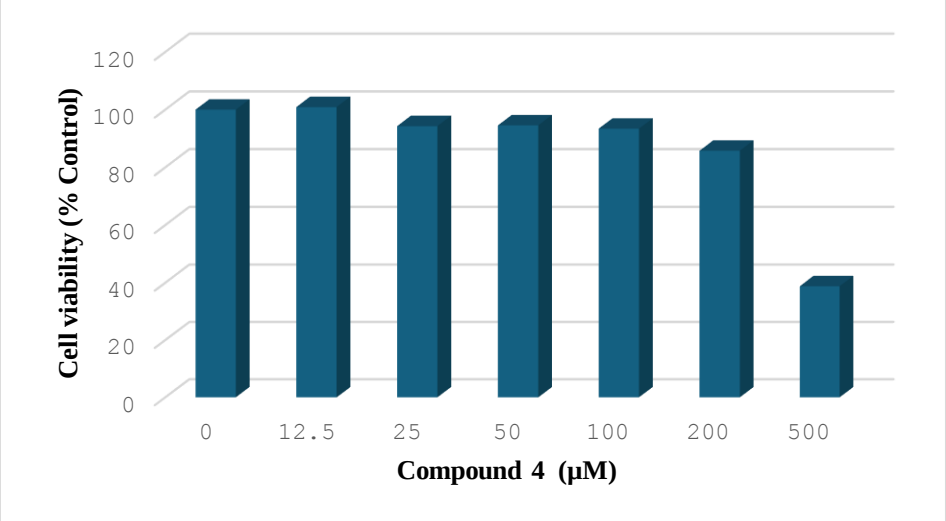


Figure 2. Time-dependent effects of compound **4** on MCF-7 cell viability. (A) Cell viability after 24 h treatment (%); (B) Cell viability after 48 h treatment (%).

Table 1. Effect of compound 4 on MCF-7 cell viability according to dose and treatment duration.

Compound 4 Concentration (µM)	**24 hours** ***% Viability*** $\overline{X} \pm S_{\bar{x}}$	***Significance (p)***	**48 hours** ***% Viability*** $\overline{X} \pm S_{\bar{x}}$	***Significance (p)***
Control	100,00±1,15[a]		100,00±1,00[a]	
12,5	98,43±1,28[a]	*p*>0,05	100,80±1,84[a]	*p*>0,05
25	94,85±1,21[a,b]	*p*>0,05	94,29±0,26[a,b]	*p*>0,05
50	88,86±1,38[b.c]	***	94,56±1,16[a,b]	*p*>0,05

100	82,98±1,89[c]	***	91,22±0,57[b,c]	*
200	73,65±0,76[d]	***	85,77±1,22[c]	***
500	66,10±1,36[e]	***	38,78±4,02[d]	***

Averages bearing different superscript letters within the same column are statistically significantly different (According to control group; *0,01 ≤ p < 0.05; ***p < 0.001).

In this study, compound 4, a benzimidazolium salt derivative, was synthesized, and its cytotoxic and antiproliferative effects on the MCF-7 human breast adenocarcinoma cell line were evaluated *in vitro* across 24- and 48-hour incubation periods (Figure 1).

The obtained MTT assay findings revealed that compound 4 exhibited a marked dose- and time-dependent inhibition of MCF-7 cell viability. During the 24-hour incubation period, lower concentrations (12.5 µM and 25 µM) showed no statistically significant cytotoxicity compared to the control group (p > 0.05); however, a prominent and statistically significant decrease in cell viability was detected at concentrations of 50 µM and above (p < 0.001). When the incubation duration was extended to 48 hours, the antiproliferative effect of compound 4 accelerated, particularly at higher concentrations. In the 48-hour treatment group, viability progressively decreased starting from the 100 µM dose, triggering a profound cytotoxic response. Remarkably, the further reduction at 48 hours compared to the viability observed at 24 hours for the 500 µM concentration indicates that the compound induces cumulative and irreversible cytotoxic damage in the cells (Table 1).

CONCLUSIONS

Breast cancer exhibits the highest incidence among women globally and represents one of the leading causes of cancer-related mortality.[6] The systemic toxicity, adverse effects on healthy tissues, and emergence of multidrug resistance associated with current chemotherapeutic agents necessitate the development of novel small-molecule anticancer agents endowed with enhanced selectivity and unique mechanisms of action.[1,2] In this context, the benzimidazole ring system, defined as a "privileged scaffold" in medicinal chemistry, has gained prominent attention in anticancer research due to the pronounced effects of its derivatives on cell cycle arrest, apoptosis induction, and the modulation of various signal transduction pathways.[10,14,15] It has been demonstrated that structural modifications—particularly the incorporation of lipophilic and aromatic substituents—can enhance the biological activity of benzimidazole derivatives and strengthen their interactions with cellular targets.[14] It is plausible that the aromatic hydrophobic groups and the benzonitrile moiety present in the structure of compound **4** contributed to the observed cytotoxic activity.

The Tukey HSD multiple comparison results obtained in this study align with these literature data and confirm that compound **4** potently suppresses proliferation in MCF-7 breast cancer cells.

In conclusion, the newly synthesized benzimidazole derivative, compound **4**, exhibited potent dose- and time-dependent cytotoxic and antiproliferative activity against MCF-7 human breast cancer cells. The significant reductions in cell viability observed at 24 and 48 hours of treatment indicate that this molecule merits further cellular and molecular investigation as a potential candidate therapeutic agent or lead compound for breast cancer therapy.

Conflict of Interest

The authors have no conflict of interest to declare.

Acknowledgments

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NON-CODING RNA NETWORKS AND MOLECULAR SIGNALING PATHWAYS IN THE DEVELOPMENT OF CASTRATION-RESISTANT PROSTATE CANCER PROGRESSION

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ÖZET
Kastrasyon dirençli prostat kanseri (KDPK), androjen yoksunluğu tedavisine (ADT) rağmen tümör hücrelerinin proliferasyonunu sürdürebildiği ileri evre prostat kanseridir. Klinik olarak prostat spesifik antijen (PSA) değerinde yükselme, lokal nüks ve uzak metastaz ile karakterize olup tedavi yönetimi açısından önemli bir klinik sorun oluşturmaktadır. Bu derleme çalışması kapsamında, KDPK patogenezinin ilerlemesinde ve gelişiminde kritik roller üstlendiği bilinen mikroRNA (miRNA), uzun non-coding RNA (lncRNA) ve dairesel RNA (circRNA) gibi temel non-coding RNA (ncRNA) sınıflarının hücre içerisinde oluşturduğu çok katmanlı düzenleyici ağlar kapsamlı bir şekilde ele alınmıştır. Söz konusu ncRNA ağlarının; başta Androjen Reseptörü (AR) ve bunun yapısal olarak sürekli aktif olan varyantı AR-V7 olmak üzere, Wnt/β-katenin, PI3K/AKT ve EGFR/RAS/MAPK gibi temel onkojenik sinyal yolaklarını moleküler düzeyde nasıl modüle edebildiği detaylandırılmıştır. Bu hücresel etkileşimlerin, yarışan endojen RNA (ceRNA) tabanlı olası "süngerleme" mekanizmaları üzerinden yeni nesil antiandrojenler ve taksan temelli kemoterapilere karşı tedavi direncini tetikleyebileceği moleküler boyutta tartışılmıştır. Ayrıca, mevcut çalışmaların bu ncRNA ağlarının epitelyal-mezankimal geçiş (EMT) ve invaziv metastatik süreçleri düzenleyebildiğini gösterdiği vurgulanmıştır. Sonuç olarak, KDPK'de ncRNA aracılı moleküler ağların bütüncül olarak anlaşılması, hastalığın biyolojisinin aydınlatılmasının yanı sıra tedavi direncini hedefleyen yeni terapötik yaklaşımların geliştirilmesine temel oluşturabilir.
Anahtar Kelimeler: Kastrasyon Dirençli Prostat Kanseri, non-coding RNA, Sinyal Yolakları, AR-V7, Tedavi Direnci, ceRNA Mekanizması.

ABSTRACT
Castration-resistant prostate cancer (CRPC) is an advanced-stage prostate cancer in which tumor cells maintain proliferation despite androgen deprivation therapy (ADT). Clinically characterized by rising prostate-specific antigen (PSA) levels, local recurrence, and distant metastasis, CRPC poses a significant clinical challenge in terms of treatment strategies. Within the scope of this review, the intracellular multilayered regulatory networks formed by key non-coding RNA (ncRNA) classes such as microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) that play critical roles in the development and progression of CRPC pathogenesis are comprehensively discussed. It is detailed how these ncRNA networks may modulate key oncogenic signaling pathways at the molecular level, primarily the androgen receptor (AR) and its constitutively active variant AR-V7, as well as Wnt/β-catenin, PI3K/AKT, and EGFR/RAS/MAPK. The molecular mechanisms through which these cellular interactions may trigger the development of treatment resistance against next-generation antiandrogens and taxane-based chemotherapies via competing endogenous RNA (ceRNA)-based putative 'sponging' mechanisms are discussed. Furthermore, current studies demonstrate that these ncRNA networks can regulate epithelial-mesenchymal transition (EMT) and invasive metastatic processes. Consequently, a holistic understanding of ncRNA-mediated molecular networks in CRPC may not only elucidate the underlying biology of the disease but also provide a basis for the development of novel therapeutic approaches targeting treatment resistance.
Keywords: Castration-Resistant Prostate Cancer, non-coding RNA, Signalling Pathways, AR-V7, Treatment Resistance, ceRNA Mechanism.

Introduction

Globally, prostate cancer (PCa) is the second most prevalent cancer among men and represents a major cause of cancer-related mortality, particularly when the disease progresses to CRPC (Huang et al., 2018). ADT is widely used in advanced PCa to limit tumor growth by reducing circulating androgen availability (Harris et al., 2009; Wadosky & Koochekpour, 2016). Despite an initial therapeutic response, prostate tumor cells may adapt to androgen-depleted conditions and regain proliferative capacity, resulting in increasing prostate-specific antigen (PSA) levels and, in some cases, metastatic disease (Karantanos et al., 2013; Martínez-Breijo et al., 2018).

The emergence of CRPC from androgen-dependent PCa is driven by a range of genomic, transcriptomic, and epigenetic alterations. Although changes affecting protein-coding genes, such as AR amplification and mutation, have been extensively characterized, the non-coding transcriptome also plays an important role in cellular adaptation to androgen deprivation. In particular, long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) participate in the regulation of androgen receptor (AR) signaling as well as alternative pathways that promote tumor cell survival under androgen-depleted conditions (Altschuler et al., 2021; Mao et al., 2022). These ncRNA-mediated regulatory mechanisms can preserve AR signaling, promote the production of AR splice variants such as AR-V7, and establish competing endogenous RNA (ceRNA) networks, ultimately contributing to therapeutic resistance and CRPC progression.

In prostate cancer, non-coding RNAs modulate androgen receptor signaling through different regulatory mechanisms, such as post-transcriptional repression, chromatin remodeling, and direct protein binding. These interactions can influence castration resistance, androgen dependency, and therapeutic responses, potentially providing opportunities for the development of novel therapeutic strategies and future clinical applications.

Literature Search and Selection Strategy

To ensure a rigorous and transparent synthesis of the literature regarding ncRNA networks in CRPC, a systematic search strategy was conducted across major electronic databases, including PubMed/MEDLINE, Web of Science, and Scopus. The search terms combined keywords such as "castration-resistant prostate cancer", "CRPC", "non-coding RNA", "lncRNA", "miRNA", "circRNA", "AR-V7", "ceRNA network", and "therapeutic resistance". Original research articles and comprehensive reviews focusing on molecular mechanisms, signaling pathways (Wnt, PI3K/AKT, EGFR/RAS/MAPK), and drug resistance were included, while conference abstracts and non-English articles were excluded to maintain scholarly integrity.

1. Baseline Post-Transcriptional Regulation by microRNAs in Prostate Models

MicroRNAs (miRNAs) can suppress androgen receptor (AR) expression at the post-transcriptional level by recognizing specific sequences within the 3′-UTR of AR mRNA, thereby reducing protein translation and promoting mRNA degradation (Östling et al., 2011; Sikand et al., 2011). The expression of miR-34a is negatively associated with AR protein levels in prostate cancer. Data obtained from clinical prostate cancer samples indicate that miR-34a may function as a tumor suppressor by inhibiting androgen-dependent cell growth (Östling et al., 2011). Another example is miR-185, which has been shown to suppress AR protein expression and inhibit androgen-induced proliferation in prostate cancer models, as identified through gain-of-function analysis (Östling et al., 2011).

2. Transcriptional and Epigenetic Regulation by lncRNAs in CRPC

Non-coding RNAs can influence AR transcription through epigenetic mechanisms, with lncRNAs affecting AR expression by interacting with promoter regions and recruiting chromatin-modifying enzymes.

- **NXTAR:** NXTAR is located in a convergent orientation with the AR gene and is known to function as a tumor suppressor (Ghildiyal et al., 2022). Through its interaction with the region upstream of the AR promoter, NXTAR facilitates the recruitment of EZH2, a histone methyltransferase involved in epigenetic regulation. After EZH2 recruitment, AR and AR-V7 levels are reduced through epigenetic silencing. As a result, AR can bind to the NXTAR promoter (Ghildiyal et al., 2022). However, the small molecule (R)-9b prevents AR from binding to this site, leading to increased NXTAR expression. This creates a feedback loop in which NXTAR suppresses AR levels and helps overcome enzalutamide resistance in cancer cells (Ghildiyal et al., 2022).

- **HOTAIR:** HOTAIR is an androgen-repressed lncRNA that contributes to the regulation of AR signaling in CRPC. Through its interaction with Polycomb Repressive Complex 2 (PRC2), HOTAIR can promote epigenetic repression of AR transcription by facilitating PRC2 recruitment to the AR promoter (Li et al., 2015; Shih et al., 2015). In addition, HOTAIR has been shown to enhance AR stability by interfering with MDM2-mediated degradation, thereby sustaining AR activity under androgen-depleted conditions (Zhang et al., 2015).

3. Competing Endogenous RNA (ceRNA) Sponging Hubs and Drug Resistance Axes

3.1. Antiandrogen Resistance: AR-V7 and Metabolic Axes

In prostate cancer, SNHG4 contributes to cell survival and reduced sensitivity to enzalutamide by regulating the let-7a/RREB1 pathway in association with a putative ceRNA network (Dong et al., 2023). SNHG4 interacts with let-7a miRNA to induce RRM2 expression levels and trigger a feedback loop with RREB1. Elevated RRM2 expression enhances prostate cancer cell survival, thereby contributing to enzalutamide resistance (Dong et al., 2023).

Additionally, the oncogenic lncRNA DANCR has been proposed to function as a ceRNA node by interacting with miR-34a-5p, thereby modulating post-transcriptional regulation on downstream targets to sustain high AR-V7 expression and drive enzalutamide insensitivity (Ma et al., 2019).

3.2. Chemotherapy Resistance

NEAT1, as a lncRNA, induces RET expression by interacting with miR-34a, thereby contributing to docetaxel resistance (Tian et al., 2017). Upregulation of JAG1 in prostate cancer cells induces stem-like properties by activating the Notch signaling pathway, leading to docetaxel resistance (Arabpour & Rezaei, 2025; Ma et al., 2019; Qin et al., 2020). Also, the circular RNA hsa_circ_0000735 interacts with miR-7, thereby reducing docetaxel sensitivity in prostate cancer cells. Conversely, downregulation of hsa_circ_0000735 triggers apoptosis and overcomes docetaxel resistance (Gao et al., 2020).

Furthermore, aberrant activation of alternative oncogenic pathways, including PI3K/AKT/mTOR and NF-κB, acts in synergy with ncRNA networks to drive therapeutic resistance (Uo et al., 2020). For instance, regulatory molecules such as circRNF19A and miR-21 help support AR-V7 expression and fuel enzalutamid resistance (Chukhu et al., 2025; Yu et al., 2019). Meanwhile, lncRNA-mediated modulation of growth factor receptors enhances downstream survival cascades, protecting CRPC cells from chemotherapy-induced apoptosis (Altschuler et al., 2021).

3.3. Expanded Circular RNA (circRNA) Dynamics and Tumor Plasticity

Circular RNAs (circRNAs) represent a highly stable class of transcripts that lack 5' caps and 3' poly(A) tails, making them resistant to exonucleolytic degradation. In CRPC, circRNAs such as circSLC39A10 promote tumor progression by activating Wnt/β-catenin signaling through the miR-936/PROX1 axis (Chen et al., 2025). Similarly, circRNAs modulate cellular plasticity by acting as robust molecular scaffolds and interaction hubs.

3.4. Immune Escape and Stemness Mechanisms

AR activation in response to high androgen levels boosts circFKBP5 expression (Tang et al., 2022). circFKBP5 upregulates programmed death-ligand 1 (PD-L1) expression by interacting with miR-513a-5p (Tang et al., 2022). This mechanism allows tumor cells to evade immune surveillance by suppressing NK cell cytotoxicity (Tang et al., 2022). Regulation of PD-L1 through this mechanism is key to immune resistance in prostate cancer progression (Tang et al., 2022).

Similarly, KCNQ1OT1 increases PD-L1 expression by targeting miR-15a, thereby inhibiting the antitumor activity of CD8+ T cells (Chen et al., 2020). This axis activates Ras/ERK signaling and supports malignant progression and epithelial–mesenchymal transition (EMT) (Chen et al., 2020).

Furthermore, ncRNAs modulate stemness and signaling cascades:

- The oncogenic activity of miR-1301-3p is associated with the suppression of Wnt inhibitors GSK3β and SFRP1, which facilitates β-catenin translocation into the nucleus and enhances SOX2 and OCT4 expression (Song et al., 2018).
- miR-320 is a tumor-suppressor miRNA that suppresses CD44 and β-catenin under normal conditions (Hsieh et al., 2013). Loss of miR-320 leads to increased CD44 expression and the acquisition of stemness in CRPC (Hsieh et al., 2013).

- LEF1-AS1 sustains Wnt signaling and CD44 expression by interacting with miR-328 and enhancing FZD2 expression (Li et al., 2020).
- circSLC39A10 induces self-renewal by activating the Wnt/β-catenin pathway through the miR-936/PROX1 axis (Chen et al., 2025).

Table 1: Summary Table of Key ncRNAs and Molecular Axes in CRPC.

ncRNA Class	Specific Transcript	Interacting miRNA / Target	Associated Pathway / Mechanism	Clinical / Therapeutic Implication	References
lncRNA	NXTAR	EZH2 / AR promoter	Epigenetic silencing of AR / AR-V7	Overcomes enzalutamide resistance	Ghildiyal et al., 2022
lncRNA	HOTAIR	PRC2 / MDM2	AR transcriptional repression & stability	CRPC progression & AR signaling maintenance	Li et al., 2015; Zhang et al., 2015
lncRNA	SNHG4	let-7a / RREB1 / RRM2	Positive feedback loop / cell survival	Enzalutamide resistance	Dong et al., 2023
lncRNA	DANCR	miR-34a-5p / JAG1 / AR-V7	ceRNA network / AR-V7 maintenance	Docetaxel & antiandrogen resistance	Ma et al., 2019
lncRNA	NEAT1	miR-34a / RET	Growth factor receptor activation	Docetaxel resistance	Tian et al., 2017
circRNA	hsa_circ_0000735	miR-7	Apoptosis evasion	Docetaxel sensitivity reduction	Gao et al., 2020
circRNA	circFKBP5	miR-513a-5p / PD-L1	Immune evasion / NK cell suppression	Immune resistance	Tang et al., 2022
circRNA	circSLC39A10	miR-936 / PROX1	Wnt/β-catenin pathway activation	Tumor progression & self-renewal	Chen et al., 2025

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THE ATMOSPHERIC PRESENCE OF ASPERGILLUS FUMIGATUS, A WHO PRIORITY PATHOGEN IN CHENNAI, INDIA: HISTORICAL EVIDENCE FROM 1996-1998

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ABSTRACT
The fungus, *Aspergillus fumigatus* is declared as a priority fungal pathogen by World Health Organization (WHO). The fungus is the causal agent of Abstructive Broncho Pulmonary Aspergillosis (ABPA) and Aspergilloma. Further, the fungus is possessing capability to grow at wide temperature starting from 20°C to 55°C thus termed as thermotolerant fungus making the human body temperature suitable for the fungus to grow as at optimum temperature. The spore size of the fungus (1-3µm diameter), play an advantageous role in penetrating the deeper lung whenever the subjects are exposed to the fungal spores. Thus, any study reporting the presence of *Aspergillus fumigatus* is significant medically in maintaining public health. The report presented here produces the historical evidence of the presence of *Aspergillus fumigatus* in the atmosphere of Chennai from the period of October 1996 to September 1998. The prevalence of the fungus was studied in different parts of Chennai using Andersen 2-Stage sampler (USA). The study was conducted at 9 different locations (Broadway, Royapuram, Kilpauk, Basin Bridge, Mylapore, Guindy, Chrompet, Taramani and Perungudi) of Chennai at 10 days' interval missing few samples due to flooding happened in Chennai during the study period. A total of 549 samplings were conducted which yielded around 1610 colonies with a total CFU of 11366 CFU/m^3 averaging around 20.7 CFU/m^3 of air. The study provides a baseline and historical evidence of the presence of *Aspergillus fumigatus* a priority fungal pathogen of WHO. The study emphasises the need of conducting similar study during current period to learn the existence, and the difference in atmospheric presence of *Aspergillus fumigatus.* Further their thermotolerant nature need to be probed. Apart from this the antimycotic resistance by the fungi need to be given importance in further studies.
Keywords: *Aspergillus fumigatus*, ABPA, Airborne, Atmosphere, Chennai, Priority pathogenic fungus, WHO

INTRODUCTION
Aspergillus, the fungus is a causative organism of the disease Aspergillosis. The disease, Aspergillosis is caused by many species of *Aspergillus* among which the species like *Aspergillus niger, Aspergillus fumigatus* as pathogens, *Aspergillus flavus, Aspergillus oryzae, Aspergillus ochraceous* as toxigenic fungi and all other species in general are fund to be allergenic in nature depending on the immune system of the individual exposed. These fungi are generally found in spoiled organic material and come in contact with human subjects as contactants, ingestants and inhalants. The exposure to fungi as contactant and ingestant are easily avoidable. However, the airborne fungi present in the atmosphere cannot be avoided as they serve as an inhalant. *Aspergillus* is one among the fungal genera which are found abundant in the atmosphere as they are easily airborne due to the shape and size of their spores. Among the species of *Aspergillus, Aspergillus fumigatus* is the species which is widely reported as a causal organism of Aspergillosis (Carlos et al., 2026).
The fungus, *Aspergillus fumigatus* grows as velvety, white spreading colony turning to smokey, greenish grey colored due to the formation of spores. Reverse of the colony generally white, septate, uniform, branching hyphae. Conidiophores smooth walled, flask shaped with clavate vesicle (20-30µm), uniseriate, conidiospores, smooth, spherical with 2.5-3.5µm in diameter (Raper and Fennell, 1963).
The fungus, *Aspergillus fumigatus* is declared as a priority fungal pathogen by World Health Organization (WHO). The fungus is the causal agent of Abstructive Broncho Pulmonary Aspergillosis (ABPA) and Aspergilloma. Further, the fungus is possessing capability to grow at wide temperature starting from 20°C to 55°C thus termed as thermotolerant fungus making the human body temperature suitable for the fungus to grow at optimum temperature. The spore size of the fungus, play an

advantageous role in penetrating the deeper lung whenever the subjects are exposed to the fungal spores. Thus, any study reporting the presence of *Aspergillus fumigatus* is significant medically in maintaining public health. The report presented here produces the historical evidence of the presence of *Aspergillus fumigatus* in the atmosphere of Chennai from the period of October 1996 to September 1998.

MATERIALS AND METHODS

Air sampling sites: Chennai was previously called as Madras which was renamed as Chennai during the study period. The city was with the spread over area of 172 sq.km and was with the population of around 5.5 million during the study period. However, currently the city was expanded to 5900 sq.km with the estimated population of around 15 million. The city experience the climatic conditions as North East Monsoon (October –November), Winter (December – January), Hot weather (March – May) and South West Monsoon (June – September). The overlapping of climatic chances are more in Chennai. The air samples were carried in Broadway, Basin Bridge and Parrys Corner in North of Chennai, Kilpauk, Guindy and Mylapore in Central part of Chennai and Taramani, Chrompet and Perungudi in Southern part of Chennai.

Study period

The air sampling was carried from the period of October 1996 to September 1998 at 10 days interval. Few of the sampling are missed due to rainy weather or due to flood. Nearly 11 such samples were skipped resulting in 61 samples in each area totalling around 549 samples in Chennai. The study was conducted historically before 3 decades.

Air sampling method

Air sampling was carried using Andersen 2-stage viable particle sampler (Graseby Andersen, Georgia, USA). The sampler consists of 2 different stages with orifice of 200 arranged radially. The diameter of the orifice of the first stage was 1.5mm and the second stage was 0.4mm. The sampler was operated using a vacuum pump with the suction rate of 28.3L of air per minute. The sampling pump was operated using 12V battery.

Isolation of fungi

The airborne fungi were isolated using Sabouraud's Dextrose Agar (Peptone 10g, Dextrose 4g, Agar 20g, distilled water of 1L, Himedia Inc. Bombay, India). The petridishes containing SDA are exposed in 2 different stage of the sampler. After exposure the plates were brought to the laboratory and incubated at 28±2°C. The developing fungal colonies were recorded among which the count for *Aspergillus fumigatus* was maintained separately after reading their colony morphology, macroscopic appearance and microscopic features.

Presentation of Data:

$$\textbf{Total average CFU/m}^3\textbf{ of air} = \frac{\text{Conversion factor x No. of colonies}}{\text{No. of samplings}}$$

Where conversion factor = 1000 / Total volume of air sampled, i.e. 1000/141.5 = 7.06

$$\textbf{Percent occurrence} = \frac{\text{No. of samples where } \textit{Aspergillus fumigatus} \text{ was isolated}}{\text{Total number of samples studied (61)}} \times 100$$

RESULTS

A total of 549 samplings were conducted which yielded around 1610 colonies with a total CFU of 11366 CFU/m^3 averaging around 20.7 CFU/m^3 of air in Chennai during the period of October 1996 – September 1998. The total CFU/m^3 of air recorded was highest in Perungudi environment and the least was recorded in Taramani. An average CFU/m3 of air recorded was 46.06 CFU/m3 of air in Perungudi followed by Kilpauk with an average of 21.99 CFU/m3 and Chrompet with 21.87 CFU/m3 of air on an

average. The site, Taramani in Chennai recorded only 13.07 CFU/m3 of air which is least among the sites studied. The average cfu/m3 of air recorded for the fungus, *Aspergillus fumigatus* during the period of October 1996 and September 1998 in different sites of Chennai is presented in Fig. 1.

The presence of fungi in number of samplings studied shows its prevalence in the atmosphere. The study reveals that the fungus, *Aspergillus fumigatus* was present in 73.77 percent of samplings followed by Parrys corner (65.57 %) and Chrompet (50.81%). The fungus was recorded in least number of samplings in th sampling site Guindy (39.34%). The total CFU rcorded in each sampling site and percent occurrence of the fungus, *Aspergillus fumigatus* in different sampling sites of Chennai is presented in Table 1.

As the study was conducted using Andersen 2-stage viable sampler, the Respirable Fraction of the fungus can be easily calculated, i.e. the fungal colonies recorded in 2nd stage of the sampler reveals the respirable fraction of the fungus, *Aspergillus fumigatus.* The study revealed that nearly 73 % of the fungus was classified under respirable fraction in Chrompet followed by Basin bridge with 71.86%. The least number of the fungus was recorded as respirable fraction in the sampling site Taramani (46.6%). The respirable fraction of the fungus, *Aspergillus fumigatus* recorded in different sampling sites of Chennai during October 1996 to September 1998 is presented in Fig. 2.

The seasonal variation of the fungus was recorded for every month of the study period. The average cfu/m3 of air recorded for the fungus, *Aspergillus fumigatus* was studied which revealed that there is no typical month which favours the fungal growth. The peak was registered during October 1996 for the sampling site Broadway, March 1998 in Parrys corner, May 1998 for Basin bridge, March 1997 in Kilpauk, July 1997 in Mylapore, January 1998 in Guindy, February 1998 in Taramani, March 1998 in Perungudi and May 1997 in Chrompet. The seasonal distribution of the fungus, *Aspergillus fumigatus* in the atmosphere of Chennai in different sampling sites during the period of October 1996 to September 1998 is presented in Fig. 3.

DISCUSSION

Aspergillus fumigatus is the fungus which is present wherever organic materials are available. Their atmospheric presence is due to their advantage of the spore size and shape which gives them the better buoyancy to suspend in air for a longer time. They are also carried to longer distance in the atmosphere depending upon the weather parameters like temperature, humidity and wind. Their sustainability in wide temperature range is the other advantage for the organism. Although, they are present in significant number, it is not sure whether they are capable of inducing disease. But, this cannot be completely ruled out as they are widely reported as pathogen in Invasive Aspergillosis (Castro-Fuentes et al., 2025).

The study revealed their presence in almost all the environments studied in Chennai, The study is 2 year long study conducted at the interval of 10 days provide a better data in the presense and the prevalence of the fungus significantly. The fungus is recorded almost all the continents of the world and Peninsular India is no exception to this. In India, the study provides the historical evidence of the atmospheric distribution of the fungus, *Aspergillus fumigatus* in Chennai almost 3 decades back. The study revealed that the fungus is widely prevalent in the study sites within Chennai. The fungus was found to occur almost half of the samplings conducted revealing their presence in more than 50% of the sampling conducted. The presene of the fungus *Aspergillus fumigatus* was recorded in 279 samples out of 549 samples recording 50.82% as its prevalence.

The fungus was dominantly recorded in the subjects reporting Chronic Obstructive Pulmonary Disease (COPD) (Out et al., 2023), Allergic Broncho Pulmonary Aspergillosis (ABPA) (Olum et al., 2021), immune compromised patients in Intensive Care Unit, Aged people with weak immune system (Ao et al., 2023), patients with lung cancer (Katada et al., 2022), HIV (Truda et al., 2023) and currently the patient infected with COVID-19 (Gaoia et al., 2024). Thus, it is utmost important to know the presence of the fungus in any environment so as to avoid the exposure.

The thermophilic nature of the fungus *Aspergillus fumigatus* and recording the thermophilous strain of *Aspergillus fumigatus* as the dominant fungus in the atmosphere of Chennai was reported by our earlier studies (Prakash and Vittal 2003; Udayaprakash and Vittal, 2010; Udayaprakash and Vittal, 2005; Srinivasan et al., 2005; Prakash et al., 2011 and Kannaian and Ranga 2005). Thus in studying the prevalence of *Aspergilus fumigatus*, probing the thermophilic nature of the fungus is highlighted by the present study. Nowadays due to extensive usage of antibiotics, the resistance to antimycotic agent by the fungus *Aspergillus fumigatus* is increasing. This may also be attributed to the adaptation of the

fungus to wide range of temperature, where the antimycotic agent may not retain its nature in controlling the fungus. The probe towards this angle is recommended.

The study also reveals that there is no seasonal influence on the presence of airborne *Aspergillus fumigatus* emphasizing the need of continuous monitoring of the fungus in order to prevent infection and safeguard the general public.

The study provides a baseline and historical evidence of the presence of Airborne *Aspergillus fumigatus* during the period of October 1996 to September 1998 which is almost 3 decades before. The study emphasises the need of conducting similar study during current period to learn the existence, and the difference in atmospheric presence of *Aspergillus fumigatus.* A priority pathogen of WHO. Further their thermotolerant nature need to be probed. Apart from this the antimycotic resistance by the fungi need to be given importance in further studies.

CONCLUSION

The study reports the prevalence of the WHO priority pathogen, *Aspergillus fumigatus* in the atmosphere of Chennai almost 3 decades back providing historical evidence. Nearly 9 sites of Chennai was continuously monitored for 2 year period at the interval of 10 days. A total of 549 samplings were conducted which yielded around 1610 colonies with a total CFU of 11366 CFU/m^3 averaging around 20.7 CFU/m^3 of air. There is no seasonal influence on the airborne nature of the fungus *Aspergillus fumigatus.* The study emphasises the need of conducting similar study during current period to learn the existence, and the difference in atmospheric presence of *Aspergillus fumigatus.* A priority pathogen of WHO. Further their thermotolerant nature need to be probed. Apart from this the antimycotic resistance by the fungi need to be given importance in further studies.

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Table 1. List of sampling sites in Chennai, Total CFU recorded and the percent occurrence of *Aspergillus fumigatus* during October 1996 to September 1998

Sl. No.	Sampling site	Total CFU	Percent Occurrence
1	Broadway	988.4	39.34
2	Parrys Corner	1108.4	65.57
3	Basin Bridge	1179.02	44.26
4	Kilpauk	1341.4	49.18
5	Mylapore	981.34	49.18
6	Guindy	826.02	39.34
7	Taramani	797.78	45.9
8	Perungudi	2809.88	73.77
9	Chrompet	1334.34	50.81

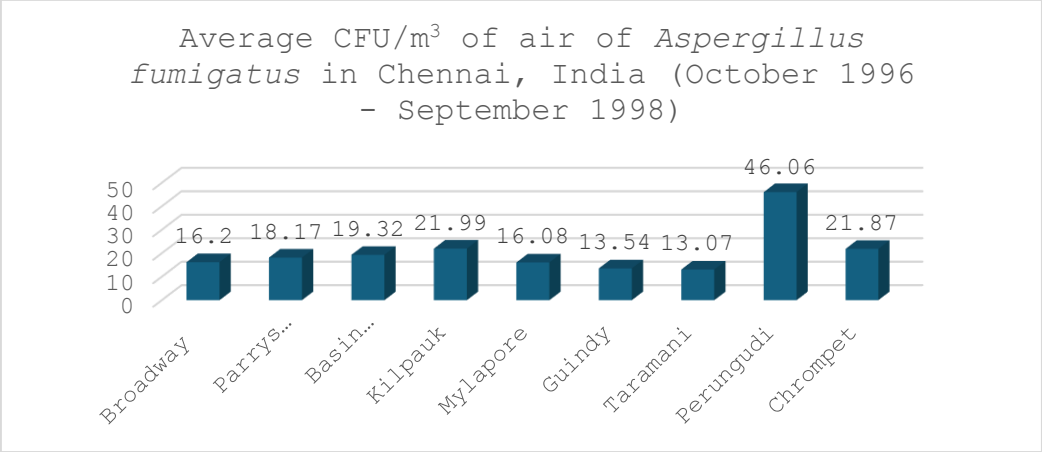


Fig. 1. Average CFU/m3 of air of *Aspergillus fumigatus* in different parts of Chennai

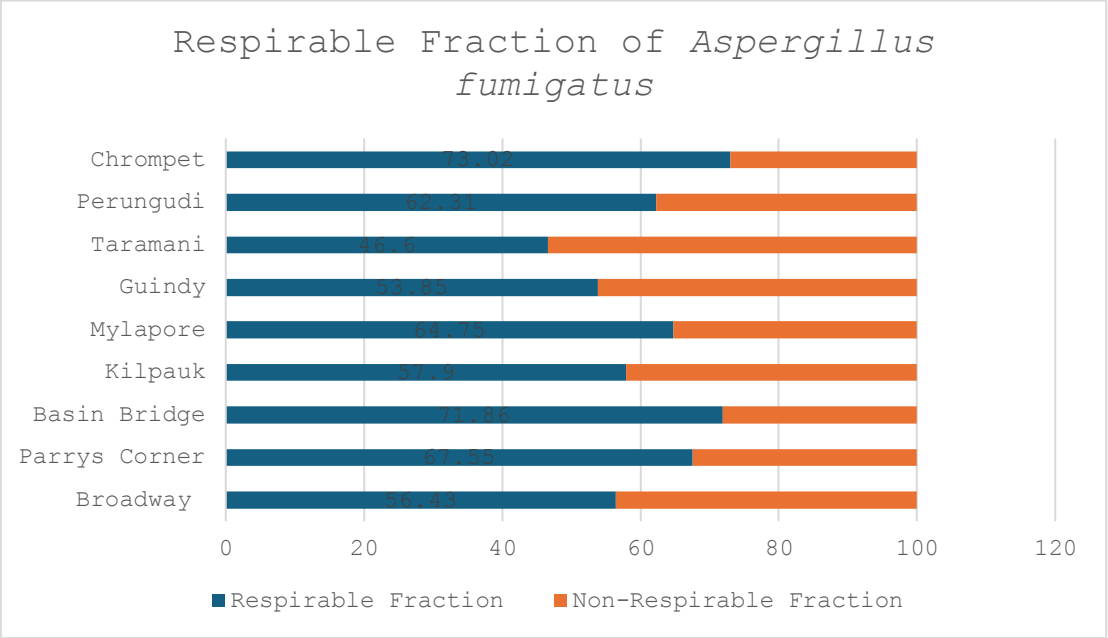


Fig. 2. Respirable fraction recorded for the fungus, *Aspergillus fumigatus* in different sampling sites of Chennai, India

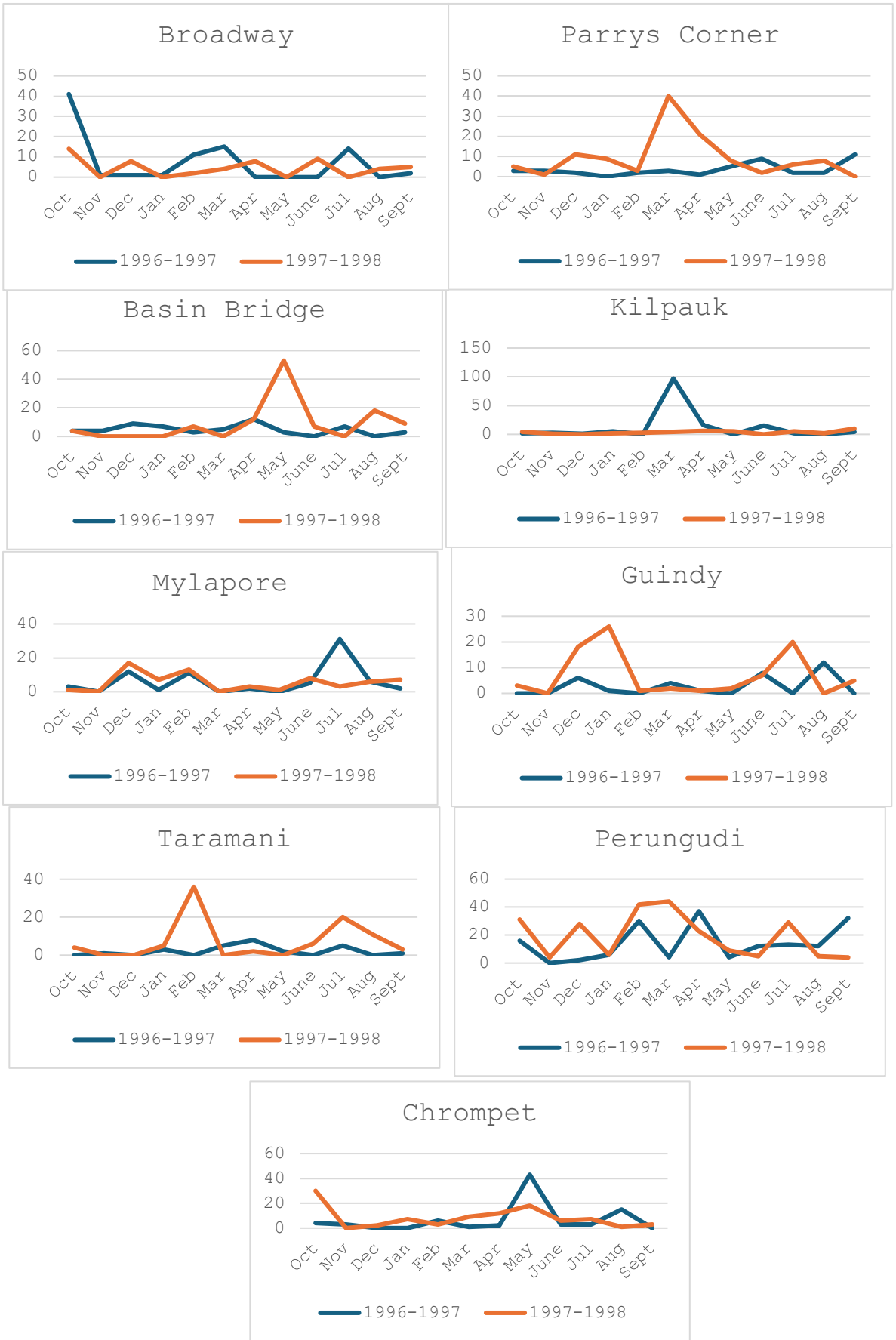


Fig. 3. Seasonal Distribution of the fungus, *Aspergillus fumigatus* in the atmosphere of different sampling sites in Chennai during October 1996 to September 1998.

ADSORPTION OF CRYSTAL VIOLET DYE ONTO THE SOIL OF OUR REGION: CHARACTERISATION, ISOTHERMS, THERMODYNAMICS, KINETICS

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ABSTRACT

Introduction: One of the most significant environmental pollution issues is water pollution.

Objective

In this scientific study, crystal violet dye found in wastewater from the textile industry was adsorbed onto an inexpensive and abundant natural soil material found in our region, in an effort to remove it from the wastewater.

Materials and Methods

The characterisation of our natural soil material, sourced from the Erciş/VAN region, was carried out using SEM, SEM-EDX, FTIR and BET analyses. Our adsorbate, crystal violet dye, was commercially obtained in analytical grade. The physical/chemical adsorption process was carried out at various time intervals, dye concentrations, and temperatures, and the amount of adsorbed dye was measured using a UV viscometer. Equilibrium studies of the adsorption process were conducted to determine the adsorption isotherm at a constant temperature; the thermodynamics of the adsorption process were examined to determine spontaneity, endothermic/exothermic nature, and entropy; and the kinetics of the adsorption process were calculated and examined to measure the rate at which the adsorbate binds to the surface of the solid soil adsorbent and the mechanisms affecting this rate.

Results

SEM imaging revealed a dense cubic/cylindrical structure and a low proportion of octahedral structure. SEM-EDX analysis revealed oxygen and calcium content expected in soil, as well as a C/Si ratio consistent with adsorption. FTIR analysis indicated that adsorption binding occurred via Ca and Si elements. BET surface area analyses, when examined in terms of adsorption/desorption diagrams, revealed a Type 3 adsorption isotherm, whilst the specific surface area and average pore diameter values indicated a mesoporous adsorbent structure. Experimental data from the adsorption equilibrium study determined the adsorption rate to be 77.2% and the q_{max} value to be 97.5% under ambient conditions. The adsorption isotherm was found to follow the Freundlich equation; the thermodynamics of adsorption were endothermic and indicated chemical binding; and the adsorption kinetics were consistent with a second-order (pseudo-second) kinetic model.

Conclusion: Dyes that do not biodegrade in nature are toxic to living organisms, carcinogenic to humans, and toxic to aquatic life. Wastewater treatment is essential.

Keywords: adsorption, soil, crystal violet dye, wastewater

1. INTRODUCTION

Water treatment methods are physical, chemical, biological and advanced treatment processes used to remove toxic substances from water and wastewater. These methods vary depending on the type and degree of water pollution (Anonymous, 2026a).

1. Physical Treatment Methods: Screening and Straining, Sedimentation and Clarification, Sand Filters, Flotation
2. Chemical Treatment Methods: Coagulation and Flocculation, Neutralisation, Chlorination and Ozonation
3. Biological Treatment Methods: Activated Sludge Systems, Aerobic and Anaerobic Treatment
4. Advanced Treatment Methods: Reverse Osmosis, Ultraviolet (UV) Disinfection, Activated Carbon Filtration and adsorption methods are utilised.

1.1 Adsorption

This is the process of purifying water by retaining all substances—such as dyes, heavy metals, pharmaceuticals and waste materials—on a selected adsorbent (binding agent) under appropriate temperature, duration, concentration and pH conditions. The purification process occurs through physical or chemical binding, and, rarely, through ion exchange (Alaqarbeh, 2021).
In the scientific study conducted, crystal violet—one of the dyes used in the textile industry—was adsorbed onto a cheap and abundant natural soil material sourced from the Erciş district of Van province, in an attempt to remove it from the waste water of textile factories.

2. MATERIALS AND METHODS

Calcareous soil (adsorbent) obtained from the Erciş district of Van province was washed 10 times with distilled water for 24 hours each, then dried 10 times at 60 °C for 48 hours each. The particles, which passed through a 100-mesh sieve after being ground in a mortar, were stored in a desiccator for use. Characterisation analyses were carried out at Van YYÜ BAUM using SEM, SEM-EDX, FTIR and BET instruments. Crystal violet (CV) ($C_{25}H_{30}ClN_3$ – C.I. 42555) dye was commercially obtained in analytical grade.

Table 1. Schematic representation of the instruments used for UV-vis spectroscopic measurements and adsorbent characterisation

Technique	Purpose	Instrument
SEM/SEM-EDX	Morphology, composition	Zeiss Gemini Sigma 300
FTIR	Functional groups	Nicolet iS10, ATR, 500–4000 cm^{-1}
BET	Surface area, porosity	Quadrasorb SI, N_2, 77 K
UV	Adsorption quantity	The Thermo Scientific Genesys 10S

Our adsorbent was used at a fixed mass of 0.1 grammes. The adsorption process was carried out in solutions of our adsorbate (KV dye) at concentrations of 10, 20, 30, 40, 50, 60, 70 and 80 ppm, over 15 different time periods and at temperatures of 25, 35 and 50 °C. The stirrer speed was maintained at a constant 400 revolutions per minute. The equilibrium point was determined at a dye concentration of 20 ppm, at room temperature, and an adsorption time of 180 minutes. At the point of equilibrium, a 2 ml sample was taken from the solutions and centrifuged at 2000 revolutions per minute for 3 minutes. Following centrifugation, the samples were measured on a UV spectrophotometer at a wavelength of 590 nm; the concentration of the remaining dye (Ce) in the solution was then determined by performing the necessary calculations. The isothermal, thermodynamic and kinetic data for our adsorption process were calculated and the findings were recorded.

3. FINDINGS:

Crystal violet (CV) is a dark purple cationic dye used in microbiology to classify bacteria and in cell biology to stain proteins and DNA. In chemistry, it is classified as a textile dye (Anonymous, 2026b,c).

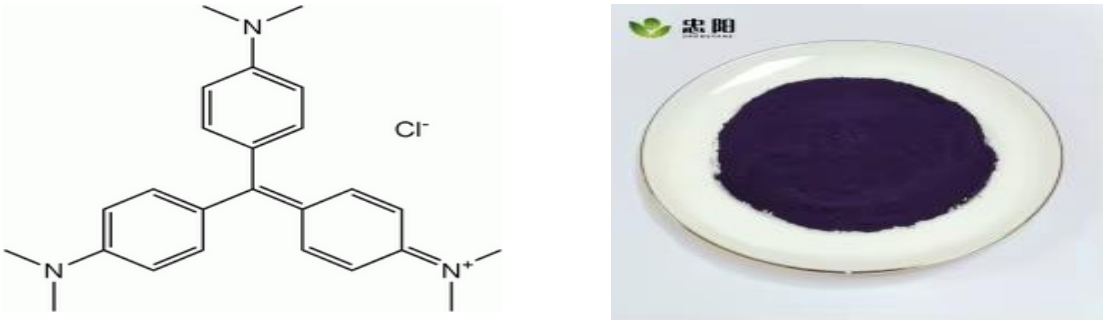


Figure 1. The formula ($C_{25}H_{30}ClN_3$) and structure of crystal violet (Mittal et al., 2010).

3.1 Equilibrium study

Our equilibrium study, which investigated the optimum conditions, revealed that at a temperature of 25 °C, the adsorption percentage of the dye at 20 ppm was 77.2 per cent and the qmax value was 97.5 per cent (Erçetin and Yalçın, 2002; Yagub et al., 2014).

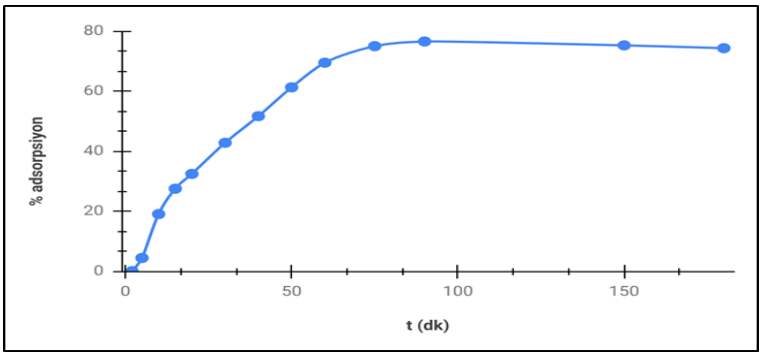
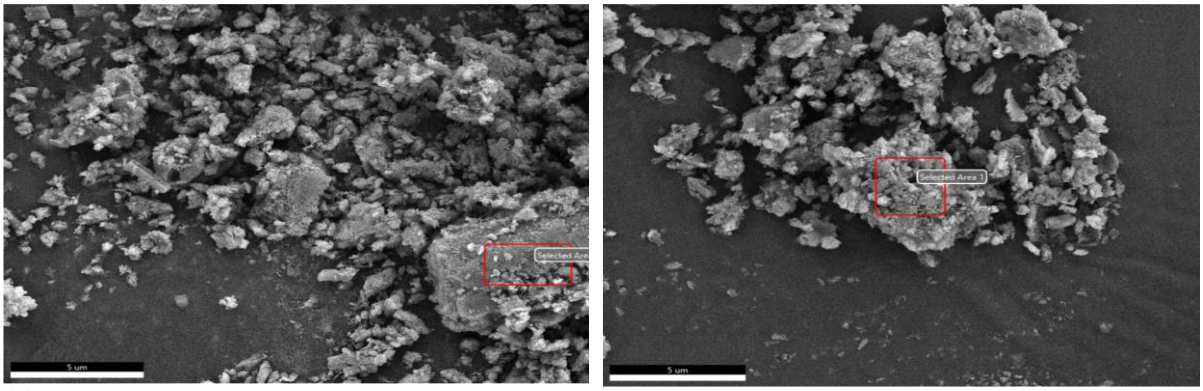


Figure 2. Adsorption plot of crystal violet dye as a function of time (m: 0.1 g, V: 0.05 ml, C_o: 20 ppm, T: 298 K).

3.2 SEM-SEM EDX analysis of adsorbent and adsorbate materials

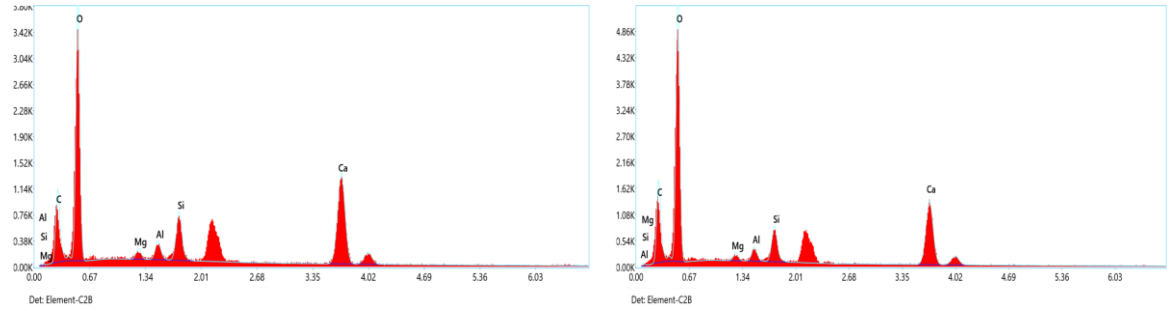
For the SEM-SEM EDX analyses of the soil and painted soil, the samples were left in the oven for 3 days.



(a) (b)

Figure 3. SEM (5 µm) images of our soil (a) and painted soil (b) samples.

SEM analysis revealed a dense cubic/cylindrical particle structure with a minor octahedral fraction; a large surface area, consistent with the BET results (Sen et al., 2024).



(a) (b)

Element	Weight%	Atomic%	Net Int.	Error%	R	A	F
C K	8.16	14.45	155.94	10.68	0.8929	0.3243	1.0000
O K	43.70	58.09	769.30	10.10	0.9066	0.2514	1.0000
MgK	0.95	0.83	38.36	12.99	0.9274	0.6951	1.0064
AlK	1.77	1.39	71.44	9.04	0.9321	0.7887	1.0106
SiK	4.93	3.73	197.72	5.91	0.9366	0.8508	1.0139
CaK	40.49	21.49	495.86	4.21	0.9614	0.9804	1.0103

(a)

Element	Weight %	Atomic %	Net Int.	Error %	R	A	F
C K	10.71	17.74	249.64	9.97	0.8999	0.3339	1.0000
O K	48.59	60.45	1117.72	9.62	0.9130	0.2772	1.0000
MgK	0.88	0.72	41.92	12.86	0.9329	0.6978	1.0059
AlK	1.60	1.18	76.89	8.87	0.9373	0.7916	1.0098
SiK	4.35	3.08	206.91	5.86	0.9415	0.8538	1.0128
CaK	33.88	16.82	491.71	4.28	0.9648	0.9815	1.0110

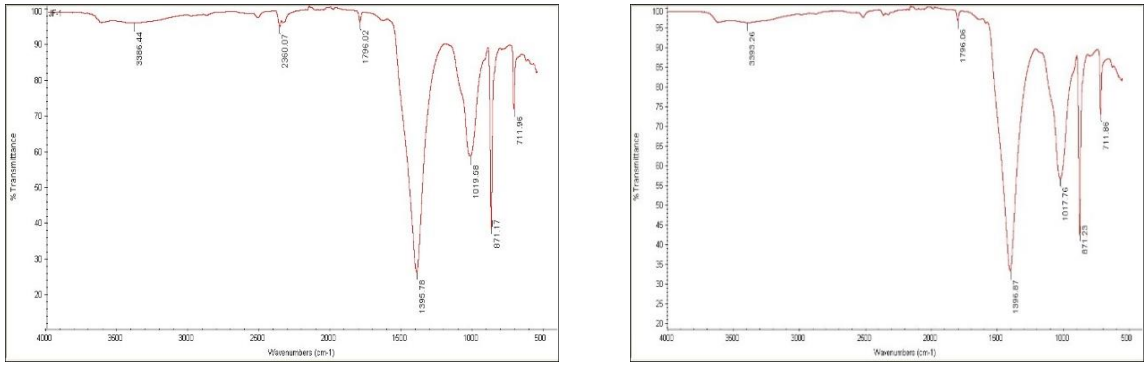
(b)

Figure 4. SEM-EDX analysis data for our soil (a) and dyed soil (b) samples.

SEM-EDX analysis revealed oxygen and calcium contents typical of calcareous soil; the C/Si ratio was consistent with dye adsorption onto the surface. Both before and after adsorption, the intensities of the C–H and SiO_2 signals decreased following adsorption, indicating that crystal violet occupies the soil's active binding sites — in agreement with the FTIR results (Alobani et al., 2021; Grim, 1939).

3.2 Fourier Transform Infrared Spectroscopy (FTIR) analysis:

FTIR spectra of the soil (adsorbent) and the dye-loaded soil (adsorbate) were used to characterise molecular bonds and identify aliphatic and/or aromatic functional groups. The results of the FTIR analysis of the soil (adsorbent) and the soil + crystal violet (adsorbate) samples revealed the structure and type of the calcareous soil. Our soil, which also possesses an anionic structure, exhibited a high degree of adsorption of the cationic crystal violet dye by binding to the =O and -OH groups (2360 cm^{-1}) of the Ca=O and Ca-OH bonds. Furthermore, there is binding of the dye to the C–H bond at 3386. The peaks at 1796 correspond to C=C and C=O bonds, whilst those at 1017, 871 and 712 correspond to Si–O bonds (Canizo et al., 2019).



(a) (b)

Figure 5. FTIR spectrum images of soil (a) and soil with KV adsorbed (b) samples.

3.3 Surface Area and Porosity (BET) Analysis of the Adsorbent (Calcareous Soil)

Parameter	Single pt.	BJH micro	BJH macro
Surface area (m^2/g)	15.5611	12.595	19.1337
Pore volume (cm^3/g)	0.048759	0.054223	0.061154
Pore radius (Å)	124.2068	172.207	127.845

Table 2. BET analysis data for our soil adsorbent

The BET surface area analysis data are consistent with the values expected for calcareous soil and are more favourable for the adsorption process than the average soil analysis values. The adsorption process arises from an imbalance between the surface and the surrounding medium. This imbalance is related to the effects of concentration, pressure or electrostatic forces. Consequently, every substance possesses some degree of adsorption capacity; however, this capacity varies depending on the substance's surface area and surface properties. Furthermore, this relationship also depends on the number and size of the pores present in the adsorbent (Ngo et al., 2020).

3.5 Isotherms, Thermodynamics and Kinetics of the Adsorption Process

Table 3. Isotherm data calculated from the adsorption of Crystal Violet dye onto Van/Erciş soil ((m: 0.1 g, V: 0.05 ml, C_o: 20 ppm, T: 298 K)

T(K)		298	308	323
Langmuir	K_L	-1.5078	2.7525	1.5334
	Q_m	15.2750	25.8260	49.1533
	R^2	0.8485	0.6815	0.9543
Freundlich	n	2.7268	2.2367	1.7437
	1/n	0.3667	0.4471	0.5735
	K_F	12.7086	14.5719	28.0935
	R^2	0.5421	0.8012	0.9774
Temkin	B	4.7808	6.5545	9.6846
	K_t	32.9113	16.2006	20.2161
	b_t	0.5182	0.3780	0.2558
	R^2	0.3202	0.6089	0.9523
D-R	q_m	21.3573	23.7280	32.1261
	E	3.3084	3.2556	3.4940
	D	0.0457	0.0472	0.0410
	R^2	0.5698	0.7204	0.9518

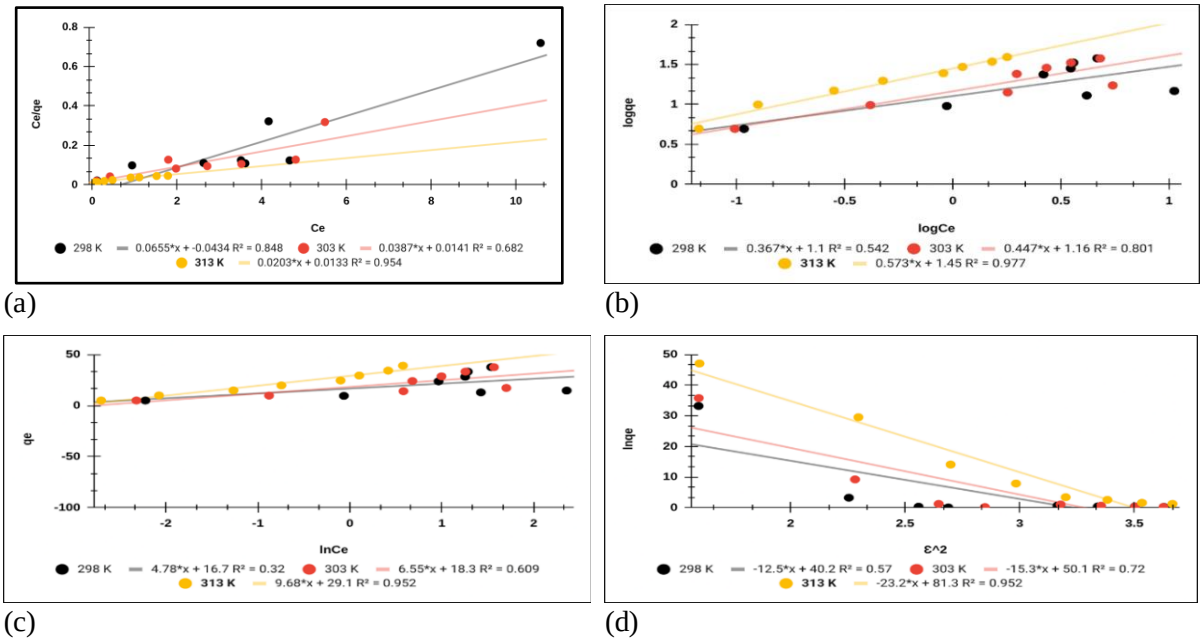


Figure 6. Langmuir (a), Freundlich (b), Temkin (c) and D-R (d) isotherm plots for Crystal Violet dye on Van/Erciş soil.

Freundlich fit best — indicating multilayer adsorption onto a heterogeneous soil surface, consistent with the varied particle morphology (SEM) and multiple binding sites (FTIR). Adsorption realized on the different areas of the surface (Alacabey, 2014).

Table 4. Equations and findings relating to the adsorption isotherms

Model	Linearised Form	Result
Langmuir	Ce/qe = 1/(qm·KL) + Ce/qm	Monolayer assumption
Freundlich	ln qe = ln Kf + (1/n) ln Ce	Best fit — highest R^2, most linear plot
Temkin	qe = (RT/bT) ln(AT·Ce)	Heat-of-adsorption assumption
D–R	ln qe = ln qm − Kad·ε²	Porosity-based assumption

Table 5. Thermodynamic data calculated from the adsorption of crystal violet dye on Van/Erciş soil ((m: 0.1 g, V: 0.05 ml, C_0: 20 ppm, T: 298 K)

	T (K)	Kc	lnKc	ΔG°, KJ/mol	ΔH°, KJ/mol	ΔS°, KJ/mol.K
10 mg/L	298	45.6681	3.8214	-9.4678	15.9106	0.0848
	308	50.4165	3.9203	-9.7129		
	323	74.2384	4.3073	-10.6716		
				0.0000		
20 mg/L	298	10.1598	2.3184	-5.7441	65.7700	0.2399
	308	23.5500	3.1591	-7.8270		
	323	79.1178	4.3709	-10.8293		
				0.0000		
30 mg/L	298	3.1043	1.1328	-2.8066	91.4979	0.3156
	308	7.8654	2.0625	-5.1099		
	323	52.6538	3.9637	-9.8204		
				0.0000		
40 mg/L	298	1.3900	0.3293	-0.8159	110.8570	0.3728
	308	3.1430	1.1452	-2.8373		
	323	41.5787	3.7276	-9.2354		
				0.0000		
50 mg/L	298	9.0195	2.1994	-5.4491	35.8063	0.1379
	308	12.1525	2.4975	-6.1878		
	323	27.1274	3.3005	-8.1773		
				0.0000		
60 mg/L	298	8.0480	2.0854	-5.1668	39.0118	0.1475
	308	10.5587	2.3569	-5.8395		
	323	26.5685	3.2797	-8.1258		
				0.0000		
70 mg/L	298	9.1934	2.2185	-5.4965	29.9148	0.1177
	308	9.4446	2.2454	-5.5632		
	323	22.5521	3.1158	-7.7197		
				0.0000		

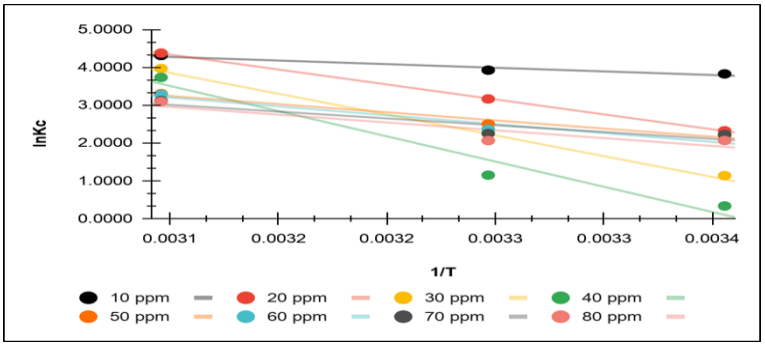


Figure 7. Thermodynamic graphs plotted for Crystal Violet dye on Van/Erciş soil

The thermodynamic data for the adsorption process indicate that endothermic chemical bonding has taken place**;** ΔG° is negative and the process is spontaneous, whilst ΔH° and ΔS° are positive, indicating that the process occurs by absorbing heat and transitioning to an ordered structure. The vast majority of chemical adsorption processes are irreversible, i.e. they cannot be reversed. The removal of adsorbed substances (regeneration) is generally achieved by heating to very high temperatures. Furthermore, the adsorbed substances do not move across the interface due to their strong bonding to the surface. These strong bonds generally become even stronger with an increase in temperature (Şahan, 2007; Alacabey, 2014; Uraz, 2015, Azadi et al., 2025).

Table 6. Kinetic data calculated from the adsorption of crystal violet dye onto Van/Erciş soil (m: 0.1 g, V: 0.05 ml, C_o: 20 ppm, T: 298 K)

T(K)		**298**	**308**	**323**
Fractional power	**v**	0.009	0.086	0.715
	k	4.751	3.130	0.177
	R^2	0.844	0.967	0.800
Pseudo-first order	**k_{1p}**	0.017	0.041	0.054
	qe,calc	0.085	1.231	2.224
	qe,exp	4.946	4.531	2.919
	R^2	0.413	0.973	0.906
Pseudo-second order	**k_{2p}**	1.15778	0.06579	0.00696
	qe,calc	4.946	4.791	4.530
	qe,exp	4.946	4.531	2.919
	R^2	1.000	0.999	0.853
Intraparticle diffusion	**k_p**	0.017	0.150	0.325
	R^2	0.663	0.983	0.822

The adsorption kinetics (pseudo-second) were found to conform to a second-order kinetic model (R^2 = 0.99) (Alyafei and Hassanien, 2026).

CONCLUSION

The objective of this scientific study is adsorbing crystal violet dye onto a natural, low-cost calcareous soil from Erciş /Van region, and to characterise the resulting adsorption process — isotherm, thermodynamics and kinetics. The results could be summerizable as below;

* Under ambient conditions, the soil removed the large majority of crystal violet dye from solution, supporting its use as a low-cost textile-wastewater adsorbent. Regional calcareous soil is an effective, low-cost adsorbent for crystal violet dye removal (≈77,2% removal, qmax 97.5%).

* Oxygen and calcium content typical of calcareous soil; C/Si ratio consistent with dye adsorption onto the surface.
* C–H and SiO_2 signal intensities decrease after adsorption, indicating that crystal violet occupies the soil's active binding sites — in agreement with the FTIR results.
* There is triarylmethane backbone with three dimethylamino-substituted phenyl rings.
* Delocalised positive charge — classified as a cationic (basic) dye.
* High molar mass and planar aromatic structure favour surface adsorption over biodegradation.
* Cationic triarylmethane dye is commercial analytical grade. Its cationic character promotes strong electrostatic interaction with the anionic calcareous soil surface.
* The anionic soil binds the cationic dye mainly through Ca and Si functional groups, consistent with a calcareous soil composition.
*BET analysis results showed that the adsorbent has been shown to have larger pore sizes than those typically found in soil products.
* The process follows the Freundlich isotherm — multilayer adsorption onto a heterogeneous surface with the varied particle morphology (SEM) and multiple binding sites (FTIR).
* Thermodinamic analysis showed that adsorption process was an endothermic, spontaneous adsorption process consistent with a chemical binding mechanism.
* The kinetic analysis verified; the pseudo-second-order model gave the best fit, indicating that the rate-limiting step involves interaction between dye molecules and the soil's active binding sites, rather than simple mass transfer.
* The approach offers a scalable option for regions with limited access to commercial adsorbents.
* Only crystal violet was tested; competitive adsorption with dye mixtures remains unstudied.
* Results are from batch experiments; column / continuous-flow performance is not yet established.
* Adsorbent reuse and desorption/regeneration cycles were not evaluated in this study.
* Experiments used prepared dye solutions rather than actual textile-industry effluent.
KV, which has a wide range of applications, is a carcinogenic dye; furthermore, as it is cationic, it can cause eye irritation and permanent damage to the cornea. In extreme cases, it can lead to respiratory problems and kidney failure (Saeed et al., 2010; Chakraborty et al., 2011). It must be treated.
Textile wastewater containing crystal violet — a non-biodegradable, toxic, carcinogenic dye — poses a significant environmental risk. Among available treatment methods (physical, chemical, biological, advanced), adsorption offers a low-cost, effective route for dye removal.

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SAĞLIK STRATEJİSİNİN GELECEĞİ: NUTRİGENETİK VE SAĞLIKLI UZUN YAŞAM YAKLAŞIMIYLA YAŞLANMA YÖNETİMİ

THE FUTURE OF HEALTH STRATEGY: AGING MANAGEMENT THROUGH NUTRIGENETICS AND LONGEVITY

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ÖZET
Amaç: Dünya genelinde yaşam beklentisi artarken sağlıklı ve işlevsel bağımsızlık içinde geçirilen yıllar aynı hızda artmamaktadır. Bu derlemenin amacı, yaşlanma biyolojisi, nutrigenetik ve kişiselleştirilmiş beslenme arasındaki ilişkiyi ve Precision Longevity yaklaşımının sağlıklı yaşam süresini uzatma ve işlevsel bağımsızlığı koruma potansiyelini değerlendirmektir.
Yöntem: Bu çalışma yapılandırılmış anlatısal bir derleme olarak planlandı. PubMed/MEDLINE, Scopus, Web of Science ve Google Scholar veri tabanlarında Ocak 2013-Ağustos 2026 dönemindeki çalışmalar; sağlıklı yaşlanma, biyolojik yaş, yaşam tarzı, nutrigenetik, nutrigenomik ve kişiselleştirilmiş beslenme ile ilişkili anahtar sözcüklerle taranmıştır. İnsan çalışmaları ve güncel derlemeler önceliklendirildi; mekanistik ve preklinik veriler biyolojik açıklama amacıyla kullanılmıştır.
Bulgular: Yaşlanma; genomik kararsızlık, epigenetik değişiklikler, mitokondriyal disfonksiyon, hücresel senesens, kronik inflamasyon, proteostaz kaybı ve bağırsak mikrobiyotasındaki değişikliklerle şekillenen çok boyutlu bir süreçtir. Beslenme ve yaşam tarzı müdahalelerine yanıt; genetik, epigenetik, metabolik, mikrobiyal ve çevresel özelliklere göre değişebilmektedir. Yağ asidi ve tek karbon metabolizması, kafein yanıtı, laktoz sindirimi, vitamin durumu, glisemik kontrol ve inflamasyonla ilişkili genetik varyantlar bireysel beslenme yanıtını etkileyebilmektedir. Nutrigenetik verilerin biyolojik yaş ölçümleri, epigenetik saatler, metabolomik ve mikrobiyom analizleri, klinik bulgular ve yaşam tarzı verileriyle bütünleştirilmesi risk değerlendirmesi ve müdahale planlamasını daha bireysel hale getirebilmektedir.
Sonuç: Gelecekte yaşlanma yönetiminin, hastalık ortaya çıktıktan sonra başlatılan tedavilerden biyolojik riskleri daha erken tanımlayan koruyucu ve kişiselleştirilmiş yaklaşımlara kayması beklenmektedir. Nutrigenetik temelli beslenmenin fiziksel aktivite, uyku düzeni, stres yönetimi ve mikrobiyotayı destekleyen stratejilerle birleştirilmesi sağlıklı yaşam süresini ve işlevsel bağımsızlığı destekleyebilir. Klinik uygulamalar bilimsel kanıt, disiplinler arası değerlendirme, etik veri yönetimi ve uzun dönem izlem ile yönlendirilmelidir.
Anahtar kelimeler: nutrigenetik, sağlıklı yaşlanma, sağlıklı yaşam süresi, biyolojik yaş, epigenetik saatler, hassas beslenme, çoklu omik

ABSTRACT
Objective: While life expectancy is increasing worldwide, the number of years lived in good health and functional independence is not rising at the same rate. As a result, age-related chronic diseases, cognitive and physical decline, and care dependency have become major public health concerns. This study evaluated the relationship among aging biology, nutrigenetics, and personalized nutrition, and the potential of the Precision Longevity approach to extend healthspan and preserve functional independence.

Materials and Methods
The current literature on the biological mechanisms of aging, nutrigenetic and nutrigenomic approaches, biomarkers of biological age, epigenetic clocks, multi-omics technologies, personalized nutrition, and lifestyle interventions was conceptually reviewed.

Genetic differences associated with nutrient metabolism, inflammation, oxidative stress, DNA methylation, mitochondrial function, and the gut microbiota were examined within an integrated framework.

Results

Aging is a multidimensional process shaped by genomic instability, epigenetic alterations, mitochondrial dysfunction, cellular senescence, chronic inflammation, loss of proteostasis, and changes in the gut microbiota. Responses to dietary and lifestyle interventions may vary by genetic, epigenetic, metabolic, microbial, and environmental factors. Genetic variants related to fatty acid and one-carbon metabolism, caffeine response, lactose digestion, vitamin requirements, glycemic control, and inflammation may influence individual nutritional needs. Integrating nutrigenetic data with biological age measurements, epigenetic clocks, metabolomic and microbiome analyses, clinical findings, and lifestyle data may improve individualized risk prediction and intervention planning.

Conclusion

Future aging management should shift from treatments initiated after disease onset to preventive, personalized approaches that identify biological risks early. Combining nutrigenetics-based nutrition with physical activity, sleep regulation, stress management, and microbiota-supportive strategies may help extend healthspan and preserve functional independence. Clinical applications should be guided by scientific evidence, interdisciplinary assessment, ethical data management, and long-term monitoring.

Keywords: Nutrigenetics, longevity, healthy aging, biological age, personalized nutrition, epigenetics, precision longevity.

GİRİŞ

Yaşam beklentisindeki artış modern tıp ve halk sağlığının en önemli kazanımlarından biridir; ancak yaşam süresinin uzaması, kronik hastalık, bilişsel gerileme veya işlevsel bağımlılık olmaksızın geçirilen yılların aynı oranda artması anlamına gelmemektedir. Bu nedenle gerobilimin temel hedefi yalnızca yaşamı uzatmak değil, hastalık ve fonksiyon kaybını yaşamın daha ileri dönemlerine öteleyerek sağlıklı yaşam süresini artırmaktır. Gerobilim; kardiyovasküler hastalık, tip 2 diyabet, kanser, nörodejenerasyon, sarkopeni ve kırılganlık gibi durumları birbirinden bağımsız sonuçlar olarak değil, ortak yaşlanma biyolojisinin farklı klinik yansımaları olarak ele almaktadır.[1,2]

Kronolojik yaş bireyin biyolojik rezervini tek başına açıklamamaktadır. Aynı yaştaki kişiler; kas gücü, biliş, kardiyometabolik sağlık, inflamasyon ve toparlanma kapasitesi açısından belirgin biçimde farklı olabilmektedir. Biyolojik yaş kavramı bu heterojenliği nicelleştirmeye çalışırken nutrigenetik ve nutrigenomik, beslenme yanıtındaki bireysel farklılıkların bir bölümünü genetik ve epigenetik bağlamda açıklamayı amaçlamaktadır. Bununla birlikte tek bir varyantın veya tek bir omik ölçümün klinik kaderi belirlediği düşüncesi güncel kanıtla uyumlu değildir; genetik, fenotip, çevre ve davranış birlikte değerlendirilmelidir.[3,4,5]

Gereç ve yöntem

Bu çalışma, sağlıklı yaşlanma ile nutrigenetik ve kişiselleştirilmiş beslenme arasındaki ilişkiyi değerlendiren yapılandırılmış anlatısal bir derlemedir. PubMed/MEDLINE, Scopus, Web of Science ve Google Scholar veri tabanlarında Ocak 2013-Ağustos 2026 tarihleri arasındaki yayınlar taranmıştır. Konunun temelini oluşturan daha eski çalışmalar, mekanizma veya klinik ilişki açısından gerekli olduğunda ayrıca değerlendirilmiştir. Arama terimleri; “healthy aging/ageing”, “healthspan”, “longevity”, “geroscience”, “biological age”, “epigenetic clock”, “hallmarks of aging”, “nutrigenetics”, “nutrigenomics”, “precision nutrition” ve “personalized nutrition” kavramları etrafında oluşturulmuştur. Kaynak seçiminde insan çalışmaları, sistematik derleme ve meta-analizler, randomize kontrollü çalışmalar ve prospektif kohortlar önceliklendirilmiştir. İnsan verilerinin sınırlı olduğu mekanizmalarda preklinik çalışmalar yalnızca biyolojik açıklama amacıyla kullanılmıştır.

GELİŞME

Yaşlanma biyolojisi ve biyolojik yaş

Yaşlanma, tek bir yolaktaki bozulmadan çok, moleküler ve sistemik süreçlerin birbirini güçlendirdiği dinamik bir ağdır. Güncellenmiş Hallmarks of Aging çerçevesi genomik kararsızlık, telomer kısalması, epigenetik değişiklikler, proteostaz kaybı, bozulmuş makrootofaji, düzensiz besin algılama,

mitokondriyal disfonksiyon, hücresel senesens, kök hücre tükenmesi, hücreler arası iletişimde bozulma, kronik inflamasyon ve disbiyozisi bir arada tanımlamaktadır.[6] Bu süreçler karşılıklıdır: mitokondriyal hasar inflamatuvar sinyallemeyi artırabilir; DNA (deoksiribonükleik asit) hasarı ve telomer kaybı senesensi tetikleyebilir; senesan hücrelerin salgısal fenotipi çevre dokularda inflamasyonu ve işlev kaybını sürdürebilir. Bu nedenle tek bir "anti-aging" hedefinin yaşlanmayı bütünüyle kontrol etmesi biyolojik olarak beklenmemektedir.[2,7]

Biyolojik yaş göstergeleri kronolojik yaşın açıklayamadığı heterojenliği ölçmeyi amaçlamaktadır. Horvath ve Hannum gibi birinci nesil epigenetik saatler kronolojik yaşı tahmin ederken, PhenoAge (fenotipik yaş temelli epigenetik saat) ve GrimAge (mortalite riskini öngörmek üzere geliştirilen epigenetik saat) klinik/mortaliteyle ilişkili bilgileri, DunedinPACE (epigenomdan hesaplanan Dunedin yaşlanma hızı ölçütü) ise uzunlamasına yaşlanma hızını yakalamaya yönelmiştir.[8,9,10,11,12] GrimAge gibi mortaliteye göre eğitilmiş modeller kırılganlık ve mortalite öngörüsünde kronolojik yaşa göre eğitilmiş saatlerden daha güçlü olabilir.[13] Saatlerin farklı hedeflerle geliştirilmesi, sonuçlarının yaşlanmanın farklı boyutları olarak değerlendirilmesini gerektirir.[3,14]

Çoklu omik yaklaşımlar epigenomik, proteomik, metabolomik, transkriptomik ve mikrobiyom verilerini birleştirerek bu heterojenliği daha kapsamlı tanımlamaya çalışmaktadır. Çoklu omik modeller ve sistem-spesifik metilasyon saatleri, tek bir kan örneğinden farklı fizyolojik sistemlerde yaşlanma profilleri oluşturabilmektedir; Systems Age yaklaşımı 11 sistem için farklı yaşlanma skorları tanımlamıştır.[15,16] Bununla birlikte teknik değişkenlik, doku özgüllüğü, etnik/cinsiyet temsili, standart eşik değerlerin yokluğu ve biyolojik yaş değişiminin sert klinik sonlanımlarla her zaman doğrulanmamış olması rutin klinik kullanımın başlıca sınırlılıklarıdır.[14]

Yaşlanma mekanizmalarını hedefleyen rapamisin, metformin, NAD+ (nikotinamid adenin dinükleotidin oksitlenmiş formu) öncüleri, senolitikler ve senomorfikler de yoğun biçimde araştırılmaktadır. Rapamisin farklı türlerde yaşam süresini uzatan en tutarlı farmakolojik ajanlardan biridir; metformin AMPK (adenozin monofosfat ile aktive olan protein kinaz) ve mTOR (rapamisinin mekanistik hedefi) sinyal yolakları ile mitokondriyal/inflamatuvar yollar üzerinden aday geroterapötik olarak değerlendirilmektedir. Bununla birlikte insanlarda sağlıklı yaşam süresinin rutin farmakolojik olarak uzatılabildiğini gösteren kanıt henüz yetersizdir; güvenlilik, hedef dışı etkiler ve uzun dönem sonuçlar sağlıklı bireylerde özellikle yüksek standart gerektirir.[17,18,19]

Sağlıklı uzun yaşamın temelinde yaşam tarzı müdahaleleri

Beslenme kalitesi ve enerji kısıtlaması

İnsan verilerinde en tutarlı bulgulardan biri beslenme kalitesidir. Meyve, sebze, tam tahıl, kurubaklagil, kuruyemiş ve doymamış yağlardan zengin; işlenmiş et, trans yağ, fazla sodyum ve şekerli içeceklerin sınırlı olduğu örüntüler daha sağlıklı yaşlanmayla ilişkilidir. 105.000'den fazla katılımcının uzun süre izlendiği çalışmada AHEI (Alternatif Sağlıklı Beslenme İndeksi) skoruna en yüksek uyum gösterenlerde sağlıklı yaşlanma için odds oranı en düşük uyuma göre 1,86 (%95 güven aralığı: 1,71–2,01) bulunmuş, sağlıklı yaşlanma eşiği 75 yaşa çıkarıldığında ilişki daha da güçlenmiştir.[20]

Beslenme ve çok bileşenli yaşam tarzı müdahalelerinin epigenetik yaş göstergeleri üzerindeki etkisini inceleyen çalışmalar da bu ilişkiyi desteklemekle birlikte temkinli yorum gerektirmektedir. Fitzgerald ve arkadaşları[21] tarafından 43 sağlıklı erkekte yürütülen 8 haftalık pilot randomize çalışmada; beslenme, uyku, egzersiz ve gevşeme rehberliğini probiyotik ve fitobesin desteğiyle birleştiren müdahale, kontrol grubuna kıyasla Horvath DNAmAge (DNA metilasyonuna dayalı yaş) değerinde 3,23 yıllık azalma ile ilişkili bulunmuştur. Ancak küçük örneklem, yalnızca erkeklerin dahil edilmesi, kısa takip süresi ve epigenetik yaşın bir ara sonlanım olması nedeniyle bu sonuç klinik gençleşme veya yaşam süresinin uzaması olarak yorumlanmamalıdır. NU-AGE (Avrupa'da ileri yaştaki bireylerin sağlıklı yaşlanmasını destekleyen yeni beslenme stratejileri projesi) pilot analizinde ise 120 sağlıklı ileri yaştaki bireyde bir yıllık Akdeniz-benzeri beslenme sonrasında epigenetik gençleşme yönünde bir eğilim görülmüş; etkinin özellikle Polonyalı kadınlarda ve başlangıçta epigenetik olarak daha yaşlı olan bireylerde belirginleşmesi yanıtın ülke, cinsiyet ve başlangıç fenotipine göre değişebileceğini düşündürmüştür.[22]

Enerji kısıtlaması model organizmalarda yaşam ve sağlık süresini uzatan en güçlü genetik dışı müdahalelerden biridir ve insülin/IGF-1 (insülin benzeri büyüme faktörü 1), mTOR, AMPK, sirtuinler ve otofajiyle ilişkilidir.[23] İnsanlarda yaklaşık iki yıllık enerji kısıtlamasının bazı bileşik biyolojik yaş ölçütlerinde daha yavaş artışla ilişkili olduğu ve immünometabolik düzenleyicileri etkileyebildiği bildirilmiştir.[24,25]

Ancak ileri yaşta sarkopeni, kırılganlık, düşük vücut ağırlığı veya malnütrisyon riski varlığında hedef enerji azaltmak değil, yeterli enerji-protein alımı ile fonksiyonel rezervi korumaktır.[26] Dolayısıyla "daha az kalori = daha uzun yaşam" genellemesi klinik olarak uygun değildir.

Fiziksel aktivite ve egzersiz

Fiziksel aktivite sağlıklı yaşam süresi ve işlev açısından en güçlü yaşam tarzı araçlarından biridir. Düzenli aktivite daha düşük erken mortalite ve kronik hastalık yüküyle ilişkilidir. Kardiyorespiratuvar uygunluktaki her 1 MET (metabolik eşdeğer) artışı mortalite riskinde yaklaşık %12-15 azalma ile ilişkilidir.[27] Bu ilişkiler büyük ölçüde gözlemseldir; randomize çalışmalarda daha güçlü ve doğrudan kanıt, yaşam süresinden çok mobilite, kas gücü, denge, kırılganlık ve bağımsızlığın korunması üzerinedir.[28,29]

Direnç egzersizi sarkopeni ve işlevsel kayıp açısından, aerobik aktivite ise kardiyorespiratuvar uygunluk ve metabolik esneklik açısından tamamlayıcıdır. Egzersiz mitokondriyal biyogenez, glikoz taşınması, miyokin sinyallemesi, inflamasyon ve otofaji gibi yaşlanma yollarını etkiler.[30] Klinik uygulamada en önemli nokta, genel "egzersiz yap" önerisi yerine kişinin kas gücü, denge, kardiyovasküler kapasite, eklem sorunları, düşme riski ve uyumunu dikkate alan çok bileşenli program oluşturmaktır.

Uyku, sirkadiyen ritim ve psikolojik stres

Uyku ve sirkadiyen düzen ileri yaş sağlığının önemli bileşenleridir.[31] Çoklu omik biyolojik yaş analizlerinde uyku süresi ile yaş farkı arasında U-şeklinde ilişki bildirilmiş; organ ve cinsiyete göre en düşük yaş farkları yaklaşık 6,4–7,8 saat aralığında görülmüştür. Bu gözlemsel aralık her birey için kesin bir uyku süresi hedefi olarak yorumlanmamalıdır.[32] Uyku düzensizliği ve sirkadiyen bozulma obezite, diyabet, kardiyovasküler risk, inflamasyon ve mortaliteyle ilişkilidir; bazı çalışmalarda düzenlilik toplam uyku süresinden bağımsız bilgi taşımaktadır.[33] Giyilebilir cihazlarla ölçülen aktivite-sirkadiyen örüntülerinin dijital yaşlanma biyobelirteci olarak araştırılması bu alanın gelecekte boylamsal takibe entegre edilebileceğini düşündürmektedir.[34]

Kronik psikososyal stres ise sempatik sinir sistemi ve HPA (hipotalamus-hipofiz-adrenal) ekseni üzerinden nöroendokrin ve inflamatuvar yanıtları etkiler; glukokortikoid direnci, sitokin dengesizliği ve düşük dereceli kronik inflamasyonla ilişkilendirilmektedir.[35,36] Kümülatif stres hızlanmış GrimAge ile ilişkilendirilmiş; duygu düzenleme ve özdenetim bu ilişkinin bir bölümünü hafifletmiştir.[37] Allostatik yük, çoklu fizyolojik sistemlerde kümülatif yıpranmayı tek bir stres belirtecinden daha iyi yansıtabilir.[38] Bu nedenle uyku ve stres yönetimi, yalnızca semptom kontrolü değil, metabolik ve inflamatuvar yükün azaltılması açısından da sağlıklı yaşlanma stratejisinin parçasıdır.

Bağırsak mikrobiyotası

Bağırsak mikrobiyotası yaşlanmanın değiştirilebilir ancak henüz nedenselliği tam çözülmemiş bir katmanıdır. Daha sağlıklı yaşlanma çoğu zaman daha yüksek mikrobiyal çeşitlilik veya bireysellik, korunmuş bağırsak bariyeri ve yararlı metabolit üretimiyle ilişkilidir.[39] İleri yaşta mikrobiyomun daha bireyselleşmesi bazı kohortlarda daha iyi sağkalımla ilişkilendirilmiş; buna karşılık tek bir "uzun yaşam mikrobiyomu" tanımlanmamıştır.[40] Kısa zincirli yağ asitleri, bağırsak bariyeri, NF-κB (nükleer faktör kappa B) ile ilişkili inflamasyon, triptofan/safra asidi metabolizması ve mikrobiyota-epigenom etkileşimleri olası mekanizmalardır.[41,42] Güncel klinik yaklaşım, ticari mikrobiyom skorlarından çok kaliteli beslenme, tolere edilen lif ve bitkisel çeşitlilik gibi kanıta daha yakın müdahaleleri önceliklendirmelidir.

Sağlıklı yaşlanmada bireysel beslenme yanıtı: omega-3, kafein, laktoz, homosistein ve histamin

Hassas beslenmenin temel varsayımı, aynı miktarda alınan besin veya besin ögesinin her bireyde aynı metabolik maruziyet ve klinik yanıtı oluşturmamasıdır. Genotip bu farklılığın bir bileşenidir; fakat başlangıç beslenme durumu, yaş, cinsiyet, mikrobiyota, ilaçlar, komorbiditeler ve yaşam tarzı çoğu zaman eşit derecede önemlidir.[5] Vitamin metabolizmasına ilişkin sistematik veriler de genetik varyantların B vitaminleri-homosistein, D vitamini ve bazı antioksidan bileşenlerde yanıtı etkileyebildiğini, ancak etkilerin popülasyon ve atasal kökene göre değişebildiğini göstermektedir.[43]

Glisemik yanıtta TCF7L2 (transkripsiyon faktörü 7 benzeri 2) genindeki rs7903146 varyantı iyi çalışılmış örneklerden biridir: PREDIMED (Akdeniz diyetiyle korunma çalışması) analizinde varyant ile açlık glukozu ve kardiyometabolik risk arasındaki ilişkinin Akdeniz diyetine uyum düzeyine göre değişebildiği bildirilmiştir.[44]

İnflamatuvar yanıt ise tek bir gene indirgenemeyen poligenik ve çevreye duyarlı bir fenotiptir; yağ asidi metabolizması gibi yolaklardaki genetik farklılıklar inflamatuvar mediatör yanıtını etkileyebilse de, bağımsız genotipe dayalı antiinflamatuvar beslenme veya takviye reçeteleri için mevcut kanıt yeterli değildir.[5,45]

Kronik düşük dereceli inflamasyon, yaşlanma biyolojisinin önemli bileşenlerinden biridir.[36] EPA (eikosapentaenoik asit) ve DHA (dokosaheksaenoik asit), hücre zarı bileşimi, eikosanoidler ve inflamasyonun çözülmesini destekleyen lipid mediatörleri üzerinden inflamatuvar yanıtı etkileyebilir.[46] Bu mekanistik etki, insanlarda doğrudan yaşam süresi uzamasıyla eşdeğer değildir. Ancak gereksinim ve yanıt; başlangıç EPA/DHA düzeyi, balık tüketimi, ALA'dan (alfa-linolenik asit) uzun zincirli ürünlere dönüşüm, klinik hedef, ilaçlar, yaş, cinsiyet ve genetik yapının birleşimiyle şekillenir. FADS1 (yağ asidi desatüraz 1) ve FADS2 (yağ asidi desatüraz 2) genlerindeki varyantlar serum yağ asidi profili ve ALA'dan EPA oluşumuyla ilişkilidir.[47,48] Gillingham ve arkadaşlarının çalışmasında DHA için aynı genetik ilişki gösterilmemiştir; bu nedenle EPA'ya ilişkin bulgular DHA'ya doğrudan genellenmemelidir.

İnsan müdahale çalışmaları bağlamın önemini açıkça gösterir. VITAL (D vitamini ve omega-3 çalışması) kapsamında genel birincil korunma popülasyonunda günde 1 g deniz kaynaklı omega-3 birleşik kardiyovasküler sonlanımı anlamlı azaltmamış; REDUCE-IT (ikosapent etil ile kardiyovasküler olayları azaltma çalışması) kapsamında statin kullanan, trigliseridi yüksek ve riski artmış bireylerde 4 g/gün ikosapent etil olayları azaltmış; STRENGTH (statin tedavisine rağmen süren kardiyovasküler riski yüksek trigliseritli bireylerde omega-3 ile değerlendiren çalışma) kapsamında farklı bir yüksek doz EPA/DHA formülasyonu benzer yararı göstermemiştir.[49,50,51] DO-HEALTH (D vitamini, omega-3, sağlıklı yaşlanma ve uzun yaşam çalışması) araştırmasının 777 katılımcıyı kapsayan sonradan yapılan epigenetik analizinde, 1 g/gün omega-3 ile üç yıllık izlemde bazı DNA metilasyon göstergelerinde yaklaşık 2,9–3,8 aylık daha yavaş ilerlemeye karşılık gelen etkiler bildirilmiştir; bu umut verici bulgu yaşam süresi uzamasıyla eşdeğer değildir.[52]

CYP1A2 (sitokrom P450 1A2) kafein klirensinin başlıca enzimidir; rs762551 varyantı hızlı/yavaş metabolizma fenotipleriyle ilişkilendirilir. Bununla birlikte sigara, gebelik, ilaçlar ve alışılmış kafein alımı gerçek fenotipi değiştirebilir. Başlangıçta tedavisiz evre 1 hipertansiyonu bulunan 18–45 yaş erişkinlerden oluşan HARVEST (Venetia Hipertansiyon ve Ambulatuvar Kan Basıncı Kaydı Çalışması) kohortunun analizinde, yavaş metabolizörlerde günde üç fincandan fazla kahve tüketimi albuminüri, hiperfiltrasyon ve hipertansiyonla ilişkili bulunmuş; albuminüri için düzeltilmiş tehlike oranı 2,74 olarak bildirilmiştir.[53] Bu gözlemsel sonuçlar genel nüfusa doğrudan genellenmemelidir. Sistematik derlemeler CYP1A2'nin yanı sıra ADORA2A (adenozin A2A reseptörü) ve adrenerjik varyantların da kan basıncı yanıtlarını etkileyebileceğini düşündürmektedir.[54]

Bununla birlikte gen-kahve etkileşimi her çalışmada doğrulanmamıştır; geniş UK Biobank (Birleşik Krallık Biyobankası) analizinde kafein metabolizmasıyla ilişkili genetik özellikler kahve-kardiyovasküler hastalık ilişkisini anlamlı biçimde değiştirmemiştir.[55] Bu nedenle klinik öneri genotipe göre otomatik yasaklama değil; hipertansiyon, renal kırılganlık, aritmi, uyku, toplam doz ve tüketim zamanını birlikte değerlendirmektir.[56] Ayrıca kahve, çay ve saf kafein biyolojik olarak aynı maruziyet değildir; kahve çok sayıda biyoaktif bileşen içerir ve hazırlama yöntemi de önem taşır.[56,57]

Laktaz kalıcılığı LCT (laktaz) geni ve MCM6 (minikromozom bakım kompleksi bileşeni 6) genindeki düzenleyici varyantlarla ilişkilidir; ancak genetik laktaz non-persistansı veya malabsorpsiyon klinik intoleransla aynı değildir. Semptomlar doz, öğün bileşimi, mikrobiyota ve visseral duyarlılığa göre değişir.[58,59] İleri yaşta tüm süt ürünlerinin gereksiz çıkarılması protein, kalsiyum, D vitamini ve B12 alımını azaltabilir; bu nedenle yönetim bireysel tolerans eşiği ve beslenme yeterliliği üzerine kurulmalıdır.[60,61]

Histaminle ilişkili yakınmalarda da benzer bir ilke geçerlidir. AOC1 (bakır içeren amin oksidaz 1) geni tarafından kodlanan DAO (diamin oksidaz) enzimi histamin yıkımında rol oynasa da tek bir genotip veya serum DAO değeri tanı koydurmaz.[62] Belirtiler özgül değildir; bağırsak hastalıkları, ilaçlar, alkol ve tüketilen histamin yükü değerlendirilmelidir.[63] Histamin intoleransının hızlanmış epigenetik yaşlanmaya veya kronik sistemik inflammaging'e (yaşlanmayla ilişkili kronik düşük dereceli inflamasyon) doğrudan yol açtığını gösteren güçlü insan kanıtı yoktur. Sağlıklı yaşlanma açısından asıl amaç, gereksiz ve uzun süreli eliminasyonla besin çeşitliliğini azaltmadan semptomları kontrol etmektir; kısa süreli uyarlama ve kontrollü yeniden deneme uygun bir yaklaşım olabilir.[62]

Tek karbon metabolizması folat, B12, B6, riboflavin, kolin ve metiyonini metilasyon kapasitesi, nükleotit sentezi ve redoks dengesiyle birleştirir. MTHFR (metilentetrahidrofolat redüktaz) yeniden metillenmede kullanılan 5-metiltetrahidrofolat oluşumuna katkı sağlar ve FAD (flavin adenin dinükleotit) kofaktörü için riboflavine gereksinim duyar.[64,65] MTHFR 677TT genotipinde riboflavin desteğinin homosisteini daha belirgin azaltabilmesi, genotip ile besin durumu arasındaki etkileşimin iyi örneklerinden biridir.[65]

Yüksek homosistein, yaşla ilişkili nörodejeneratif hastalıklarda bariyer işlev bozukluğu ve nöroinflamasyonla ilişkilidir.[66] Bununla birlikte B vitaminleriyle homosistein düşürülmesini değerlendiren sistematik derlemede miyokart enfarktüsü ve tüm nedenlere bağlı mortalitede anlamlı azalma gösterilmemiş; inme açısından küçük bir yarar bildirilmiştir.[67] Bu nedenle biyokimyasal iyileşme, klinik yaşlanmanın yavaşlaması veya yaşam süresinin uzaması olarak yorumlanmamalıdır.

Sağlıklı uzun yaşam yönetiminde genotip, yaşam boyu yatkınlık hakkında bilgi sağlayan sabit bir katmandır; fenotip ise bu yatkınlığın mevcut durumda nasıl ifade edildiğini gösterir. Biyolojik yaş, kan basıncı, lipidler, glisemik göstergeler, vücut bileşimi, kas gücü, biliş, uyku, semptomlar, beslenme öyküsü ve çevresel maruziyetler genetik veriyi klinik bağlama taşır. En işlevsel model boylamsal kişiselleştirmedir: başlangıç riskinin sınıflandırılması, hedeflenebilir alanların seçilmesi, müdahale uygulanması ve gerçek yanıtın izlenmesi. Böylece genetik test "takviye listesi üreten" bir araç olmaktan çıkar ve klinik muhakemenin bir parçası olur.

Genetik risk, yaşam tarzının önemini ortadan kaldırmaz. 1998–2018 dönemini kapsayan ve bireysel takip süresi medyanı 3,12 yıl olan bir kohortta sağlıklı yaşam tarzı hem düşük hem yüksek genetik risk gruplarında daha düşük mortalite ve 65 yaşında yaklaşık 3,8-4,4 yıllık yaşam beklentisi farkıyla ilişkili bulunmuş; mutlak yarar yüksek genetik risk grubunda daha büyük olmuştur.[68] Bu bulgu, genetik bilginin kader değil, müdahale önceliklerini daha iyi hedeflemek için kullanılabilecek bir bağlam olduğunu destekler.

Tartışma ve klinik uygulamadaki sınırlılıklar

Bu derlemenin ve alanın önemli sınırlılığı, kanıt olgunluğunun başlıklar arasında eşit olmamasıdır. Fiziksel aktivite ve beslenme kalitesi için insan verileri güçlü iken epigenetik saatlerin müdahale takibi, mikrobiyom temelli tedaviler, geroterapötikler ve birçok gen-beslenme önerisi daha erken translasyon aşamasındadır. Nutrigenomik rehberli yaşam tarzı programlarını inceleyen kapsam belirleme çalışmaları, davranışsal uyum açısından umut verici sonuçlar bulunmasına karşın çalışma sayısının az, örneklemlerin küçük ve takip sürelerinin çoğu zaman kısa olduğunu göstermektedir.[69] Bu nedenle biyolojik olarak makul bir etkileşim ile klinik yararı kanıtlanmış bir öneri birbirinden ayrılmalıdır.

Doğrudan tüketiciye sunulan nutrigenetik testler klinik uygulamada ek dikkat gerektirir. 2026 tarihli bir kapsam belirleme derlemesi 104 şirket ve 204 beslenme ilişkili panel arasında gen seçimi, raporlama ve post-test desteği açısından büyük heterojenlik olduğunu göstermiştir; şirketlerin yalnızca yaklaşık %54'ü kullandıkları genleri açıkça bildirirken yaklaşık %53'ü test sonrası destek sunmuştur.[70] Panelde çok sayıda gen bulunması klinik yarar göstergesi değildir. Analitik geçerlilik, klinik geçerlilik ve klinik yarar ayrı ayrı değerlendirilmelidir; sonuçlar genetik belirlenimcilik yaratmayacak biçimde aktarılmalı, bilgilendirilmiş onam, mahremiyet, veri saklama politikaları ve ayrımcılık riski açıkça ele alınmalıdır.[45]

Yapay zekâ ve makine öğrenmesi, genomik, metabolomik, mikrobiyom, giyilebilir cihaz ve sürekli glikoz izleme verilerini birleştirerek hassas beslenmenin boyutunu genişletebilir. Ancak yüksek tahmin doğruluğu klinik yararla aynı değildir. Küçük veya temsil gücü düşük veri setlerinde aşırı uyum, farklı popülasyonlara düşük genellenebilirlik, algoritmik yanlılık, açıklanabilirlik eksikliği, veri gizliliği ve klinik sorumluluk temel sorunlardır. Yapay zekâ bu nedenle klinisyenin yerini alan karar verici değil, çok boyutlu veriyi yapılandıran ve kanıtla birlikte yorumlanması gereken karar destek aracı olarak kullanılmalıdır.[71]

SONUÇ

Sağlıklı uzun yaşamın amacı, yaşama yalnızca yıl eklemek değil, eklenen yılları mümkün olduğunca hastalıksız, işlevsel ve bağımsız geçirmektir. Yaşlanma çok katmanlı olduğu için yönetimi de tek bir gen, biyobelirteç, takviye veya farmakolojik ajan üzerinden kurulamaz. Bugün için en güçlü klinik temel kaliteli ve yeterli beslenme, düzenli fiziksel aktivite, uygun uyku-sirkadiyen düzen, stres yükünün azaltılması, tütün gibi zararlı maruziyetlerin önlenmesi ve kardiyometabolik risklerin yönetimidir. Nutrigenetik bu temelin yerine geçen değil, belirli klinik sorularda onu hassaslaştıran bir araçtır.

Geleceğin en gerçekçi modeli, "genotipten reçeteye" doğrusal bir algoritma değil, ölçüm-yorumlama-müdahale-izlem döngüsüdür. Genetik veya omik test ancak yanıtlanacak klinik soruya ek değer sağlıyorsa kullanılmalı; müdahale sonrası yalnızca laboratuvar ya da epigenetik saat değişimi değil, semptomlar, beslenme yeterliliği, kan basıncı, kas fonksiyonu, biliş, uyku, yaşam kalitesi, güvenlilik ve sürdürülebilirlik de izlenmelidir. Sağlıklı uzun yaşam yönetiminin başarısı, elde edilen veri miktarından çok verinin bilimsel olarak ne kadar doğru yorumlandığı ve kişinin gerçek yaşamına ne kadar güvenli, uygulanabilir ve sürdürülebilir biçimde çevrildiğiyle ölçülmelidir.

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TÜRKİYE'DE 0–17 YAŞ GRUBU ÇOCUKLARDA GENEL VE NEDENE ÖZGÜ ÖLÜMLER, 2015–2024

ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY AMONG CHILDREN AGED 0–17 YEARS IN TÜRKİYE, 2015–2024

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ÖZET

Amaç
Bu çalışmanın amacı, Türkiye'de 2015–2024 yılları arasında 0–17 yaş grubundaki çocuk ölümlerinin cinsiyete ve spesifik ölüm nedenlerine göre zamansal eğilimlerini, dönüm noktalarını ve yıllık yüzde değişimlerini değerlendirmektir.

Materyal ve Yöntem
Çalışmada 2015–2024 yıllarına ait Türkiye İstatistik Kurumu 0–17 yaş çocuk ölüm verileri analiz edilmiştir. Cinsiyete ve spesifik ölüm nedenlerine göre zamansal eğilimleri ve kırılma noktalarını tespit etmek amacıyla Joinpoint Regresyon Analizi (JRA) uygulanmıştır. Eğilimlerin yönünü ve şiddetini belirlemek üzere Yıllık Yüzde Değişim (YYD) ve Ortalama Yıllık Yüzde Değişim (OYYD) değerleri ve bunlara ait %95 güven aralıkları (%95 GA) hesaplanmıştır.

Bulgular
2015–2024 kapsama döneminde genel çocuk ölümleri her iki cinsiyette de istatistiksel olarak anlamlı bir artış eğilimi göstermiştir (OYYD: Erkek = %2,1, p=0,001; Kız = %2,3, p=0,018). Her iki cinsiyette de 2021 yılı bir dönüm noktası olarak saptanmıştır. 2015–2021 periyodunda çocuk ölümleri istatistiksel olarak anlamlı düşüş kaydetmişken (Erkek YYD = -%8,6; Kız YYD = -%8,3; p<0,001), 2021–2024 periyodunda keskin bir artışa geçmiştir (Erkek YYD = %17,1; Kız YYD = %20,1). Ölüm nedenleri detaylandırıldığında; 2021 sonrasındaki bu kırılmanın temel nedeni her iki cinsiyette de yükseliş gösteren "Dışsal yaralanma ve zehirlenmeler" olduğu tespit edilmiştir (2021–2024 YYD: Erkek = %106,3, p<0,0001; Kız = %176,3, p<0,0001). Buna karşın her iki cinsiyette de neoplazmlar, metabolik ve nörolojik hastalıklarına bağlı ölümlerde periyot boyunca anlamlı düşüşler görülmüştür.

Sonuç
Türkiye'de 2015–2021 yılları arasında çocuk ölümlerinde kaydedilen kararlı düşüş eğilimi, 2021 yılı sonrasında kırılarak artış trendine girmiştir. Bu olumsuz eğilimin başlıca nedeni; kazalar, yaralanmalar, doğal afetler ve zehirlenmeleri kapsayan dışsal etmenlerde yaşanan artıştır.
Anahtar Kelimeler: Çocuk ölümleri; Joinpoint regresyon analizi; Ölüm nedenleri; Türkiye.

ABSTRACT

Objective: This study aims to evaluate the temporal trends, inflection points, and annual percentage changes in child mortality in the 0–17 age group in Türkiye between 2015 and 2024, stratified by sex and specific causes of death.

Methods
Mortality data for children aged 0–17 years for the period 2015–2024 were obtained from the Turkish Statistical Institute. Joinpoint Regression Analysis (JRA) was applied to identify temporal trends and inflection points by sex and specific causes of death. Annual Percentage Change (APC) and Average

Annual Percentage Change (AAPC) values along with their 95% confidence intervals (95% CI) were calculated to determine the direction and magnitude of the trends.

Results
Over the 2015–2024 coverage period, overall child mortality showed a statistically significant increasing trend in both sexes (AAPC: Boys = 2.1%, p = 0.001; Girls = 2.3%, p = 0.018). The year 2021 was identified as an inflection point for both sexes. While child mortality recorded a statistically significant decline during 2015–2021 (APC: Boys = -8.6%; Girls = -8.3%; p < 0.001), it experienced a sharp surge during 2021–2024 (APC: Boys = 17.1%; Girls = 20.1%). Cause-specific analysis revealed that the primary driver of this post-2021 reversal was "External causes of injury and poisoning", which increased in both sexes (2021–2024 APC: Boys = 106.3%, p < 0.0001; Girls = 176.3%, p < 0.0001). Conversely, deaths due to neoplasms, metabolic, and neurological diseases showed significant declining trends in both sexes throughout the period.

Conclusion
The steady decline in child mortality observed in Türkiye between 2015 and 2021 reversed after 2021, entering an upward trend. The primary contributor to this adverse trend is the increase in external factors, accidents, injuries, natural disasters, and poisonings.
Keywords: Child mortality; Joinpoint regression analysis; Causes of death; Türkiye.

GİRİŞ

Çocukluk çağı ölümleri, bir ülkenin gelişmişlik düzeyini, sağlık sisteminin etkinliğini ve toplum sağlığı politikalarının başarısını yansıtan en temel epidemiyolojik göstergelerden biridir.[1] Çocuk popülasyonundaki ölüm hızlarının ve nedenlerinin zaman içindeki değişimini izlemek; yalnızca geçmişteki sağlık dinamiklerini anlamak açısından değil, aynı zamanda geleceğe yönelik koruyucu ve önleyici sağlık stratejilerinin planlanması açısından da kritik önem taşır.

Zaman serisi ve izlem verilerinde zamana bağlı değişimleri değerlendirmek için sıklıkla doğrusal regresyon modelleri veya basit oran karşılaştırmaları tercih edilmektedir. Ancak uzun dönemli izlem verilerinde ölüm eğilimleri her zaman sabit veya doğrusal bir seyir izlemez. Toplumsal değişimler, sağlık politikalarındaki reformlar, tanı ve tedavi imkanlarındaki gelişmeler veya küresel/bölgesel krizler (pandemi, afetler vb.) zaman serisi üzerinde kırılma noktalarının (*joinpoint*) ortaya çıkmasına neden olabilir. Bu tür karmaşık ve doğrusal olmayan boylamsal verilerin tek bir doğrusal model ile analiz edilmesi, eğilimdeki ani yön değişimlerini maskeleyebilir ve hatalı çıkarımlara yol açabilir.

Joinpoint Regresyon Analizi (JRA), veri setindeki istatistiksel olarak anlamlı değişim noktalarını (kırılmaları) tespit ederek zaman serisini alt periyodlara bölen ve her bir periyot için Yıllık Yüzde Değişimi (YYD) ile tüm süreç için Ortalama Yıllık Yüzde Değişimi (OYYD) hesaplayan esnek ve güçlü bir metodolojik yaklaşımdır.[2,3] Bu yöntem, zaman içindeki eğilim değişikliklerinin tespit edilmesine ve belirli dönemlerdeki yükseliş veya düşüşlerin istatistiksel olarak modellenmesine olanak tanır.

Bu çalışmanın amacı, Türkiye'de 2015–2024 yılları arasındaki 10 yıllık dönemde 0–17 yaş grubundaki çocuk ölümlerine ait eğilimleri ve kırılma noktalarını Joinpoint Regresyon Analizi ile değerlendirmektir.[4] Çalışmada ölüm eğilimleri cinsiyete ve spesifik ölüm nedenlerine göre alt gruplarda incelenerek, son on yılda çocuk sağlığı alanında yaşanan metodolojik ve epidemiyolojik değişimlerin ortaya konulması hedeflenmiştir.

Materyal Ve Metod

Veri Kaynağı ve Çalışma Tasarımı

Bu çalışma, 2015–2024 yılları arasında Türkiye'de gerçekleşen 0–17 yaş grubu çocuk ölümlerinin retrospektif ekolojik bir zaman serisi analizidir. Veriler, Türkiye İstatistik Kurumu (TÜİK) Merkezi Dağıtım Sistemi (MEDAS) veri tabanında yer alan resmi "Ölüm ve Ölüm Nedeni İstatistikleri'nden elde edilmiştir. Çalışmada kişisel tanımlayıcı içermeyen ve kamuya açık ikincil idari veriler kullanıldığından yerel mevzuat gereği etik kurul onayından muaftır.

Ölüm Nedenlerinin Sınıflandırılması

Ölüm nedenleri, Dünya Sağlık Örgütü'nün Uluslararası Hastalık Sınıflandırması 10. Revizyonu (ICD-10) kodlama sistemine göre ana başlıklar altında incelenmiştir:

1. Dolaşım sistemi hastalıkları (I00–I99)

2. Dışsal yaralanma ve zehirlenmeler (V01–Y89)
3. Endokrin, beslenme ve metabolizma hastalıkları (E00–E90)
4. Sinir sistemi ve duyu organları hastalıkları (G00–H95)
5. Solunum sistemi hastalıkları (J00–J99)
6. Malign ve benign neoplazmlar (C00–D48)
7. Diğer nedenler ve semptomlar (R00–R99 ve diğer)

İstatistiksel Analiz

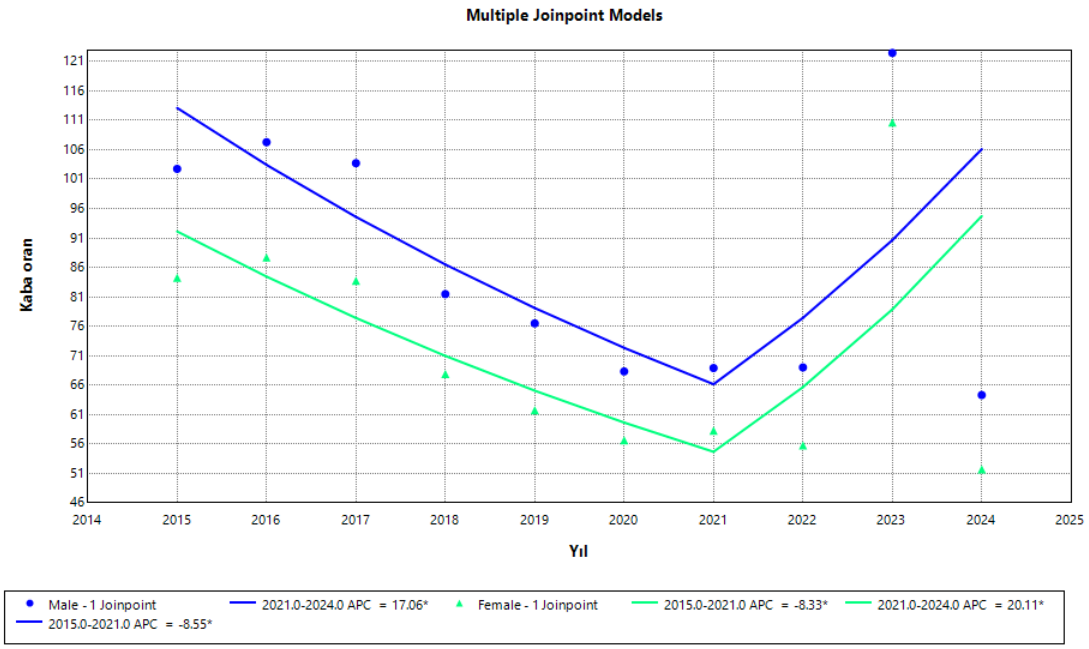
Zamansal eğilimlerin ve kırılma noktalarının (joinpoints) modellenmesinde Joinpoint Regresyon Analizi (JRA) kullanılmıştır. JRA, zaman serisi boyunca log-lineer modeller oluşturarak trendin istatistiksel olarak yön değiştirdiği en uygun değişim noktalarını tespit eder. Optimum kırılma noktası sayısı, Grid Search yöntemi ve Monte Carlo Permütasyon testi ($p<0,05$) uygulanarak belirlenmiştir. Modelde maksimum kırılma noktası sayısı 10 yıllık periyot için 1 veya 2 olarak sınırlandırılmıştır. Her bir doğrusal segment için Yıllık Yüzde Değişim (YYD), tüm çalışma dönemi için ise segmentlerin ağırlıklı ortalamasını temsil eden Ortalama Yıllık Yüzde Değişim (OYYD) ve %95 güven aralıkları (%95 GA) hesaplanmıştır. Analizler, ABD Ulusal Kanser Enstitüsü (NCI) tarafından geliştirilen Joinpoint Regression Programı (versiyon 4.9.1.0) ile yürütülmüştür.[2,3,5]

Bulgular

Türkiye'de 2015–2024 yılları arasında 0-17 yaş grubundaki çocuk ölüm verilerine uygulanan Joinpoint Regresyon Analizi (JRA) sonuçları; genel cinsiyet eğilimleri, kırılma noktaları (joinpoint) ve spesifik ölüm nedenlerine göre detaylandırarak aşağıda sunulmuştur.

2015–2024 kapsama döneminde Türkiye'de genel çocuk ölümleri incelendiğinde, Ortalama Yıllık Yüzde Değişim (OYYD) değerleri hem erkek hem de kız çocuklarında istatistiksel olarak anlamlı bir artış eğilimi göstermiştir. 2015–2024 dönemi genelinde OYYD; erkek çocuklarda %2,1 (%95 GA: 1,1; 3,1; p=0,001), kız çocuklarında ise %2,3 (%95 GA: 0,5; 4,4; p=0,018) olarak saptanmıştır (Tablo 1).

Zamana bağlı eğilim kırılmaları (joinpoint) incelendiğinde, her iki cinsiyette de 2021 yılı belirgin bir dönüm noktası (inflection point) olarak öne çıkmaktadır (Şekil 1). Erkek Çocuklarda, 2015–2021 yılları arasındaki birinci periyotta yıllık yüzde değişim (YYD) -%8,6 ile istatistiksel olarak anlamlı bir düşüş göstermişken (%95 GA: -17,2; -5,2; p=0,0004); 2021–2024 kapsayan ikinci periyotta bu eğilim yön değiştirerek YYD %17,1 seviyesinde anlamlı bir artışa geçmiştir (%95 GA: 1,6; 45,3; p=0,022). Kız Çocuklarda ise 2015–2021 periyodunda yıllık yüzde değişim -%8,3 ile anlamlı şekilde gerilemişken (%95 GA: -15,9; -5,2; p<0,0001); 2021–2024 periyodunda YYD %20,1 oranında artış kaydetmiştir (%95 GA: 3,4; 49,3; p=0,0039).



Şekil 1. Erkek ve Kız Çocuklarında Ölüm Eğilimleri, 2015-2024

Erkek çocuklarında ölüm nedenlerine göre yapılan JRA sonuçları Tablo 2'de özetlenmiştir. 2015–2024 yılları genelinde en belirgin artış gösteren ölüm nedeni dışsal yaralanma ve zehirlenmeler olmuştur.
Dışsal Yaralanma ve Zehirlenme: 2015–2024 genel OYYD değeri %19,3 artış yönündedir (%95 GA: 4,6; 29,1; *p*=0,0039). Periyot bazlı analizde; 2015–2021 arasında YYD -%9,2 ile anlamlı olmayan bir düşüş gösterirken (*p*=0,1119), 2021–2024 periyodunda son derece yüksek ve istatistiksel olarak anlamlı bir sıçrama yaşanmıştır (YYD = %106,3; *p*<0,0001).
Malign ve Benign Neoplazmlar: 2015–2024 dönemi genelinde OYYD -%1,9 oranında anlamlı bir düşüş göstermiştir (*p*=0,0004). 2015–2021 yılları arasında azalan bir seyir izleyen neoplazmlara bağlı ölümler (YYD = -%5,2; *p*=0,0028), 2021–2024 döneminde durağanlaşmıştır (YYD = %5,0; *p*=0,1512). Diğer Doğal Hastalık Gruplarında, dönem boyunca istikrarlı anlamlı düşüşler gözlenmiştir.
Dolaşım Sistemi Hastalıkları: 2015–2024 dönemi boyunca tek bir trend izlemiş olup zamana bağlı bir değişim sergilememiştir (OYYD = -%0,9; *p*=0,2395).
Kız çocuklarında ölüm nedenlerine göre Joinpoint regresyon sonuçları Tablo 3'te sunulmuştur.
Dışsal Yaralanma ve Zehirlenme: Erkek çocuklarına benzer şekilde, kız çocuklarında da en keskin artış bu grupta gerçekleşmiştir. 2015–2024 genel OYYD değeri %32,5 artış olarak saptanmıştır (%95 GA: 12,1; 45,9; *p*<0,0001). 2015–2021 periyodunda eğilim anlamlı bir değişim göstermezken (YYD = -%8,3; *p*=0,1739), 2021–2024 periyodunda devasa bir yükseliş yaşanmıştır (YYD = %176,3; %95 GA: 51,8; 609,6; *p*<0,0001).
Endokrin ve Metabolik Hastalıklar: 2015–2024 döneminde genel OYYD -%3,7 seviyesinde anlamlı bir düşüş kaydetmiştir (*p*<0,0001). 2015–2021 periyodunda anlamlı düşüş gösterirken (YYD = -%6,5; *p*=0,0088), 2021 sonrasında durağan seyretmiştir (YYD = %2,1; *p*=0,6259).
Malign ve Benign Neoplazmlar ile Sinir Sistemi Hastalıkları: Her iki neden grubunda da 2015–2024 dönemi boyunca tek hat üzerinde istatistiksel olarak anlamlı azalma eğilimleri görülmüştür. OYYD değerleri sırasıyla neoplazmlar için -%2,9 (%95 GA: -5,4; -0,6; *p*=0,0179) ve sinir sistemi/duyu organı hastalıkları için -%3,0 (%95 GA: -4,5; -1,8; *p*=0,0156) olarak tespit edilmiştir.
Solunum ve Dolaşım Sistemi Hastalıkları: Dolaşım sistemi hastalıkları (OYYD = -%0,1; *p*=0,9082) ve solunum sistemi hastalıkları (OYYD = -%2,9; *p*=0,0795) dönem boyunca istikrarlı bir düşüş göstermemiştir.

Tablo 1. Cinsiyete Göre Ölüm Eğilimlerinin JRA Sonuçları, Türkiye, (2015-2024)*

	OYYD(GA %95) (2015-2024)	Periyot I		Periyot II	
			YYD(GA %95)		YYD(GA %95)
Erkek	2.1 (1.1 ; 3.1) (p=0.0010)	2015-2021	-8.6 (-17.2 ; -5.2) (p=0.0004)	2021-2024	17.1 (1.6 ; 45.3) (p=0.0220)
Kız	2.3 (0.5 ; 4.4) (p=0.0180)	2015-2021	-8.3 (-15.9 ;-5.2) (p<0.0001)	2021-2024	20.1 (3.4 ; 49.3) (p=0.0039)

*GA: Güven Aralığı, YYD: Yıllık Yüzde Değişim, OYYD: Ortalama Yıllık Yüzde Değişim

Tablo 2. Seçili Ölüm Nedenlerine Göre Joinpoint Regresyon Analizi Sonuçları (Erkek) (2015-2024)

Nedenler	OYYD(GA %95) (2015-2024)	Periyot I		Periyot II	
			YYD(GA %95)		YYD(GA %95)
Dolaşım sistemi hastalıkları	-0.9 (-2.6 ; 0.7) (p=0.2395)	2015-2024	-0.9 (-2.6 ; 0.7) (p=0.2395)	-	-
Dışsal yaralanma ve zehirlenme	19.3 (4.6 ; 29.1) (p=0.0039)	2015-2021	-9.2 (-38.0 ; 2.4) (p=0.1119)	2021-2024	106.3 (29.1 ; 324.5) (p<0.0001)
Endokrin, beslenme ve metabolizma hastalıkları	-3.9 (-7.7 ; -0.4) (p=0.0276)	2015-2019	-8.9 (-24.0 ; 8.6) (p=0.0970)	2019-2024	0.3 (-17.9 ;19.8) (p=0.7270)

Sinir sistemi ve duyu organları					-
Solunum sistemi	-3.6 (-6.6 ;-0.8) (p=0.0156)	2015-2024	-3.6 (-6.6 ;-0.8) (p=0.0156)	-	
Malign ve Benign neoplazmlar				-	-
Diğer	-3.6 (-7.3 ; -0.3) (p=0.0324)	2015-2024	-3.6 (-7.3 ; -0.3) (p=0.0324)	2021-2024	5.0 (-1.1 ; 14.7) (p=0.1512)
	-1.9 (-3.6 ; -0.8) (p=0.0004)	2015-2021	-5.2(-10.9 ; -3.3) (p=0.0028)		-
	-7.4 (-10.4 ;-4.9) (p<0.0001)		-7.4 (-10.4 ;-4.9) (p<0.0001)		

*GA: Güven Aralığı, YYD: Yıllık Yüzde Değişim, OYYD: Ortalama Yıllık Yüzde Değişim

Tablo 3. Çocuklarda Ölüm Nedenlerine Göre Ölüm Eğilimlerinin (Kız), Türkiye, (2015-2024)*

Nedenler	**OYYD (2015-2024)**	**Periyot I**		**Periyot II**	
			YYD		**YYD**
Dolaşım sistemi hastalıkları	-0.1 (-4.7 ; 4.5) (p=0.908)	2015-2024	-0.1(-4.7 ; 4.5) (p=0.908)	-	-
Dışsal yaralanma ve zehirlenme	32.5 (12.1 ; 45.8) (p<0.0001)	2015-2021	-8.3 (-40.9 ; 4.7) (p=0.1740)	2021-2024	176.3 (51.8;609.6) (p<0.0001)
Endokrin, beslenme ve metabolizma hastalıkları	-3.7 (-5.6 ; -2.5) (p<0.0001)	2015-2021	-6.5 (-12.8 ; -4.4) (p=0.0090)	2021-2024	2.1(-4.1 ; 11.7) (p=0.6260)
Sinir sistemi	-3.0 (-4.5 ; -1.7) (p=0.0160)	2015-2024	-3.0(-4.5 ; -1.7) (p=0.0160)	-	-
Solunum sistemi					
Malign ve benign neoplazmlar	-2.9 (-6.2 ; 0.4) (p=0.0790)	2015-2019	-8.2 (-23.5 ; 8.0) (p=0.0850)	2019-2024	1.6 (-13.9 ; 19.7) (p=0.5010)
Diğer	-2.9 (-5.4 ;-0.6) (p=0.0180)	2015-2024	-2.9(-5.4 ;-0.6) (p=0.0180)	-	-
	-7.5 (-10.1 ; -5.4) (p<0.0001)		-7.5(-10.1 ; -5.4) (p<0.0001)	-	-

*GA: Güven Aralığı, YYD: Yıllık Yüzde Değişim, OYYD: Ortalama Yıllık Yüzde Değişim

Tartışma

Bu çalışma, Türkiye'de 2015–2024 yılları arasında 0–17 yaş grubu çocuk ölümlerinin zamansal eğilimlerini, dönüm noktalarını ve spesifik ölüm nedenlerindeki değişimleri JRA yöntemiyle ulusal ölçekte inceleyen kapsamlı bir epidemiyolojik değerlendirmedir. Çalışmanın temel bulgusu; 2015–2021 yılları arasında çocuk ölümlerinde her iki cinsiyette de kararlı ve istatistiksel olarak anlamlı bir düşüş seyrinin yaşandığı, ancak 2021 yılının belirgin bir kırılma noktası (joinpoint) oluşturarak 2021–2024 periyodunda çocuk ölümlerinde keskin bir artış eğilimine girildiğidir. Detaylı neden analizleri, 2021 sonrası gözlenen bu olumsuz dönüşün ana nedeninin "Dışsal yaralanma ve zehirlenmeler" kategorisindeki yüksek sıçrama olduğunu; buna karşın neoplazmlar, metabolik ve nörolojik hastalıklara bağlı çocuk ölümlerinde 10 yıllık periyot genelinde anlamlı gerilemelerin devam ettiğini ortaya koymuştur.

2015–2021 Dönemindeki İyileşme ve Sağlık Politikalarının Etkisi

Çalışmamızda 2015–2021 yılları arasında genel çocuk ölümlerinde her iki cinsiyette de yıllık ortalama %8'in üzerinde gerçekleşen belirgin gerileme (Erkek YYD = -%8,6; Kız YYD = -%8,3), Türkiye'nin son yirmi yılda çocuk sağlığı alanında yürüttüğü kararlı politikaların bir yansımasıdır. Dünya Sağlık Örgütü (DSÖ) ve UNICEF raporlarında da belirtildiği üzere, Türkiye 2000'li yılların başından itibaren Bebek ve Çocuk Ölüm Hızlarını (BÖH ve ÇÖH) düşürmede Binyıl Kalkınma Hedefleri ile Sürdürülebilir Kalkınma Amaçları doğrultusunda dikkate değer bir başarı elde etmiştir.[1,6-9]

Bu dönemde kaydedilen istikrarlı düşüşte birkaç temel faktör öne çıkmaktadır. İlk olarak, birinci basamak sağlık hizmetlerinin güçlendirilmesi, Aile Hekimliği Sistemi üzerinden yürütülen gebe, bebek ve çocuk izlem protokollerinin yaygınlaştırılması ve Genişletilmiş Bağışıklama Programı'nın (Genişletilmiş Aşı Programı) yüksek kapsayıcılık oranlarına ulaşması çocukluk çağı enfeksiyonlarına bağlı ölümleri önemli ölçüde azaltmıştır.[7] İkinci olarak, Pediatrik Acil ve Çocuk Yoğun Bakım ünitelerinin teknik altyapı ve uzman insan kaynağı açısından niteliksel ve niceliksel olarak geliştirilmesi, ayrıca Yenidoğan Yoğun Bakım Ağlarının standartlaştırılması kritik hastalıklarda sağkalım oranlarını yükseltmiştir.[8] Çalışmamızın bulgularında neoplazmlar (Erkek OYYD = -%1,9; Kız OYYD = -%2,9), endokrin/metabolik hastalıklar (Erkek OYYD = -%3,9; Kız OYYD = -%3,7) ve sinir sistemi hastalıklarında (Erkek OYYD = -%3,6; Kız OYYD = -%3,0) 10 yıl boyunca gözlenen sürekli gerileme, tanı-tedavi imkanlarındaki bu klinik ve teknolojik ilerlemeleri desteklemektedir. Özellikle ulusal düzeyde yürütülen Yenidoğan Tarama Programları (Fenilketonüri, Biyotinidaz Eksikliği, Kistik Fibrozis, KKH ve son dönemde eklenen SMA taramaları) metabolik ve nörolojik kökenli çocuk ölümlerinin erken tanı ve tedavi ile önlenmesinde hayati rol oynamıştır.[9]

2021–2024 Dönemindeki Kırılma: Dışsal Yaralanmalar ve Afet Dinamikleri

Çalışmamızın en çarpıcı ve alarm verici bulgusu, 2021 yılı sonrasında çocuk ölümlerinde her iki cinsiyette de (Erkek YYD = %17,1; Kız YYD = %20,1) ortaya çıkan şiddetli artış eğilimidir. Nedene özgü regresyon analizleri, bu artışın doğrudan "Dışsal yaralanma ve zehirlenmeler" (ICD-10: V01-Y89) grubundaki olağanüstü yükselişten kaynaklandığını net biçimde göstermektedir (2021–2024 YYD: Erkek = %106,3; Kız = %176,3). Bu rekor artışın arkasındaki temel epidemiyolojik faktörleri değerlendirirken Türkiye'nin yakın dönemde yaşadığı makro düzeydeki çevresel ve toplumsal olayları dikkate almak zorunludur. Türkiye İstatistik Kurumu (TÜİK) ölüm nedeni sınıflandırma standartlarında, deprem, sel ve doğal afetler gibi kitle ölümlerine yol açan çevresel yıkımlar "Dışsal yaralanma ve zehirlenmeler" ana başlığı altında kodlanmaktadır.[4,10] 6 Şubat 2023 tarihinde meydana gelen Kahramanmaraş merkezli şiddetli depremler, 11 ili kapsayan geniş bir coğrafyada doğrudan yıkıma yol açmış ve TÜİK verilerine göre 45 binin üzerinde yurttaşın hayatını kaybetmesine neden olmuştur.[4] Depremden etkilenen nüfusun önemli bir bölümünü çocukların oluşturduğu dikkate alındığında, 2023 yılı TÜİK verilerine yansıyan kitlesel çocuk kayıpları, 2021–2024 dönemi dışsal yaralanma istatistiklerinde yapısal bir sıçramaya ve JRA modelinde kırılmaya yol açmıştır. Küresel literatürde de büyük doğal afetlerin meydana geldiği yıllarda çocuk ve ergen ölümlerinde dışsal nedenli dramatik kırılmaların yaşandığı bildirilmektedir.[11,12] Afet etkisine ek olarak, COVID-19 pandemisi kısıtlamalarının (kapanma ve hareketlilik kısıtlamaları) 2021 ortalarından itibaren kaldırılmasıyla birlikte çocukların sosyal yaşama, trafiğe ve açık alanlara dönüşü; motorlu araç kazaları, suda boğulmalar, düşmeler ve ev içi kazalarında artışı beraberinde getirmiştir.[4,10-14] Pandemi sonrası dönemde artan çocukluk çağı yaralanmaları ve zehirlenmeler, gelişmekte olan ülkelerde önlenebilir çocuk ölümlerinin en başında gelmeye devam etmektedir.[15]

Çalışmamızda kız çocuklarında dışsal nedenlerdeki artış hızının (YYD = %176,3) erkek çocuklara (YYD = %106,3) kıyasla matematiksel olarak daha yüksek çıkması, kız çocuklarında baseline (taban) ölüm oranlarının tarihsel olarak daha düşük olmasından kaynaklanan oransal hassasiyet ve afet anındaki maruziyet dinamikleri ile açıklanabilir.

Güçlü Yönler ve Sınırlılıklar

Bu çalışmanın en güçlü yönü, Türkiye'yi temsil eden 10 yıllık ulusal veri setini kapsaması ve eğilim analizlerinde doğrusal olmayan kırılma noktalarını tarafsız biçimde saptayabilen JRA metodolojisini kullanmasıdır. Geleneksel doğrusal modellerin aksine JRA, 2021 yılındaki kritik kırılmayı objektif olarak ortaya koyarak çocuk sağlığı politikalarında acil müdahale gerektiren alanı (dışsal nedenler) netleştirmiştir.

Çalışmanın bazı sınırlılıkları mevcuttur. İlk olarak, verilerin TÜİK ikincil idari kayıtlarına dayanması nedeniyle, yaralanma ve dışsal ölümlerin alt detaylarına (örneğin trafik kazası, boğulma, deprem, zehirlenme ayrımına) mikro düzeyde ulaşılması mümkün olmamıştır. İkinci olarak, ölüm kayıtlarında coğrafi ve sosyoekonomik düzey değişkenleri bulunmadığından, bölgesel eşitsizliklerin kırılma noktalarına etkisi bu çalışmada analiz edilememiştir.

2021–2024 dönemindeki sert kırılmanın (YYD artışının) analizinde, 6 Şubat 2023 Kahramanmaraş depremlerinin yarattığı ani şok etkisi göz önünde bulundurulmalıdır. JRA algoritması periyot boyunca süreğen bir trend değişimi varsaydığından, tek bir yıldaki afet kaynaklı kitlesel mortalite sıçraması tüm periyodun eğimini yukarı çekebilmektedir. TÜİK veri tabanında afet ölümleri dışsal nedenlerden ayrıştırılamadığı için depremden arındırılmış bir duyarlılık analizi yapılamamış olması çalışmamızın temel epidemiyolojik sınırlılığıdır.

Politika Önerileri ve Sonuç

Çalışmamızdan elde edilen bulgular, Türkiye'de çocuk sağlığı göstergelerinin geliştirilmesinde paradigma değişimine ihtiyaç duyulduğunu göstermektedir. Tıbbi/doğal hastalıklara ve enfeksiyonlara bağlı ölümlerde elde edilen başarı takdire şayan olmakla birlikte, çocuk ölümlerini düşürmedeki nihai başarı artık dışsal ve önlenebilir nedenlerin kontrol altına alınmasına bağlıdır.

Bu doğrultuda şu stratejik adımların atılması önerilmektedir:

Afet Odaklı Çocuk Koruma Stratejileri: Deprem ve doğal afet riskinin yüksek olduğu ülkemizde, afet yönetim planlarında çocuk popülasyonuna özgü arama-kurtarma, koruma ve acil sağlık müdahale protokolleri standartlaştırılmalıdır.

Çevre ve Ev İçi Güvenlik Standartları: Bütüncül bir "Çocuk Yaralanmalarını Önleme Ulusal Eylem Planı" oluşturulmalı; trafik güvenliği, okul ve ev içi kaza önleyici tedbirler, suda boğulma risklerine karşı denetimler artırılmalıdır.

Sürdürülebilir Sağlık Hizmetleri

Klinik başarının sağlandığı çocukluk çağı neoplazmları, metabolik ve nörolojik hastalıklarda erken tanı, tarama ve nitelikli pediatrik bakım olanakları kararlılıkla sürdürülmelidir.

Sonuç olarak, Türkiye'de 2015–2021 yılları arasında çocuk ölümlerinde sağlanan kararlı düşüş eğilimi, 2021 sonrasında dışsal etkenlerin (afetler, kazalar ve yaralanmalar) etkisiyle tersine dönmüştür. Çocuk sağlığı politikalarında acilen tıbbi tedavilerin ötesine geçilerek çevresel risk azaltımı, afet hazırlığı ve kaza önleme odaklı çok sektörlü yaklaşımların hayata geçirilmesi gerekmektedir.

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MIXTURE-AWARE SYSTEMS PHARMACOLOGY MAPS HAZELNUT-OIL CONSTITUENTS ONTO PHASE-SPECIFIC HUMAN WOUND-REPAIR STATES

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ABSTRACT
Hazelnut oil is a chemically heterogeneous lipid matrix whose biological activity cannot be represented by a single compound-target interaction. We formulated its potential action on cutaneous repair as a constituent-resolved, mixture-aware perturbation problem. A versioned registry separated saponifiable fatty-acyl composition from intact unsaponifiable constituents and linked 13 components to strictly filtered human bioactivity evidence. Donor-time pseudobulks from human acute wounds (GSE241132) defined cell-type-specific D1-D0, D7-D1 and D30-D7 programs, which were evaluated in independent spatial transcriptomics (GSE241124), diabetic foot ulcer (GSE165816), venous ulcer (GSE265972) and temporal proteomics (PXD052154). Composition-weighted target-to-program proximity was tested against 10,000 degree-matched nulls in STRING functional and physical interactomes and against almond, olive and sunflower-oil counterfactuals. Strict spatial mappings replicated all nine tested cell-type-transition programs in every available donor. Healing diabetic-foot-ulcer samples differed in 8 of 12 projected programs at false-discovery rate <0.05, whereas venous ulcers showed large early/proliferative displacement with incomplete late resolution. The target-covered hazelnut fatty-acyl fraction was proximal to 9 of 53 functional-network and 2 of 53 physical-network modules; early myeloid D1-D0 convergence was robust across both networks (z=5.09 and 2.71). No matched hazelnut-versus-olive comparison produced non-overlapping composition-uncertainty intervals, identifying an oleic-rich oil-class topology rather than hazelnut specificity. A measured-x-y/modelled-z scenario analysis further localized predicted exposure toward wound-edge and epidermal compartments unless distributed delivery was imposed. The framework therefore prioritizes stage-, cell-state- and formulation-specific mechanisms for experimental testing; it does not infer whole-oil target engagement or therapeutic efficacy.
Keywords: hazelnut oil; cutaneous wound healing; systems pharmacology; spatial transcriptomics; network proximity; mixture modelling; counterfactual oils

Introduction
Cutaneous repair is not a monotonic return to intact skin. It is an ordered, overlapping sequence of haemostatic, inflammatory, proliferative and remodelling processes in which the same molecular activity can be adaptive at one stage and maladaptive when prolonged.[1,2] Human single-cell and spatial studies have now resolved this temporal coordination across keratinocytes, fibroblasts, endothelial cells and immune populations, while comparisons with chronic wounds indicate that non-healing states fail to enter or exit selected repair phases rather than simply opposing an "intact-skin" signature.[3] This phase dependence imposes a stringent requirement on computational intervention studies: favorable modulation cannot be defined as indiscriminate reversal toward baseline.
Botanical oils create an additional modelling problem. Hazelnut oil contains triacylglycerols, a fatty-acyl distribution dominated by oleic acid, and a lower-abundance unsaponifiable fraction containing tocopherols, phytosterols and squalene.[4,5] Their abundance varies by cultivar, geography and processing, while intact triacylglycerols, liberated fatty acids and minor lipophilic constituents cannot be assumed to share cellular availability.

A single-node representation of "hazelnut oil", or an unweighted union of all reported targets, therefore discards the chemical structure of the intervention before biological analysis begins.

We asked whether the literature-defined hazelnut-oil chemical space converges on phase- and cell-type-specific modules of successful human acute repair that are displaced in chronic wounds. The study was designed as a sequence of falsifiable gates. First, chemical composition and human target evidence were versioned and tiered. Second, acute wound programs were estimated with donor-time, rather than cell, as the biological replicate and were stress-tested spatially and proteomically. Third, the programs were projected independently into diabetic-foot-ulcer (DFU) and venous-ulcer (VU) cohorts without cross-study cell pooling. Fourth, mixture proximity was calibrated against degree-matched random targets, two interactome definitions, composition uncertainty, leave-one-component-out ablation and matched botanical-oil counterfactuals. Finally, measured spatial coordinates were used to construct a transparent three-dimensional scenario layer that distinguishes measured geometry from modelled depth and transport.

This architecture yields a positive but bounded computational result: the target-covered fatty-acyl fraction has a reproducible early-myeloid network signal and a formulation-dependent epidermal exposure profile, while comparator analyses reject hazelnut-unique topology. These results define a biotechnology layer for constituent and assay prioritization and a medical-technology layer for phase-aware spatial scenario testing. They do not substitute network proximity for direction of effect, tissue exposure or wound closure.

Results

A constituent-resolved evidence model prevents chemical and statistical category errors

The chemical registry contained 14 composition records representing 13 unique hazelnut-oil components. Saponifiable fatty-acyl composition, intact triacylglycerols and unsaponifiable constituents were encoded as separate representations (Fig. 1). Fatty-acyl percentages were not converted into free-fatty-acid doses, and minor constituents reported in mg kg^{-1} were not pooled numerically with fatty-acid percentages. Cultivar and processing ranges were propagated as triangular composition distributions. Among 1,546 retrieved ChEMBL activity records, strict filtering for human single proteins, binding or functional assays, eligible quantitative endpoints, exact relations, pChEMBL ≥5, absence of validity warnings and non-duplicate records retained 17 records, 12 targets and four target-supported constituents: oleic acid, linoleic acid, alpha-tocopherol and beta-sitosterol. The retained targets included PPARA, PPARD, PPARG, FABP1, FABP4, FABP5, FAAH and PTPN1, among others. This is experimentally curated compound–protein evidence; it is not evidence of target engagement by applied whole oil.

Repository-level integrity testing also detected a material inherited error. A pathway/transcription-factor table had reported 3,549 exact P values of zero and 6,376 discrepancies among 17,577 rows. Enumeration of all 2^3 sign assignments for three paired donors showed that the minimum attainable two-sided exact P value was 0.25. The source file was preserved, corrected values were written to a new provenance-tracked table, and the affected table was excluded from confirmatory claims. This audit changed the evidential hierarchy of the study: gene-level donor-aware programs became the primary acute reference, whereas pathway and regulator results remained descriptive.

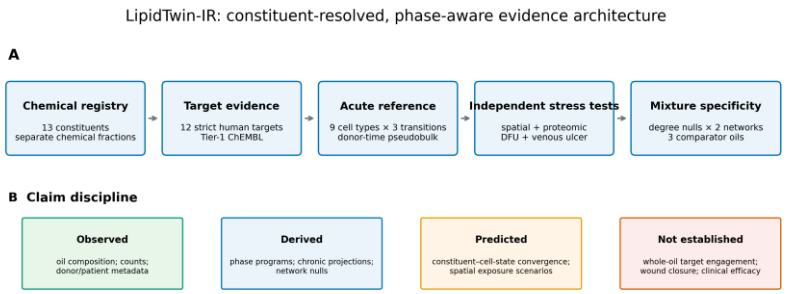


Figure 1 | Constituent-resolved evidence architecture and claim discipline.

The workflow separates chemical registry, target evidence, donor-aware acute reference, independent stress tests and matched mixture specificity. Observed, derived and predicted outputs are distinguished from whole-oil target engagement, wound closure and clinical efficacy, which are not established.

Donor-aware acute programs reproduce in independent spatial tissue sections

The biological question was whether successful acute repair could be represented by phase-specific programs that were stable across individuals. GSE241132 provided 12 donor-time samples from three donors at D0, D1, D7 and D30. Nine major cell types met the prespecified requirement of all 12 pseudobulks and at least 20 cells per pseudobulk. Within each cell type, a donor-fixed-effect model estimated categorical adjacent transitions. Stable genes required Benjamini–Hochberg false-discovery rate (FDR) <0.05, |log2 fold-change| ≥0.5, identical direction in all three donors and leave-one-donor-out sign stability. Up to 50 genes per direction and transition produced 2,206 ranked program memberships (Fig. 2A).

Spatial validation used 22,915 GSE241124 Visium spots from 16 donor-time sections and four donors, but inference was performed on donor-time-region pseudobulks rather than on spots. Under strict anatomical mappings, keratinocyte, fibroblast and endothelial programs showed the expected positive change in all nine matched cell-type–transition tests in every available donor. Mean paired program-score changes were 1.57, 0.81 and 0.33 for keratinocyte D1–D0, D7–D1 and D30–D7; 1.22, 1.09 and 0.65 for fibroblasts; and 1.01, 0.99 and 0.49 for endothelial cells. Seventeen of 18 tests remained all-donor positive when expanded anatomical mappings were included. With only four donors the minimum two-sided exact sign P value was 0.125, so the evidence rests on effect-size consistency and complete donor-direction replication rather than an unattainable conventional P-value threshold.

Chronic wounds occupy phase-specific displaced states

The next question was whether independently acquired chronic wounds failed to enter or exit the acute programs. Acute gene weights were transferred into each cohort separately, after homologous cell-type mapping, within-dataset normalization and sample-level pseudobulking. No cells were pooled across studies.

GSE165816 contributed 33 foot-skin libraries and 94,325 input cells; 82,694 cells retained stable annotations across two marker resolutions. Four homologous cell classes had 92.3% aggregate program-gene coverage. Compared with non-ulcer diabetic foot skin, healing DFU samples differed in 8 of 12 cell-type–transition projections at within-comparison FDR <0.05 (Fig. 3A). The largest standardized separation was the fibroblast D7–D1 program (mean difference 0.856, bootstrap 95% confidence interval 0.571–1.115; Hedges g=2.64; exact P=0.00033; FDR=0.00395). Keratinocyte, endothelial and myeloid projections showed coordinated early entry and later exit patterns. Non-healing versus healing DFU comparisons trended in the opposite direction for **selected programs but did not survive family-wise** FDR correction, which prevents a categorical non-healer claim.

GSE265972 was assembled from official segmented archives and validated at the byte and nested-ZIP levels before analysis. Official annotations yielded 48,346 cells, four VU patients and five healthy controls. All acute-program genes were represented. VU samples showed large positive displacement along early and proliferative reference programs together with negative late-transition scores (Fig. 3B). The fibroblast D7–D1 score had a mean difference of 0.946 (95% CI 0.557–1.332; Hedges g=2.61; exact P=0.00794), while endothelial D30–D7 was negative (difference -0.861, 95% CI -1.394 to -0.261; g=-1.68). No one of the 12 contrasts crossed global FDR 0.05; the minimum FDR was 0.0762. Taken together, the two chronic cohorts support a phase-trapping model—enhanced or persistent early/proliferative activity with incomplete resolution—rather than a simple global deficiency.

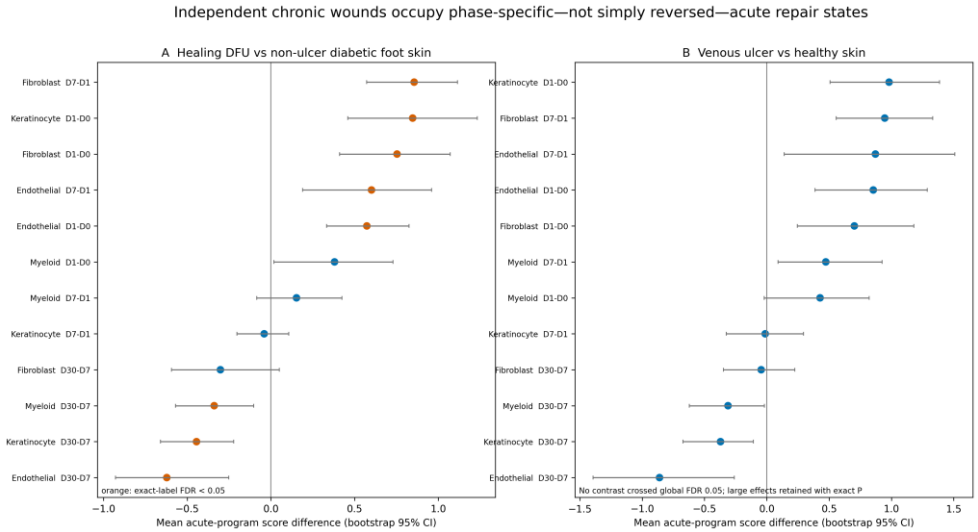


Figure 3 | Independent chronic wounds occupy phase-specific acute-program states**.**

Forest plots show mean projection-score differences and bootstrap 95% confidence intervals for (A) healing DFU versus non-ulcer diabetic foot skin and (B) VU versus healthy skin. Orange points in A pass within-comparison FDR <0.05. No VU point passes global FDR <0.05.

Temporal proteomics validates structure but exposes compartment-dependent inversion

Independent protein data were used to test temporal coherence, not oil response. PXD052154 contained 4,631 quantified proteins across 14 participants and three time points. Official UniProt mapping resolved 4,000 accessions (86.4%) and participant-paired analysis identified 1,070 D2–D1 and 1,971 D7–D1 proteins at FDR <0.05. Comparison with the acute RNA programs used 10,000 gene-label permutations within prespecified scopes (Fig. 2B). In the time-matched D7–D1 comparison, three Spearman tests and two signed-weight tests were significant at within-scope FDR <0.05. Keratinocyte RNA–protein rank association was strongly negative (rho=-0.629; FDR=0.0008), as were lymphoid and hair-follicle associations, whereas mast-cell signed alignment was positive. In an explicitly exploratory timing comparison, D2–D1 protein changes were positively associated with RNA D1–D0 programs across keratinocyte, hair-follicle, endothelial and fibroblast compartments. Thus, the independent proteome supports the existence of ordered wound states but also shows that transcript-to-protein timing is cell-compartment dependent. Uniform multi-omic concordance would have been biologically and statistically inaccurate.

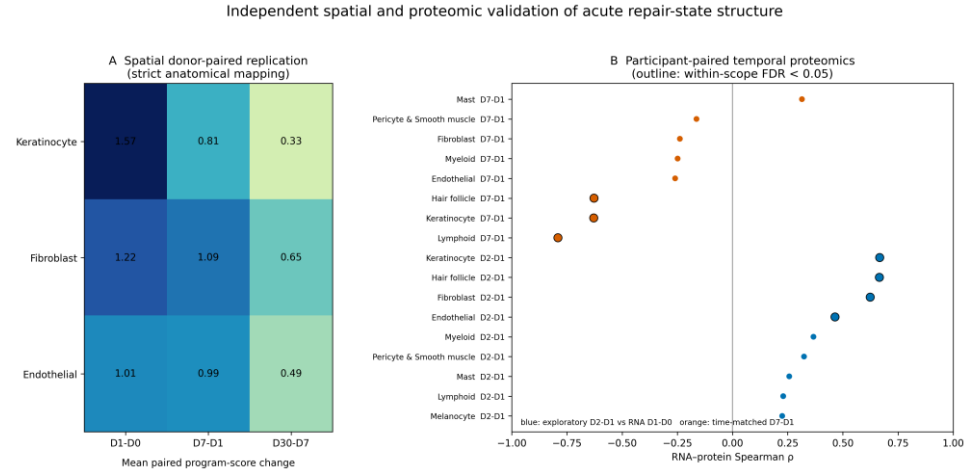


Figure 2 | Independent spatial and proteomic validation of acute repair-state structure**.**

(A) Mean donor-paired spatial-program changes under strict anatomical mapping. Every cell-type–transition pairing is positive in all available donors. (B) Participant-paired protein changes compared with acute RNA programs. Point outline indicates within-scope FDR <0.05; orange is the primary D7–

D1 time-matched comparison and blue is the exploratory D2–D1 protein *versus* D1–D0 RNA comparison.

The fatty-acyl fraction converges on selected wound modules across network nulls

We next asked whether experimentally supported constituent targets were unusually close to the acute modules. Targets were filtered for expression in the relevant acute cell type and mapped to STRING v12 functional and physical networks at combined score ≥700. Functional and physical graphs contained 16,201 nodes/236,930 edges and 10,746 nodes/86,519 edges, respectively. For every constituent–module test, targets were replaced 10,000 times with expressed proteins from matched log2-degree bins. Composition uncertainty was propagated with 2,000 draws. Weights were normalized only within the saponifiable or unsaponifiable fraction; the fractions were never combined into an artificial common mass scale.

The target-covered hazelnut fatty-acyl fraction was significant in 9 of 53 tested functional-network modules and 2 of 53 physical-network modules after FDR correction across every oil, fraction and program tested in each network (Fig. 4). The strongest result shared by both networks was the myeloid D1–D0 up-program (functional z=5.09, FDR=0.00193; physical z=2.71, FDR=0.00606). Hair-follicle D1–D0 up was also significant in both. Additional functional-network priorities included lymphoid D1–D0 up, pericyte D1–D0 down, endothelial D1–D0 down, endothelial D30–D7 up and myeloid D7–D1 up. Overall functional-versus-physical mixture rankings correlated only moderately (Spearman rho=0.309, $P=7.76\times10^{-11}$), demonstrating substantial interactome sensitivity.

No unsaponifiable mixture test crossed FDR 0.05. Coverage was often limited to alpha-tocopherol, causing identical topology for comparator oils that shared the same single target-covered constituent. The correct inference is therefore asymmetric: the target-covered fatty-acyl fraction supports selected network-proximity hypotheses, whereas the unsaponifiable fraction remains a lower-coverage experimental priority rather than a negative biological conclusion.

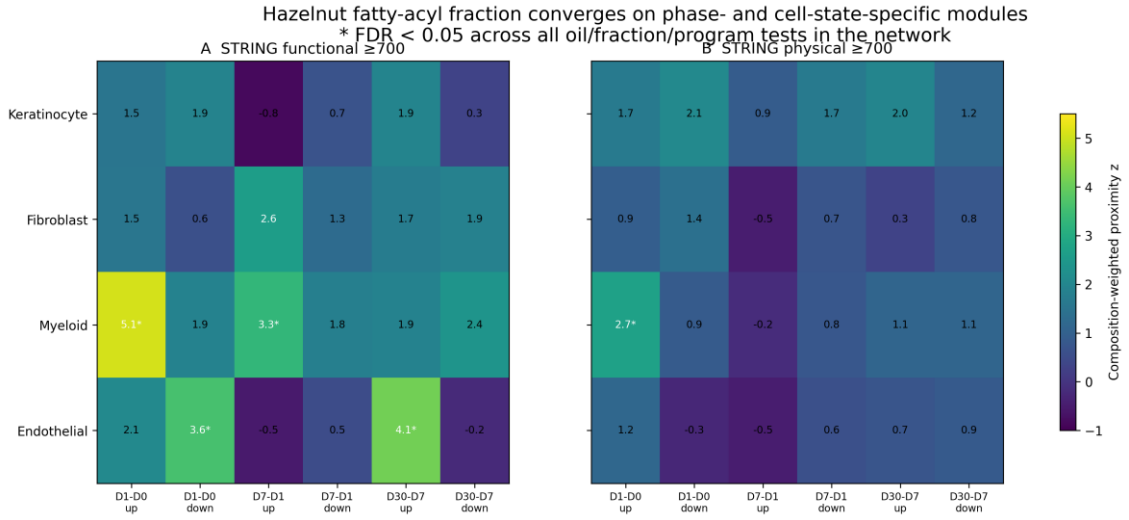


Figure 4 | Hazelnut fatty-acyl targets converge on selected phase- and cell-state modules.

Composition-weighted proximity z scores are shown in STRING functional and physical networks. Asterisks indicate FDR <0.05 across all oil, fraction and program tests within the corresponding network. Proximity is unsigned.

Comparator oils falsify hazelnut-unique topology

Chemical specificity was tested rather than assumed. Primary-study composition profiles for almond, olive and sunflower oils were processed through the identical targets, programs, networks, nulls and uncertainty propagation (Fig. 5). Across 106 matched hazelnut-versus-olive tests spanning both networks, no pair had non-overlapping composition-uncertainty intervals; the median hazelnut-minus-olive z difference was 0.019. The hazelnut score was also not consistently greater than almond. Comparisons with linoleic-rich sunflower oil changed sign across network definitions: hazelnut tended to be greater in the functional network but smaller in the physical network. These counterfactuals reject a hazelnut-specific network claim.

Leave-one-component-out analysis showed why. Omitting oleic acid reduced the median functional-network mixture z by 0.418 but changed the physical-network median by only 0.002; linoleic-acid omission changed the corresponding medians by 0.137 and 0.104. The attribution of proximity to a single major fatty acid is therefore network dependent. The supported conclusion is a broader oleic-rich botanical-oil class topology with composition-dependent quantitative variation, not a unique hazelnut mechanism.

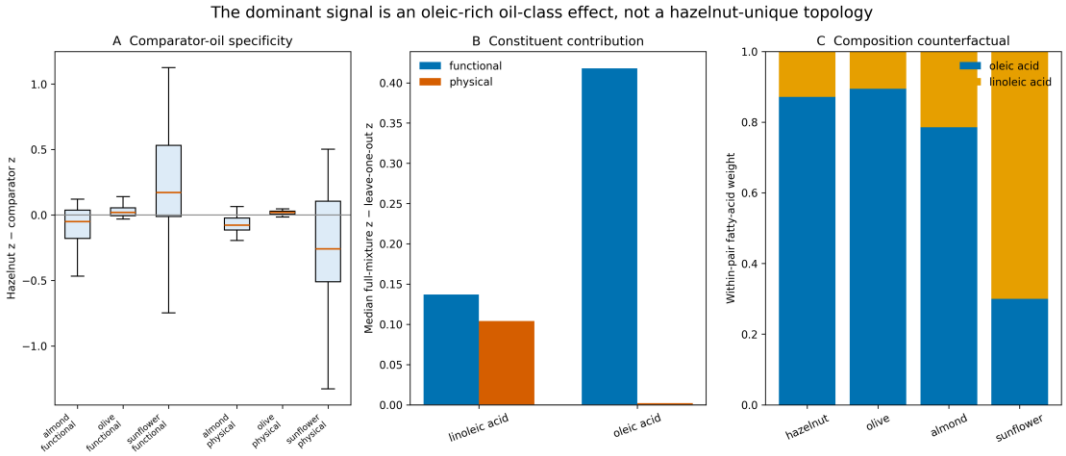


Figure 5 | Comparator and ablation analyses identify an oleic-rich oil-class topology.

(A) Hazelnut-minus-comparator z distributions. (B) Median change after leaving out each target-covered fatty acid. (C) Relative oleic/linoleic weights in the comparator registry. The cross-study composition counterfactual does not support hazelnut-unique topology.

Directional evidence narrows the predicted effect architecture

Network proximity is unsigned, so we separately evaluated perturbational direction. Free oleic acid in mouse macrophages was mapped through 18,782 one-to-one mouse–human orthologues and compared with the human myeloid programs using 10,000 gene-label permutations. Early D1–D0 alignment was positive but did not survive within-signature correction (weighted alignment 0.234, z=1.85, P=0.0668, FDR=0.200). A stearic-acid control produced a similar nominal signal. Non-equivalent ethyl linoleate/oleate exposure in reconstructed human skin (n=2) yielded no FDR-significant alignment. Positive inflammatory and formulation controls behaved as expected, demonstrating that the test could detect strong directional structure.

The effect prediction must therefore be stated at the correct level. The analyses prioritize where and when the target-covered mixture may engage repair biology—most robustly the early myeloid module and, under spatially available exposure, epidermal programs—but do not resolve whether whole oil activates, suppresses or beneficially redirects those states. A development program should measure both early immune engagement and the ability to exit inflammatory/proliferative states, rather than optimize a single generic “wound-healing” score.

A measured-x-y/modelled-z layer makes formulation dependence explicit

The medical-technology layer embedded measured GSE241124 Visium x-y coordinates from a representative wound section into a 24×48×64 grid. Wound-edge spots defined 225 measured surface-source locations; 1,104 spots were assigned prespecified z-depths by anatomical compartment. Gaussian diffusion–reaction fields were evaluated under surface-retained, intermediate and distributed scenarios, with molecular-weight scaling and separate chemical fractions (Fig. 6). No measured partition coefficient, diffusivity, dose or clearance was supplied, so all exposures are dimensionless relative scenarios.

Under the intermediate fatty-acyl scenario, median relative exposure was 0.0367 in keratinocyte-associated spots, 8.6×10^{-9} in fibroblast spots and zero in endothelial spots. The distributed scenario increased medians to 0.0493, 1.86×10^{-4} and 2.62×10^{-4}, respectively. Surface retention yielded essentially no deep-compartment exposure.

When exposure was multiplied by a conservative cross-network up-versus-down topology contrast, non-zero estimates remained dominated by surface and wound-edge compartments. Consequently, the computationally predicted action is formulation contingent: an unmodified surface-retained preparation is most plausibly tested for epidermal/wound-edge biology, whereas claims involving fibrovascular compartments require a delivery system demonstrated to distribute beyond the surface.

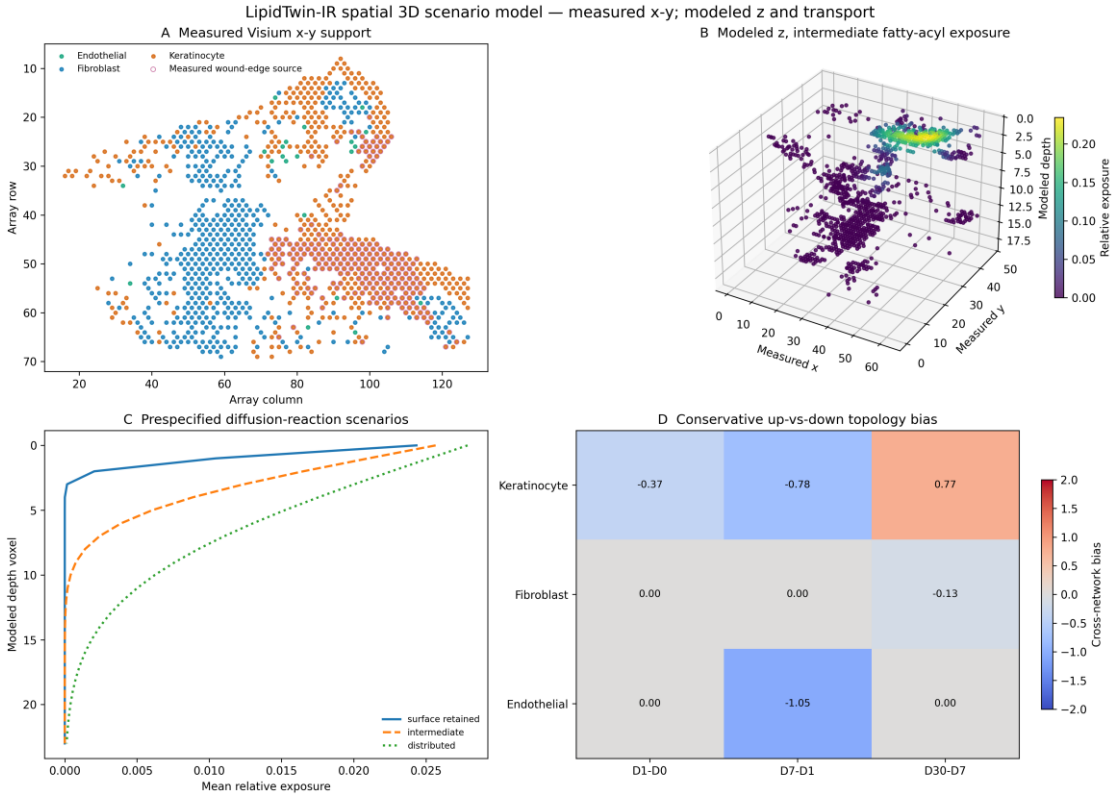


Figure 6 | Measured-x-y/modelled-z spatial 3D scenario model.

(A) Measured Visium coordinates and wound-edge source spots. (B) Anatomical spots embedded in modelled depth and coloured by intermediate-scenario fatty-acyl exposure. (C) Prespecified diffusion–reaction depth profiles. (D) Conservative cross-network up-versus-down topology contrast. Exposures are dimensionless relative scenarios, not measured pharmacokinetics.

Discussion

This study reframes a botanical-oil question as a falsifiable mixture and state-transition problem. Its principal result is not a generic list of wound genes. It is a constrained mechanistic architecture in which: (i) successful repair is represented by donor-aware adjacent-stage programs; (ii) those programs reproduce spatially and distinguish selected chronic-wound states; (iii) experimentally supported fatty-acyl targets show null-calibrated proximity to a restricted subset of programs; (iv) early myeloid convergence is robust to functional-versus-physical interactome choice; (v) comparator oils reject hazelnut uniqueness; and (vi) spatial scenario modelling places delivery depth upstream of any cell-compartment claim.

The chronic-wound projections are biologically important for interpretation. Early inflammation is required for repair, and its wholesale suppression is not a valid therapeutic objective.[2,3] VU samples in this analysis were not globally deficient in acute programs; instead, they expressed large early/proliferative displacements while showing reduced late-transition scores. Healing DFU samples were likewise enriched for selected acute programs. These observations imply that the relevant intervention question is whether a formulation moves a stalled state toward its next appropriate phase. A compound that increases an early myeloid program could be adaptive before adequate inflammatory engagement but counterproductive if the same state is already persistent. This is why a phase-aware assay panel is more informative than a single wound-closure endpoint.

The cross-interactome myeloid result provides the strongest biotechnology hypothesis. Oleic and linoleic acid target evidence connects to lipid sensing, fatty-acid transport and immunometabolic regulation through PPARs, FABPs, FAAH and related proteins. Their proximity to the early myeloid module supports experiments that combine constituent-resolved exposure with macrophage state, cytokine trajectory and resolution timing. However, the absence of corrected directional alignment for free oleic acid prevents assignment of "pro-inflammatory" or "anti-inflammatory" action to the whole mixture. The appropriate experiment is therefore bidirectional and time resolved: measure entry into an early defense state and subsequent transition out of it.

The comparator result is a strength rather than a failure. Hazelnut and olive profiles were indistinguishable by the predefined network-specificity criterion, so the analysis falsified the attractive but unsupported claim that the topology is uniquely hazelnut derived. This shifts product development toward compositional standardization, minor-fraction coverage and delivery performance. Hazelnut oil may still differ in experimentally relevant batch chemistry, oxidation products, sensory properties, skin partitioning or safety, but those differences must be measured. They cannot be inferred from a shared oleic-acid-rich topology.

The 3D layer is intentionally a scenario model rather than a pharmacokinetic digital twin. Its value is decision support: it separates hypotheses that remain plausible under surface retention from those that require distributed delivery, and it exposes which parameters must be measured to progress toward a calibrated twin. The next model version should incorporate batch-specific composition, vehicle-controlled release, stratum-corneum partitioning, diffusion and clearance estimates, followed by calibration against depth-resolved tissue measurements. Until then, the numerical fields are relative and must not be interpreted as concentration or dose.

Several limitations define the inference boundary. First, no qualifying dataset directly exposes human wound tissue or a validated wound model to composition-measured whole hazelnut oil; therefore target engagement, direction of state change and wound closure are not measured here. This is not a lack of computational evidence: the network and state-transition evidence is statistically explicit and independently stress-tested. It is a boundary between mechanistic inference and intervention efficacy. Second, the composition registry describes literature-defined chemical space rather than a batch-matched formulation, and comparator oils were assembled from cross-study primary measurements. Third, acute reference inference is limited to three donors; exact sign tests cannot reach $P<0.05$, making leave-one-donor-out stability and independent four-donor spatial replication essential. Fourth, the two interactomes agreed only moderately, and constituent ablation was network sensitive. Fifth, chronic cohorts differ in anatomical site, disease context and sample size; analyses were therefore kept within cohort and not interpreted as batch-corrected pooled biology. Sixth, direct directional priors were cross-species or chemically non-equivalent and were treated as priors, not substitutes for whole-oil perturbation. Seventh, the unsaponifiable fraction had low target coverage, and no safety or sensitization conclusion is supported.

Within these boundaries, the study supports a concrete development sequence. A batch-specific oil should first be analytically characterized. It should then be compared with an oleic-matched oil, a linoleic-shifted oil, the isolated fatty-acyl fraction, the unsaponifiable fraction and leave-one-component-out reconstitutions. A human-relevant cell or tissue model should sample early immune entry, keratinocyte migration, fibroblast matrix transition, endothelial response and late inflammatory resolution at multiple time points. Measured depth profiles should calibrate the spatial model. This design would convert the present crossmatched mechanism into a direct causal test without discarding the mixture structure that motivated the analysis.

Methods

Study design and claim classes

The primary question was whether composition-weighted hazelnut-oil constituents were more proximal than degree-matched nulls to cell-type- and phase-specific programs of successful human repair, whether those programs were displaced in independent chronic wounds, and whether any predicted topology exceeded chemically relevant comparator oils. Conclusions were labelled as observed (directly measured public data), derived (statistics calculated from measured data), predicted (model output) or not established. Network proximity was never interpreted as activation, inhibition or efficacy.

Chemical registry and comparator oils

Hazelnut composition was curated from cultivar-resolved primary studies.[4,5] Each record included chemical identifier, formula, structure, fraction, central value, range, unit, analytical basis, cultivar/process metadata and source. Saponifiable fatty-acyl percentages, intact triacylglycerols and unsaponifiable mg kg^{-1} measurements remained separate. Almond, olive and sunflower comparators were derived from primary composition studies and processed through the same unit policy.[6–9] When lower, central and upper estimates were available, uncertainty was sampled from triangular distributions. "Literature-defined hazelnut-oil chemical space" denotes these empirical ranges and is not a batch-specific formulation.

Tier-1 compound–target evidence

ChEMBL records were restricted to *Homo sapiens*, single-protein targets, binding or functional assays, EC50/IC50/Kd/Ki/Potency endpoints, exact equality relations, pChEMBL ≥5, no data-validity warning and no potential duplicate.[10] Measured and predicted target evidence were never merged. Target availability was subsequently restricted to genes expressed in the relevant GSE241132 cell-type pseudobulk and present in the evaluated interactome.

Acute wound pseudobulk modelling

GSE241132 contains three paired donors at intact D0, D1, D7 and D30.[3] Raw counts were aggregated within donor, time and main cell type. A cell type was modelled if all 12 donor-time pseudobulks were present with at least 20 cells. Genes required ≥1 count per million in at least three samples, total count ≥20 and exclusion from the technical-gene list. log2(CPM+0.5) was modelled with an intercept, donor fixed effects and categorical time coefficients. Residual variances were moderated with an empirical-Bayes prior.[11] Contrasts were D1–D0, D7–D1 and D30–D7. FDR was controlled with the Benjamini–Hochberg method.[12] Stable genes required FDR <0.05, |log2FC| ≥0.5, concordant direction across all donors and leave-one-donor-out sign stability. The top 50 genes per direction were ranked by -log10(FDR)×|log2FC|. Signed program weights were log2FC divided by the sum of absolute log2FC within each cell-type–transition program. The design explicitly avoids treating individual cells as replicates.[13]

Spatial validation

GSE241124 Visium counts, annotations and coordinates were grouped into strict and expanded anatomical mappings for keratinocyte, fibroblast and endothelial compartments.[3] Counts were aggregated as donor-time-region pseudobulks, normalized within cell type and scored with the acute signed weights. Donor-paired changes were calculated for the matched transition. Exact two-sided sign P values enumerated all donor sign assignments; leave-one-donor-out direction and the number of positive donors were also reported. Spot-level scores were retained only for visualization and spatial modelling.

Chronic-wound projection

For GSE165816, reference-marker transfer was performed at two annotation resolutions; primary analyses retained cells whose broad assignments were stable across resolutions. Counts were aggregated within sample and homologous cell type for DFU healer, DFU non-healer, non-ulcer diabetic and non-diabetic foot-skin groups.[14] For GSE265972, the processed archive was byte-assembled, SHA-256 checked and recursively tested before official annotations were used.[3] VU and healthy samples were aggregated within patient/sample and cell type. Within each cohort and cell type, program genes were z-standardized across samples and combined with acute signed weights. Group differences were summarized by means, Hedges g and 5,000 (DFU) or 10,000 (VU) bootstrap resamples for 95% confidence intervals. Exact label permutations were exhaustive when feasible. FDR was controlled within each DFU clinical comparison and globally across the 12 VU tests. No cross-dataset integration or cell-level hypothesis test was performed.

Temporal proteomic validation

PXD052154 quantified 4,631 proteins from paired human skin wounds.[15] Accession mapping used the official UniProt mapping service.[16] Protein effects were estimated within participant for D2–D1 and D7–D1 and collapsed to genes. Acute RNA program effects were compared with protein effects using

Spearman correlation, a signed weighted score and sign concordance. Gene labels were permuted 10,000 times, and FDR was controlled within the primary time-matched or exploratory timing scope.

Network proximity, mixture uncertainty and specificity

STRING v12 human functional and physical links were filtered at score ≥700.[17] For a component target set T and program module M, the observed distance was the mean shortest-path distance from expressed targets to M. Each target was independently replaced with an expressed non-target protein from the same floor(log2 degree) bin; when fewer than 20 candidates were available, the nearest degree bin was used. Ten thousand random target sets defined the null. Proximity was z=(mean null distance-observed distance)/SD null distance, so positive z denotes closer-than-random topology.[18] Empirical P included a +1 correction.

For each oil and chemical fraction, component distances and nulls were combined using normalized central composition weights. Two thousand uncertainty draws propagated the empirical composition ranges. Mixture FDR was controlled across every oil, fraction, cell type, transition and direction tested within a network. Specificity required non-overlap of hazelnut and comparator 95% composition-uncertainty intervals and a positive hazelnut-minus-comparator z. Leave-one-component-out analyses renormalized remaining within-fraction weights. Functional-versus-physical rank correlation quantified interactome sensitivity.

Directional perturbation priors

Verified free-oleic-acid mouse macrophage signatures were mapped using one-to-one Mouse Genome Informatics orthologues.[19] A chemically non-equivalent ethyl linoleate/oleate reconstructed-skin signature was analysed separately and never labelled as hazelnut oil. Signature effects were rank-normalized; acute-program weights were multiplied by matched effects and compared with 10,000 gene-label permutations. FDR was controlled within signature. Lipid, inflammatory and formulation controls assessed specificity and assay sensitivity.

Spatial 3D scenario model

Measured x-y coordinates and anatomical annotations from GSE241124 Donor1_Wound1 were projected to a 24×48×64 z-y-x grid. Wound-edge spots at the surface were the source mask. Prespecified depths represented wound-edge, suprabasal, basal, fibroblast and lymphatic-endothelial compartments. Surface-retained, intermediate and distributed Gaussian diffusion–reaction fields used sigma_xy/sigma_z/loss parameters of 1.5/1/0.60, 3/4/0.30 and 5/8/0.15. Component diffusivity was scaled relative to oleic acid by the cube root of inverse molecular weight, and fractions were combined only with within-fraction weights. A conservative topology contrast was the smaller absolute functional/physical up-minus-down z when the two networks agreed in sign and zero otherwise. The output is a dimensionless exposure-weighted topology scenario, not concentration, pharmacokinetics or predicted wound closure.

Reproducibility and software

All analyses used deterministic seed 20260805 unless a dataset-specific seed was declared. Public archives, STRING files and intermediate assemblies were SHA-256 tracked. The workflow was implemented in Python using NumPy, pandas, SciPy, statsmodels, anndata, h5py, NetworkX and Matplotlib; dependency constraints are recorded in pyproject.toml. Machine-readable outputs include component, mixture, null, projection, spatial, proteomic, 3D and claim-ledger tables. Automated tests cover exact permutations, archive integrity, score construction and output invariants.

Data availability

Public data are available from Gene Expression Omnibus under GSE241132, GSE241124, GSE265972 and GSE165816; proteomics are available from ProteomeXchange/PRIDE under PXD052154. STRING v12 human links and protein information were obtained from STRING. ChEMBL bioactivity records and primary composition sources are identified in the versioned registry. This study generated no new participant data.

Code availability

The complete deterministic workflow, environment specification, integrity audits, machine-readable results and figure-generation scripts are contained in the LipidTwin-IR repository accompanying this manuscript. A public archival URL and DOI should be added after repository release.

Author contributions

Proposed CRediT statement—confirmation by all authors is required before submission. Z.B.C. conceived and supervised the study and contributed to methodology, interpretation and manuscript revision. D.K. contributed to bioinformatic methodology, data curation, formal analysis, software, visualization and the original draft. B.A. contributed to evidence curation, validation, biomedical-engineering interpretation and manuscript revision. All authors reviewed and approved the final manuscript.

Competing interests

The authors should confirm the competing-interests declaration before submission. No commercial efficacy, safety or product-performance conclusion is made in this manuscript.

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ADSORPTION TECHNOLOGIES AND THE HEALTH EFFECTS OF HEAVY METALS: A MULTIDISCIPLINARY REVIEW WITH EXAMPLES FROM THE WORLD AND TURKEY

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ABSTRACT
Heavy metals and toxic pollutants are among the contaminants that seriously affect the health of living organisms through biomagnification and bioaccumulation, exhibiting persistence in both environmental and biological systems. Industrial activities, mining, rapid urbanization, fossil fuel consumption, and inadequate waste management practices have accelerated the release of toxic elements such as lead (Pb), arsenic (As), cadmium (Cd), mercury (Hg), chromium (Cr), nickel (Ni), antimony (Sb), and thallium (Tl) into the environment. These metals can exert toxic effects even at low concentrations; since they cannot be eliminated through the body's excretory pathways (kidney, liver, intestine, lung, skin) without specific support, they accumulate in biological organisms and, upon reaching effective doses, may lead to serious health problems—including thyroid disorders, neurological diseases, cardiovascular and renal damage, carcinogenic effects, autism, and infertility—or even death. In this review, the environmental transport and bioaccumulation properties of heavy metals, along with the pathological effects of each metal on human health, are addressed individually; the physical and chemical mechanisms of adsorption, together with the Langmuir and Freundlich isotherms, are explained. Furthermore, the role of activated carbon, zeolites, iron-oxide-based, and metal-organic framework (MOF)-based adsorbents in water treatment and air quality applications is examined, along with clinical/biomedical applications such as activated charcoal, hemoperfusion, and nanoscale drug delivery systems. Finally, this study aims to provide a current and holistic evaluation of the subject through global case examples such as Minamata disease, the Bangladesh arsenic crisis, and Itai-Itai disease, as well as examples from Turkey including the Ergene Basin, İzmit Bay, and the Kütahya-Euphrates Basin.
Keywords: Heavy metals, adsorption, heavy metal toxicity, water treatment, environmental pollution

1. INTRODUCTION
The adsorption method has recently become one of the most preferred approaches to environmental problems that have gained importance owing to the toxicity and persistence of pollutants. Through this method, heavy metals in wastewater are both detected and methods are developed to remove these metals from the environment (Pang et al., 2024). Although water is an essential element for all living organisms, most of the heavy metals present in the ecosystem originate from human activities; industrialization, mining, metallurgical processes, and industrial discharges cause metals such as As, Hg, Pb, and Cd to be released into water and soil (Zaki et al., 2023; Qiu et al., 2025). In addition, chemicals such as pesticides and fertilizers used in agriculture also contaminate agricultural land; motor-vehicle emissions, waste incineration, inadequate wastewater treatment, and irregular storage further increase the spread of these toxic pollutants into the environment. These heavy metals are generally found in wastewater, which necessitates special treatment processes to protect living health (Elwakeel et al., 2025; Shuang et al., 2025).
In this context, adsorption technologies are considered among the highly effective, economical, and industrially applicable methods for removing toxic pollutants from aqueous solutions and the gas phase (Fu & Wang, 2011). Adsorption is based on the attachment of atoms, ions, or molecules in the gas or liquid phase to a solid surface through physical or chemical interactions (Dąbrowski, 2001). Owing to their large specific surface area, high selectivity, mechanical stability, and regeneration (reusability) advantages, porous adsorbents based on activated carbon, zeolites, biopolymers, and metal-organic frameworks (MOFs) are widely used in health and environmental applications (Crini & Lichtfouse, 2019).
The main objective of this review is to address, in a holistic and multidisciplinary manner, the environmental transport and bioaccumulation properties of heavy metals, their pathological effects on human health, and the role of advanced adsorption technologies in the selective removal of these pollutants.

1.1. Environmental and Biological Properties of Heavy Metals

Heavy metals are generally defined in the scientific literature as elements with a density greater than 5 g/cm³ and a high toxicity potential even at low concentrations (Argun et al., 2007). Although these metals can occur in the earth's crust through natural geochemical processes, the primary reason for their uncontrolled spread into the ecosystem is human activity (Nagajyoti et al., 2010). Mining (UNEP, 2019), metal smelting and plating facilities, fossil fuel combustion, industrial treatment sludge, and agricultural chemicals (particularly phosphate fertilizers) release millions of tons of heavy metals into the environment each year (United Nations Environment Programme [UNEP], 2019).

One of the most dangerous characteristics of heavy metals is that they cannot be broken down by the body and can accumulate in increasing amounts through the food chain (Ali & Khan, 2018). For example, because lead resembles calcium, it settles into the bones once it enters the body and can remain there for years, even decades (ATSDR, 2022). According to the ATSDR (2022) report:

- Inorganic Pb in sub-micron-sized particles can be almost completely absorbed via the respiratory tract.
- The proportion of ingested Pb absorbed from the gastrointestinal tract depends on many factors, including age, diet, nutritional status, and the physical properties of the Pb in the ingested medium.

Children can absorb 40-50% of an orally ingested dose of water-soluble Pb, whereas this proportion is 3-10% in adults (ATSDR, 2022).

1.2. Effects of Heavy Metals on Human Health

Individuals exposed to heavy metals, whether children or adults, are adversely affected. The most well-known of these metals can be listed as lead, cadmium, mercury, arsenic, antimony, and thallium.

1.2.1. Lead (Pb)

Lead exposure remains a serious health problem today, and the measures and educational efforts undertaken in this regard have not yet achieved the expected effect. Although lead toxicity generally follows an asymptomatic course, the developing brain—particularly in young children—can be adversely affected by this exposure even when blood lead levels are below what is considered a normal threshold, leading to various disorders in mental/neuropsychological function (Köle & Vural, 2016). In adults, the clinical picture differs; chronic lead accumulation leads to endothelial dysfunction, causing a marked increase in the risk of hypertension, chronic renal failure, and cardiovascular mortality (Onursal, Kul, & Yavuz, 2019).

1.2.2. Cadmium (Cd)

Cadmium enters the atmosphere through both natural sources and human activities, and both animals and humans can be affected by this exposure in different ways. Cadmium contamination in aquatic environments occurs through processes such as adsorption, industrial waste discharges, and surface runoff, whereby the element passes into sediment, soil, and sludge. Humans can be exposed to this heavy metal through the consumption of cadmium-rich foods, inhalation of contaminated air, or ingestion of contaminated water, and may face the risk of poisoning. On the other hand, cadmium has no known biological function that contributes to plant growth or metabolic processes (Mitra et al., 2021).

1.2.3. Mercury (Hg)

Mercury, which also occurs naturally in the biosphere, is one of the heavy metals that poses a serious threat to humanity. In recent years, it has become an increasingly prevalent pollutant due to human activities, with a corresponding increase observed in atmospheric mercury levels. Anaerobic bacteria living in aquatic environments convert inorganic mercury into methylmercury, a far more toxic compound (Gworek et al., 2020). This compound reaches the human body through the food chain via fish, seafood, and wildlife that consume contaminated microorganisms—particularly through the consumption of predatory fish species at the upper levels of the food chain (WHO, 2021). Methylmercury, once absorbed into circulation, can cause various neurological disorders, particularly during the fetal period and early childhood, leading to cerebellar atrophy and impaired visuomotor function (Rice et al., 2014). The historical, industrially caused Minamata disaster is regarded as the most concrete and striking case demonstrating the devastating effects of mercury toxicity on the nervous system (Harada, 1995).

Mercury is toxic to human health and poses a serious threat, particularly to fetal development in the womb and to children in early life. All people are exposed to certain levels of mercury, mainly through

two pathways: inhalation of elemental mercury vapor released during industrial processes, and consumption of contaminated fish and shellfish. Indeed, in some communities that depend on fishing for their livelihood, cognitive effects related to the consumption of mercury-containing fish are estimated to occur in 1.5 to 17 per 1,000 children (WHO, 2021).
Mercury can occur in nature in three different forms: elemental (metallic) mercury, inorganic mercury (e.g., mercuric chloride), and organic mercury (e.g., methyl- and ethylmercury). Each of these forms can exhibit different toxic effects on the nervous, digestive, and immune systems, as well as on the lungs, kidneys, skin, and eyes.

1.2.4. Arsenic (As)

Exposure to arsenic causes cognitive decline in the central nervous system. This exposure is associated with a broad spectrum of neurological diseases, including neurodevelopmental changes, and leads to a marked increase in the incidence of neurodegenerative diseases. In addition, arsenic poisoning can cause various changes in synaptic transmission and neurotransmitter balance (Garza-Lombó et al., 2019).

1.2.5. Antimony (Sb)

Antimony is a metal that can react particularly with freshly formed hydrogen and can enter the human body through inhalation, ingestion, or skin or eye contact. Exposure can lead to symptoms such as irritation of the eyes, skin, nose, and throat, cough, dizziness, headache, nausea, vomiting, diarrhea, abdominal cramps, insomnia, loss of appetite, and impaired sense of smell. The National Institute for Occupational Safety and Health (NIOSH), under the Centers for Disease Control and Prevention (CDC), identifies the eyes, skin, respiratory system, and cardiovascular system as the target organs of antimony exposure (NIOSH, 2005).
Antimony mining can release this metal(loid) into the environment, allowing it to accumulate in nature and thereby pose a risk to all living organisms and ecosystems (Guo et al., 2009). Inorganic antimony compounds such as SbH_3, SbF_3, $SbCl_3$, $SbCl_5$, Sb_2O_3, Sb_2O_5, Sb_2S_3, and Sb_2S_5, as well as metallic antimony, can exhibit toxic effects on living organisms (Güven et al., 2004); adverse effects on plant growth and nitrification can also be expected (IARC, 1989; Okkenhaug & Mulder, 2017). In short, antimony is an element capable of producing adverse environmental effects through both natural pathways and human activities, and scientific interest in antimony toxicity is therefore steadily increasing. The main harmful effects of antimony can be summarized as follows:

- Carcinogenic effect: Inhaled antimony(III) oxide has been shown to cause lung cancer in female rats (Gebel, 1997).
- Genotoxicity: Antimony can cause genetic toxicity in mammalian cells, including DNA damage, gene mutations, chromosomal abnormalities, and aneuploidy (Asakura et al., 2009).
- Occupational exposure effects: Respiratory tract irritation, lung tissue reactions such as pneumoconiosis, antimony spots on the skin, and gastrointestinal symptoms may occur (NIOSH, 2005).
- Respiratory diseases: Conditions such as chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesions, and upper respiratory tract inflammation with chronic cough/wheezing may develop (NIOSH, 2005).

In addition, small-particle aerosols composed of poorly water-soluble antimony compounds (e.g., antimony oxide) remain in the lungs for a much longer period compared with larger, more water-soluble particles (e.g., antimony tartrate) (Yalçın & Atakoğlu, 2024).

1.2.6. Thallium (Tl)

Thallium is a highly toxic heavy metal with no vital function in the body, but owing to its structural similarity to potassium (K^+), it can substitute for potassium in biological systems. This element can cause serious adverse effects at the cellular level, including mitochondrial dysfunction, increased oxidative stress, and inhibition of protein synthesis. The lethal oral dose range in humans is estimated at 10-15 mg/kg; in acute exposures, the mortality rate is reported to vary between 6-15%, and approximately 55% of survivors develop permanent neurological findings. Considering that approximately 5,000 metric tons of thallium are released into the environment annually from industrial and mining sources, the high absorption rate of this element and its capacity to affect multiple systems simultaneously in a non-specific clinical manner make the development of more effective treatment methods an urgent necessity (Avendaño-Briseño et al., 2025).

2. ADSORPTION MECHANISMS

Adsorption is a process based on electrostatic, chemical, or van der Waals interactions between a solid surface (adsorbent) and substances in the liquid phase (adsorbate), and it occurs through two main mechanisms: physical adsorption and chemical adsorption (chemisorption) (Alaqarbeh, 2021). In physical adsorption, the bond energy is low (20-40 kJ/mol) and the process is reversible; in chemical adsorption, covalent or ionic bonds form, resulting in high bond energy (80-400 kJ/mol), and a monolayer structure is generally observed (Dąbrowski, 2001).

The main factors determining the performance and selectivity of adsorption in aqueous environments are as follows:

- Surface area and pore structure: The distribution of micro- (<2 nm), meso- (2-50 nm), and macropores (>50 nm) affects the rate at which the substance transfers to the adsorbent (Fu & Wang, 2011).
- Surface functional groups: Groups such as carboxyl, hydroxyl, amine, and thiol can form complexes with metal ions (Crini & Lichtfouse, 2019).
- Solution pH: Affects the surface charge of the adsorbent (point of zero charge) and the form in which metal ions will be present (hydrolysis state) (Argun et al., 2007).
- Ionic strength and competing ions: Ions such as Ca^{2+}, Mg^{2+}, and Na^{+} present in the medium compete with the target heavy metals for active sites on the adsorbent (Ali & Khan, 2018).

The two most commonly used models for mathematically expressing adsorption equilibrium are the Langmuir and Freundlich isotherms.

The Langmuir model assumes that the surface is energetically homogeneous and that all active sites are equivalent (Langmuir, 1918). In this model, qe represents the adsorption capacity at equilibrium (mg/g), qm the maximum monolayer capacity, KL the Langmuir constant (L/mg), and Ce the equilibrium concentration remaining in solution (mg/L).

The Freundlich model, on the other hand, describes multilayer adsorption occurring on heterogeneous surfaces; the parameters KF and n represent the adsorption capacity and intensity, respectively (Aladağ, 2023).

2.1. Adsorption Technologies in Water Treatment

Access to safe drinking water is a fundamental public health priority. Compared with conventional methods such as chemical precipitation or membrane filtration, adsorption stands out because it does not generate sludge and can remove metals even at very low concentrations (Fu & Wang, 2011).

2.2. Activated Carbon

Activated carbons, produced by subjecting carbon-rich biomass to thermal or chemical treatment, have a high surface area (500-1500 m^2/g) (Marsh & Rodríguez-Reinoso, 2006). Granular activated carbon (GAC) provides long-term use in fixed-bed column systems, while powdered activated carbon (PAC) can be applied directly in cases of sudden contamination; modified forms in particular are widely used for the removal of lead, mercury, and nickel (Crini & Lichtfouse, 2019).

2.3. Zeolites

These natural or synthetic aluminosilicate materials have a high ion-exchange capacity owing to the exchangeable cations (Na^{+}, K^{+}, Ca^{2+}) in their crystal structure, and are highly effective in selectively removing Pb^{2+}, Cd^{2+}, and NH_4^{+} ions from water (Wang & Peng, 2010).

2.4. Iron Oxide-Based Adsorbents

Iron nano-oxides such as magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), and goethite (α-FeOOH) exhibit a strong chemical affinity for arsenate (As(V)) and arsenite (As(III)) oxyanions. The magnetic properties of these materials allow for easy phase separation after adsorption using an external magnetic field (Tang & Lo, 2013).

2.5. MOF-Based Adsorbents

Metal-organic frameworks (MOFs) are a new generation of highly porous hybrid crystalline materials formed through the coordination of metal ions with organic linkers (Li et al., 2016). Owing to their tunable pore diameters and record-level surface areas (>4000 m^2/g), functionalized MOF structures such as thiol-modified UiO-66 can reduce mercury and arsenic ion concentrations to below parts-per-billion (ppb) levels within seconds (Khan et al., 2013).

2.6. Air Quality and Adsorption

Indoor air quality is a vital parameter in the prevention of chronic respiratory diseases. Gas-phase toxic pollutants such as volatile organic compounds (VOCs), formaldehyde, benzene, and nitrogen oxides (NOx) increase the long-term risk of sick building syndrome and lung damage (USEPA, 2020). In gas-phase adsorption processes, activated carbon filters serve as the primary barrier in industrial flue-gas cleaning facilities, hospital ventilation units, and chemical laboratory masks, trapping these gases within their pores (Marsh & Rodríguez-Reinoso, 2006).

3. CLINICAL AND BIOMEDICAL APPLICATIONS

3.1. Activated Charcoal

Activated charcoal is one of the primary treatment methods used in emergency departments for drug overdose and poisoning cases. It binds toxins in the intestine, preventing them from entering the bloodstream, and facilitates their elimination from the body (Chyka et al., 2005).

3.2. Hemoperfusion

The patient's blood is passed through an adsorbent column (activated carbon or synthetic resin) to remove toxins, heavy metals, and harmful waste products from the blood. It is used as a supportive therapy in liver and kidney failure (Ronco et al., 2000).

3.3. Drug Delivery Systems

Nanoscale adsorbents (e.g., MOF/silica nanoparticles) are used to deliver drugs to target tissues. Controlled release reduces side effects and increases drug efficacy (Langer, 1998).

4. ENVIRONMENTAL CASE STUDIES FROM AROUND THE WORLD

4.1. Minamata Disease

In the 1950s, methylmercury discharged into the sea by a factory in Japan caused severe neurological diseases and congenital disorders in thousands of people through contaminated fish (Harada, 1995).

4.2. Bangladesh Arsenic Crisis

As a result of groundwater wells drilled in the 1970s tapping into arsenic-bearing strata, 35-77 million people were exposed to chronic arsenic poisoning. The WHO has described this as the largest mass poisoning in history (Smith et al., 2000).

4.3. Itai-Itai Disease

In Japan, cadmium from mine waste entered rice through irrigation water; people who consumed this rice suffered kidney damage and severe bone pain/fractures (Inaba et al., 2005).

5. EXAMPLES FROM TURKEY

5.1. Ergene Basin

In this region, where the textile and chemical industries are concentrated, lead, cadmium, and chromium levels in the river have been found to be far above permissible limits, posing a risk for agricultural irrigation (Tokatlı, 2019).

5.2. İzmit Bay

In this bay, where industrial and maritime traffic are intense, high accumulation of mercury, copper, zinc, and nickel has been identified in sediments, posing a bioaccumulation risk for marine organisms (Pekey, 2006).

5.3. Kütahya and Euphrates Basin

Field studies have shown that, due to mining activities, arsenic and lead levels in regional water resources exceed permissible limits (Gemici & Tarcan, 2004).

6. CONCLUSION

Heavy metals are released into the environment not only through natural geochemical processes but also through anthropogenic activities such as mining, industrial discharges, fossil fuel use, and agricultural chemicals; through bioaccumulation and biomagnification, they accumulate in the food chain and can cause serious neurological, cardiovascular, renal, and carcinogenic health problems—via elements such as lead, cadmium, mercury, arsenic, antimony, and thallium—even at low concentrations. As discussed in this review, the toxicity mechanism and the systems affected differ for each metal, which requires

that removal and treatment approaches also be developed in a metal-specific manner. Adsorption technologies—including activated carbon, zeolites, iron-oxide-based, and metal-organic framework (MOF)-based adsorbents—stand out for their high removal efficiency, low sludge generation, and economic applicability in removing pollutants from the aqueous and gas phases; the same adsorption principle also plays a critical role in removing toxins from the human body through clinical applications such as activated charcoal and hemoperfusion. Historical cases such as Minamata, Bangladesh, and Itai-Itai, together with examples from Ergene, İzmit, and Kütahya-Euphrates, concretely illustrate the consequences that can arise both globally and locally in the absence of preventive measures. In conclusion, it is of great importance that adsorption-based approaches for both reducing heavy metal pollution at its source and effectively removing it from already contaminated environments continue to be developed and disseminated through a multidisciplinary perspective that brings together the disciplines of environmental engineering, toxicology, and clinical medicine.

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HEAVY METAL POLLUTION AND BIOLOGICAL EFFECTS IN MARINE ECOSYSTEMS

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Abstract
Heavy metal pollution remains an important environmental problem in marine ecosystems because these pollutants can persist for long periods, be taken up by organisms and move through food chains. The harmful effects of thallium (Tl), mercury (Hg), lead (Pb), cadmium (Cd), arsenic (As), chromium (Cr), nickel (Ni) and manganese (Mn) can vary depending on their chemical form, pH and oxygen-related conditions in the environment, organic matter content and the characteristics of exposed organisms. Methylmercury is of particular concern because it can move efficiently through aquatic food webs and accumulate in organisms at higher levels of the food chain, creating a possible route of human exposure through seafood consumption. This review examines how heavy metals enter marine environments, how they are taken up and accumulated by organisms, their main effects on invertebrates, fish and higher-level consumers, and current approaches to monitoring and risk management using verifiable scientific and institutional sources. The evidence shows that total metal concentration alone may not always be enough to explain ecological risk. Chemical form, biological responses and long-term monitoring data should therefore be considered together. This integrated approach can improve the assessment of biological effects and potential human exposure. In Türkiye, the Marmara Sea case highlights the need to reduce pollution sources, strengthen wastewater control and maintain continuous environmental monitoring.
Keywords:heavy metals, marine pollution, bioaccumulation, biomagnification, ecotoxicology

1. INTRODUCTION

Heavy metals, one of the most permanent and widespread forms of environmental pollution, are among the main pollutants in marine ecosystems. Heavy metals can be found in nature as a result of geological processes. However, anthropogenic activities such as mining, metal processing, fossil fuel use, industrial production, port activities and wastewater discharges can increase the amount of heavy metals in the seas (Altunkaynak, Canpolat, & Aslan, 2023). Since a significant portion of these pollutants do not break down easily, they can be displaced among water, particles in the water, seabed sediments and living things. Therefore, when assessing environmental risk, not only the total amount of metal should be considered, but also in what chemical form the metal exists and to what extent it can be absorbed by living things (Luoma & Rainbow, 2008).

Mercury is a good example of this situation. Under the influence of certain microorganisms and environmental conditions, inorganic mercury can be converted into methylmercury. Methylmercury is more easily taken up by living things and can be transported throughout the food chain. For this reason, the tendency to accumulate increases especially in living things at the upper levels of the food chain (Barquero, Hidalgo, Esbrí, Higueras, & García-Ordiales, 2025). The global assessment by the United Nations Environment Programme (UNEP) likewise shows that mercury emitted into the air, mercury reaching the aquatic environment, and mercury levels measured in living things constitute an interconnected, global environmental problem (UNEP, 2019).

1.1. Sources, Speciation and Bioavailability

Heavy metals reaching the seas may originate from atmospheric deposition, transport by rivers, surface runoff, industrial and urban wastewater, and coastal activities. Sediments on the seabed constitute a long-term accumulation area for many metals. However, changes in the oxygenation conditions of the environment or remixing of the bottom sediments may cause the metals held there to pass back into the water. For this reason, metals accumulated in the sediment should not be considered completely neutralized, but rather as a pollutant source that can be reactivated under suitable conditions (Luoma & Rainbow, 2008).

One of the most important factors that determine the extent to which a metal can be absorbed by living things is the chemical form in which the metal is found. Ions dissolved in water, metals bound to organic substances or particles, and organometallic compounds interact with living cells in different ways.

The transformation of mercury into methylmercury is particularly important in this respect: since methylmercury is more easily retained in living tissues, its transport throughout the food chain is strengthened (Barquero, Hidalgo, Esbrí, Higueras, & García-Ordiales, 2025).

1.2. Invertebrates and Biomarker Responses

Mussels, oysters, polychaete worms and other bottom-dwelling invertebrates can absorb metals from water, sediment and food. Filter-feeding organisms such as mussels and oysters are used as indicator organisms in monitoring coastal pollution because they can accumulate environmental pollutants in their tissues. Some proteins called metallothioneins help reduce harmful effects by binding metals such as cadmium (Cd), copper (Cu), zinc (Zn) and mercury (Hg) within the cell. Under appropriate conditions, the level of these proteins can be considered an indicator of metal exposure (Amiard, Amiard-Triquet, Barka, Pellerin, & Rainbow, 2006).

Exposure to heavy metals can cause harmful oxygen species to increase in cells and strain the cell's protective systems. As a result, damage to cell membranes and other cellular structures may occur. Evaluating such stress indicators alone in marine organisms may not be sufficient. When enzymatic and other cellular-level indicators are considered together, the biological effects of chemical pollutants can be evaluated more accurately (Regoli & Giuliani, 2014).

1.3. Developmental and Physiological Effects in Fish

Fish can absorb heavy metals through their gills, skin and digestive systems. Early life stages, such as embryos and larvae, may be more sensitive to heavy metals due to rapid growth and organs still developing. Studies show that heavy metal exposure may be associated with developmental disorders, reduced hatching success, and increased mortality in fish embryos and larvae (Jezierska, Ługowska, & Witeska, 2009).

The effects of mercury are not limited to its accumulation in tissues. Comprehensive evaluations on living creatures in the Arctic region show that negative effects may be seen on the nervous system, hormone system, immune system and reproduction, depending on the exposure level and species (Dietz et al., 2013). Therefore, in the risk assessment of fish, not only the amount of mercury in the muscle tissue consumed, but also the biological changes occurring in the liver, gills and other tissues should be taken into account.

1.4. Trophic Transfer and Upper-Level Consumers

Transport of heavy metals throughout the food chain does not occur in the same way for each metal. How long a metal remains in the living body, how much it is absorbed from food, and how quickly it is excreted from the body determine whether its amount increases or decreases throughout the food chain. Studies in marine food webs have shown that while mercury tends to biomagnify toward higher-level consumers, other elements such as lead, arsenic, cadmium, cobalt, manganese, nickel, thallium and copper may instead decrease in concentration as one moves up the food chain (Wang, 2002).

Marine mammals and seabirds, which live long and are at the upper levels of the food chain, can accumulate high amounts of metals in their bodies because they are repeatedly exposed to heavy metals throughout their lives. When determining areas where mercury pollution is intense, it is not enough to look only at water and sediment measurements. The regional distribution of mercury levels measured in living things should also be evaluated. Studies conducted in northeastern America and southeastern Canada have shown that data obtained from living things can be used to determine risky areas in terms of mercury (Evers et al., 2007).

1.5. Human Exposure and Food Safety

Seafood, particularly through methylmercury, is one of the main routes of human exposure. Scientific studies show that the period in the womb and early childhood are more sensitive to environmental substances that can affect the nervous system (Grandjean & Landrigan, 2014). For this reason, guidance on fish consumption should not recommend avoiding seafood altogether, given the beneficial nutrients it provides, but should instead offer balanced recommendations that take into account the type of fish, portion size and frequency of consumption.

In terms of arsenic, simply knowing the total amount of arsenic is not sufficient to assess health risk. While less harmful organic forms of arsenic are common in seafood, inorganic arsenic is of greater concern for health. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) has likewise emphasized that the risk of arsenic in food should be evaluated especially in terms of the amount of

inorganic arsenic present (EFSA CONTAM Panel, 2009). Also IARC; evaluated arsenic and inorganic arsenic compounds, cadmium and cadmium compounds, chromium (VI) compounds and nickel compounds in terms of their risk of causing cancer in humans (IARC, 2012).

1.6. Monitoring Approaches

In an effective monitoring program, water, sediment and living samples should be evaluated together. The total amount of metal in water can be affected by short-term environmental changes. Samples taken from sediment and living tissues, on the other hand, can provide information about exposure over a longer period. The Mussel Watch program, in which mussels and similar bivalve creatures are used as indicators, is one of the established applications that monitor the change of chemical pollutants in coastal areas over time and region (NOAA NCCOS, 2026).

Biomonitoring should not be limited to measuring the amount of metal in living tissues. The level of metal-binding proteins, the functioning of protective enzymes, and some measurements indicating cell damage can help understand the consequences of exposure on living things. However, it should not be forgotten that these biological indicators may vary depending on factors such as species, season, breeding period and nutritional status (Regoli & Giuliani, 2014).

1.7. Türkiye and the Marmara Sea Context

In order to reliably compare the heavy metal risk on Turkish coasts between different regions, it is important that the sampling stations, the living species and tissues examined, the sampling periods and analysis methods be adhered to certain standards. Collecting long-term data on the Marmara, Aegean, Mediterranean and Black Sea coasts using the same quality criteria is necessary to determine the areas where pollution is concentrated and to reliably monitor changes over time.

In terms of marine pollution management in Türkiye, the Marmara Sea holds particular importance, separate from the other seas. The Marmara Sea Protection Action Plan, announced in 2021, includes complementary measures such as developing wastewater treatment infrastructure, controlling discharges, strengthening monitoring studies and reducing pollutant inputs (Ministry of Environment and Urbanization, 2021). In monitoring heavy metal pollution, it is necessary to look not only at classical pollution indicators, but also at metal amounts and the interaction between sediment and living things.

1.8. Risk Management and Research Requirements

Effective management of heavy metal pollution starts with reducing pollutants at the source. Using cleaner production methods in industry, applying appropriate wastewater treatment technologies, controlling emissions and managing the risk posed by contaminated sediments are among the basic measures. The international approach on mercury also envisages reducing emissions to air and water and implementing control measures throughout the entire use process of mercury (UNEP, 2019).

It is important in future research to further include in routine monitoring the chemical form in which metals are present. Additionally, how climate change and ocean acidification affect the availability of metals to living things, the consequences of simultaneous exposure to multiple pollutants, and the broader effects of changes measured at the cellular level on living communities should be investigated. Thus, the relationship between the amounts of metal measured in the environment and the effects on living things can be revealed more clearly.

2. CONCLUSION

Heavy metal pollution in marine ecosystems is a long-term environmental management problem because these pollutants can persist for long periods of time and be transported among water, sediments and living things. In particular, the conversion of mercury into methylmercury and its transport through the food chain clearly illustrate the connection between pollution in marine organisms and human health. Cellular defense and stress responses in invertebrates, developmental disorders in fish, metal accumulation in creatures higher up the food chain, and human exposure through seafood reveal that heavy metal pollution is a multifaceted problem.

Therefore, it is not enough to measure only the total amount of metal in monitoring heavy metal pollution. The chemical form of the metal, the characteristics of the sediment, the living species used as indicators, and the biological changes occurring in living things should be evaluated together. In Türkiye, better control of pollutant sources, especially in the Marmara Sea and other coastal areas, maintaining long-term monitoring programs with standard methods and using the results obtained in both food safety and ecosystem management should be a priority. This holistic approach will support

the identification of the most important pollution sources and the earlier and more effective implementation of protective measures.

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THE IMPORTANCE OF ANTIOXIDANT PROPERTIES OF FRUIT SPECIES FOR HUMAN HEALTH

MEYVE TÜRKLERİNİN ANTİOKSİDAN ÖZELLİKLERİNİN İNSAN SAĞLIĞI AÇISINDAN ÖNEMİ

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Abstract
Phenolic compounds are secondary metabolites produced by plants in response to stress and for protective purposes. Due to their aromatic structures containing hydroxyl groups, they are referred to as phenolic substances. These compounds, mainly consisting of flavonoids and phenolic acids, are abundantly found in various fruit species, and their concentrations may vary depending on ecological conditions and cultivation practices. Phenolic compounds play a crucial role in human health due to their strong antioxidant properties. By neutralizing free radicals, they help prevent cellular damage, support the immune system, and reduce the risk of chronic diseases. Additionally, they are known to exhibit protective effects against cardiovascular diseases, cancer, and aging processes. In this study, the antioxidant properties of different fruit species were examined in relation to their growing conditions and evaluation methods. The results are expected to contribute to the promotion of healthy nutrition and the maintenance of an active and balanced lifestyle.
Keywords: Fruit species, phenolic compounds, antioxidant, immune system

Özet
Fenolik bileşikler, bitkilerin stres ve korunma durumları için ürettikleri sekonder metabolitlerdir. Hidroksil grubuna sahip aromatik yapılarından dolayı fenolik maddeler olarak adlandırılırlar. Flavonoidler ve fenolik asitlerden oluşan bu bileşikler meyve türlerinde yoğun olarak bulunmaktadır. Ekolojik koşullara ve yetiştirme tekniklerine bağlı olarak miktarları değişebilmektedir. Fenolik bileşikler, sahip oldukları güçlü antioksidan özellikler sayesinde insan sağlığı açısından vazgeçilmez bir öneme sahiptir. Serbest radikalleri etkisiz hale getirerek hücre hasarını önler, bağışıklık sistemini destekler ve kronik hastalıkların oluşum riskini azaltır. Ayrıca kalp-damar hastalıkları, kanser ve yaşlanma süreçleri üzerinde koruyucu etkiler gösterebildiği bilinmektedir. Bu çalışmada, farklı meyve türlerinin antioksidan özellikleri yetişme koşulları ve değerlendirme şekilleri ile ilişkili olarak ele alınmıştır. Sonuçların sağlıklı beslenme ve aktif, düzenli bir yaşam tarzının sürdürülmesine katkı sağlayacağı düşünülmektedir.
Anahtar Kelimeler: Meyve türleri, fenolik bileşikler, antioksidan, immün sistem

GİRİŞ

Fenolik bileşikler tüm meyvelerde bulunan, kimyasal olarak oldukça reaktif ve çeşitliliği yüksek ikincil metabolitlerdir. Fenoliklerle ilişkili iki önemli süreç, fenollerin antioksidan aktivitesi ve oksidatif esmerleşme reaksiyonlarıdır. Antioksidan etkileri ile oksidatif hasarı azaltmakta, esmerleşme reaksiyonlarında substrat olarak görev almaktadır (Robards et.al, 1999). Birçok fenolik bileşik (örneğin kafeik esterleri, kateşinler) hem iyi bir esmerleşme substratı hem de güçlü bir antioksidandır. Düşük konsantrasyonlarda antioksidan olarak işlev görürken, daha yüksek konsantrasyonlarda kendileri oksidasyona uğrayabildikleri için başlatıcı reaksiyonlara katılarak pro-oksidan davranış gösterebilirler. Fenoliklerin antioksidan olarak işlevi hem gıdalarda hem de insan vücudunda yararlı kabul edilir; çünkü fenolikler diğer gıda bileşenleri veya hücresel bileşenler yerine oksitlenerek koruyucu etki sağlar. Buna karşılık, fenoliklerin oksidatif esmerleşme substratı olarak rolü yalnızca gıdalarla sınırlıdır ve çoğu durumda istenmeyen bir etkidir.

Meyve fenolikleri, zararlı reaktif oksijen türlerine karşı önce kendileri oksitlenerek hücreleri korur; bu süreç fenolik bileşiklerin metal iyonlarıyla etkileşimi ve redoks davranışıyla ilişkilidir (Chen et al., 2024). Polifenoller, redoks sinyallemesini düzenleyerek hücresel antioksidan savunmayı güçlendirir (Kerimi & Williamson, 2016). Bazı bileşikler (örneğin antosiyaninler ve flavan-3-oller) vücudun kendi antioksidan enzimlerini süperoksit dismutaz, katalaz ve glutatyon peroksidaz artırabilir; bu etki özellikle antosiyanin takviyesinin antioksidan kapasiteyi yükselttiğini gösteren çalışmalarla desteklenmektedir (Zhu et al., 2015).

Meyveler fenolik bileşikler açısından zengindir. Meyve ve sebzelerin duyusal ve besinsel özelliklerden kaynaklı etkilerinden dolayı, insanlarda gösterdikleri fizyolojik aktivitelerine bağlı olarak oldukça üzerinde durulan bir konudur. Meyvelerin fenolik bileşimleri genetik ve çevresel faktörler tarafından belirlenir; ancak işleme ve depolama sırasında gerçekleşen oksidatif reaksiyonlarla değişime uğrayabilmektedir (Selcuk and Erkan, 2015).
Bu derleme, meyvelerdeki fenolik bileşiklerin antioksidan özelliklerinin durumunu ve etkilerinin rolünü incelemektedir.

1. Turunçgiller

Turunçgiller dünya genelinde en çok tüketilen meyve gruplarındandır, yüksek C vitamini içerikleriyle uzun yıllardır bilinen bir antioksidan kaynağıdır. Turunçgillerin antioksidan kapasitesi yalnızca askorbik asitten kaynaklanmadığını; özellikle flavonoidler, flavanone'ler, polimetoksile flavonlar ve fenolik asitler gibi ikincil metabolitlerin de bu kapasiteye önemli katkı sağladığını ortaya koymuştur (Wang et al., 2022; Tripoli et al., 2007). Hesperidin, naringin, narirutin ve eriocitrin en yaygın bulunan flavonlardır. Toplam fenolik içerik ve antioksidan kapasiteleritür, çeşit, olgunluk derecesi, yetişme koşulları ve meyve kısmına (kabuk, meyve eti, meyve suyu) göre önemli ölçüde değiştiği rapor edilmiştir (Arena et al., 2001; Nogata et al., 2006, Zhou et al., 2010; Barreca et al., 2020). Genel olarak kabuk kısımlarının, meyve etine kıyasla daha yüksek fenolik madde ve antioksidan aktiviteye sahip olduğu bilinmektedir (Gorinstein et al., 2001; Xu et al., 2008).
Yabani portakal, mandalina ve limon gibi turunçgil uçucu yağları, %85 ila %99 oranında uçucu bileşikler (monoterpenler, seskiterpenler de dahil olmak üzere terpenlerden) ve %1 ila %15 oranında uçucu olmayan bileşiklerden oluşmaktadır (Palazzolo et. al., 2013; Mehl et. al., 2014). Baskın bileşen limonene lipid oksidasyon döngüsünü bozarak oksidanları ortadan kaldırmakta, antioksidan potansiyeli göstermektedir (Davicino et. al., 2009; Palazzolo et. al., 2013; Anandakumar et. al., 2021). Turunçgil kabukları ve albedo tabakası meyve etine göre çok daha yüksek polimetoksillenmiş flavonoidler ve fenolik asitler içermektedir (Lazaridis et al., 2024). Bu nedenle turunçgil işleme atıkları, güçlü antioksidan özütler için değerli bir kaynaktır.

2. Yumuşak Çekirdekli Meyveler

Yumuşak çekirdekli meyveler denince elma, armut, ayva ve muşmula en önemli türler olarak akla gelmektedir. Flavonoller (kuersetin glikozitleri), hidroksisinamik asitler (klorojenik asit) ve proantosiyanidinler başlıca bulunan fenolik maddelerdir. Kabuk, meyve etine göre birkaç kat daha yüksek fenolik bileşik içermektedir ve tüketimde tüm meyve veya kabuk özütü önerilmektedir. İçerik bakımından muşmula en yüksek fenolik değere sahiptir (Campanella et. al., 2003; Stanković et. al., 2022; Lata et. al., 2024; Niston et. al., 2024). Ayva, elma ve armuttan daha iyi bir antioksidan içerik sağlar. Aşırı olgun muşmula 2 kat daha fazla antioksidan içermektedir (Niston et. al., 2024). Yüksek antioksidan içeriği gösteren, ancak daha az bilinen bir meyve türü de japon ayvasıdır. Kapsamlı karşılaştırmada yüksek potansiyel taşıyan türler/çeşitler arasında *Chaenomeles* × *californica* (Japon ayvası melezi), *Actinidia kolomikta* kivi türü ve *Mespilus germanica* (muşmula) üzümsü meyvelerden bile daha önde yer alan türlerdir (Lata et. al., 2024)

3. Sert Çekirdekli Meyveler

Hidroksisinamik asitler, neoklorojenik ve klorojenik asit, flavonoller, siyanogenik glikozitler en öneli antioksidan maddelerdir (Kim and Lee, 2002; Usenik et al., 2008). Nektarin, şeftali ve erik meyvelerinde toplam fenolik madde ile antioksidan aktivite arasında güçlü korelasyon vardır (Gil et. al., 2002). Şeftali ve kayısı çeşitlerindeki çalışmalar, fenolik içeriklerinin oldukça değişken olduğunu göstermiştir. Yüksek antioksidan etkili genotipler nadirdir, ancak 'Andross', 'Big Top' gibi bazı ticari çeşitler öne çıkmaktadır (Drogoudi et al., 2026). Kan kırmızısı etli şeftaliler beyaz etli çeşitlere göre mezokarpta daha yüksek antosiyanin içermektedir (Gil et al., 2002). Koyu renk kabuklu erik ve kiraz çeşitleri dihidroksifenilizatin gibi güçlü antioksidan kapasitesine sahip maddelerle öne çıkmaktadır (Kim et al., 2003).

4. Üzümsü Meyveler

Total fenolik ve antosiyanin içerikleri diğer birçok taze meyve türünden belirgin şekilde yüksektir. Bu bileşikler, antioksidan aktivitenin büyük kısmını belirlemektedir. Çilek, böğürtlen, mavi yemiş, ahududu taze meyveler arasında en yüksek antioksidan kapasiteye sahip gruptur ve antosiyanin yoğunluğu bu yüksek kapasitenin temel belirleyicisidir (Bisen et. al., 2026). Yüksek çalı formlu mavi yemiş çeşitleri,

özellikle kurutulmuş olarak oldukça yüksek antioksidan kapasitesine sahiptir. 'Farthing en yüksek olmak üzere, 'Misty, Eureka, Windsor ve Twilight diğer çeşitler olarak bildirilmiştir (Akbari et. al., 2026). Yetişme koşullarının etkisine bağlı olarak nötr gün çilekleri, uzun gün (Haziran) çileklerine göre daha fazla fenolik madde depolayabilmektedir (Bisen et al., 2026)

Sonuç

Antioksidan kapasite, yalnızca listelenen maddelerden değil, bunların sinerjik etkilerinden de kaynaklanmaktadır. Kabuk kısımları neredeyse tüm gruplarda meyve etine göre daha yüksek fenolik madde ve antioksidan aktivite içermektedir. Değerler çeşit, olgunluk, yetişme koşulları ve analitik yönteme (DPPH, ABTS, FRAP, ORAC) göre önemli ölçüde değişebilmektedir.

Meyvelerin değerlerinin tam anlamıyla ortaya konabilmesi açısından daha kapsamlı ve standartlaştırılmış araştırmalara ihtiyaç vardır. Özellikle farklı tür, çeşit ve genotipleri aynı koşullarda karşılaştıran çok merkezli çalışmalar, genotip × çevre etkileşimini netleştirecek tasarımlar, *in vitro* bulguların yanı sıra biyoerişilebilirlik, emilim, metabolizma, doku dağılımı gibi süreçlerin incelenmesi, klinik ve preklinik (in vivo) çalışmalarla gerçek fizyolojik etkilerin doğrulanması, fonksiyonel gıda ve nutrasötik uygulamalar için kritik öneme sahiptir.

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TÜRKİYE'DE ARAZİ TOPLULAŞTIRMASINA YÖNELİK ÇİFTÇİ ALGILARI VE YAKLAŞIMLARI (ADANA VE HATAY İLİ)

FARMERS' PERCEPTIONS AND APPROACHES TOWARD LAND CONSOLIDATION IN TÜRKİYE (THE CASE OF ADANA AND HATAY PROVINCES)

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ÖZET

Bu çalışmanın amacı, üreticilerin arazi toplulaştırmasına ilişkin algı ve düşüncelerini belirleyerek toplulaştırma çalışmalarına yönelik bilgi düzeyleri ile yaklaşımlarını ortaya koymaktır. Türkiye'de toplam 14,3 milyon hektar alan arazi toplulaştırmasına uygun olup, yaklaşık 7,4 milyon hektarlık alanda çalışmalar tamamlanarak tescillenmiştir. Araştırmanın ana materyalini, Türkiye'nin Akdeniz Bölgesi'nin doğusunda yer alan Adana ve Hatay illerinden tesadüfi yöntemle seçilen 200 üretici ile yüz yüze gerçekleştirilen anketlerden elde edilen veriler oluşturmaktadır. Tarım faaliyetlerinde verimliliği etkileyen başlıca faktörler; tohum, gübre ve ilaç kullanımı, parsel parçalanması, işlenebilir arazi büyüklüğü, parsel sayısı, mülkiyet yapısı ve kullanılan teknoloji ile makineler olarak belirlenmiştir. Bu faktörlerin planlı ve sistemli bir şekilde uygulanabilmesi açısından arazi toplulaştırma çalışmaları önemli bir araçtır. Araştırma bulgularına göre, üreticilerin çoğunluğu toplulaştırmanın üretim verimliliğini yükselttiği, arazi kullanımını kolaylaştırdığı ve ulaşım sorunlarını azalttığı yönünde görüş bildirmiştir. Bununla birlikte bazı üreticiler, bilgilendirme eksikliği, proje sürecinin uzunluğu ve uygulamalardaki altyapı sorunlarının süreci olumsuz etkilediğini belirtmiştir. Bu doğrultuda toplulaştırma çalışmalarının daha etkin yürütülebilmesi için üretici bilgilendirme faaliyetlerinin artırılması, sürecin şeffaf ve katılımcı bir yaklaşımla yönetilmesi ve altyapı yatırımlarının hızlandırılması önerilmektedir. Ayrıca tarla yolları ve sulama sistemlerinin tamamlanmasının, toplulaştırmanın üretici memnuniyetine ve kırsal kalkınma hedeflerine daha güçlü katkılar sağlayacağı değerlendirilmektedir.

Anahtar Kelimeler: Arazi toplulaştırma, parçalılık, tarımsal verimlilik, çiftçi algısı, sürdürülebilirlik.

ABSTRACT

The aim of this study is to determine farmers' perceptions and opinions regarding land consolidation and to reveal their level of knowledge and approaches toward land consolidation practices. In Türkiye, approximately 14.3 million hectares of agricultural land are considered suitable for land consolidation, and consolidation projects have been completed and officially registered on approximately 7.4 million hectares. The primary data of the study were obtained through face-to-face surveys conducted with 200 farmers, randomly selected from the provinces of Adana and Hatay, located in the eastern Mediterranean Region of Türkiye. The findings indicate that the major factors affecting agricultural productivity include the use of quality seeds, fertilizers, and pesticides, land fragmentation, the size of cultivable land, the number of parcels, land tenure structure, and the level of technology and machinery used. Land consolidation is recognized as an important instrument for enabling these factors to be managed in a planned and systematic manner. According to the survey results, the majority of farmers believe that land consolidation increases agricultural productivity, facilitates more efficient land use, and reduces transportation-related problems. However, some respondents reported that insufficient information, the lengthy implementation process, and infrastructure-related deficiencies negatively affect the effectiveness of land consolidation projects. Based on these findings, the study recommends strengthening farmer information and awareness activities, managing the consolidation process through a transparent and participatory approach, and accelerating infrastructure investments. Furthermore, the completion of farm roads and irrigation systems is expected to enhance farmer satisfaction and contribute more effectively to the objectives of rural development.

Keywords: Land consolidation, land fragmentation, agricultural productivity, farmers' perceptions, sustainability.

GİRİŞ

Dünyada hızla artan nüfus, tarımsal üretim kaynakları üzerindeki baskıyı artırmakta ve özellikle az gelişmiş ve gelişmekte olan ülkelerde artan gıda ihtiyacının karşılanmasını önemli bir sorun hâline getirmektedir (Sağlam, 2022). Ülkelerin sosyal ve ekonomik gelişiminde kırsal alanlardaki toplumsal ve ekonomik faaliyetlerin etkin ve planlı bir şekilde yürütülmesi önemli bir yere sahiptir. Hızlı nüfus artışı, sanayileşme ve kentleşme süreçlerinin yanı sıra arazilerin miras yoluyla parçalanması, tarım işletmelerinin giderek küçülmesine ve parçalı bir yapıya dönüşmesine neden olmaktadır. Bu durum işletme sayısının artmasına karşın üretim faaliyetlerinin etkinliğinin ve verimliliğinin yeterli düzeyde artmamasına yol açabilmektedir. Özellikle küçük ve düşük gelirli üreticilerin kırsal alanlardan ayrılması, tarım arazilerinin yeterince değerlendirilememesi ve sulu tarım alanlarının atıl kalması gibi sonuçlar ortaya çıkabilmektedir. Bu bağlamda, kırsal ekonomik hayatın temel unsurlarından biri olan toprak mülkiyeti ve tarımsal üretimde verimlilik, ülkelerin kırsal kalkınması açısından önemli değişkenler olarak öne çıkmaktadır (Yoğunlu, 2013).Türkiye'de tarım arazilerinin küçük ve dağınık olması, sulanabilir arazi oranlarının azalması, sulama maliyetlerinin artması, parseller arasındaki mesafelerin fazla olması ve ulaşım yollarının yetersizliği gibi yapısal sorunlar, arazi toplulaştırması uygulamalarının önemini artırmaktadır (Küsek, 2014; Demirtaş ve Sarı, 2016).

Arazi toplulaştırması, parçalı ve dağınık durumdaki tarım arazilerinin daha uygun işletme ve parsel yapısına kavuşturulmasının yanı sıra tarla içi yolların oluşturulması, sulama altyapısının geliştirilmesi ve tarımsal mekanizasyonun daha etkin kullanılmasına olanak sağlamaktadır. Bu uygulamalar, üretim maliyetlerinde tasarruf sağlanmasına, tarımsal verimliliğin artırılmasına ve üreticilerin yaşam standartlarının iyileştirilmesine katkıda bulunmaktadır (Küsek, 2014). Ayrıca arazi toplulaştırma projeleri, planlama ve uygulama süreçlerinde üreticilerin sosyal ve ekonomik durumlarının dikkate alınması yoluyla kırsal alanlarda sosyal faydalar da oluşturabilmekte; kırdan kente göçün azaltılması ve kırsal alanlarda yeni iş olanaklarının geliştirilmesine katkı sağlayabilmektedir (Altıntaş ve Akçay, 2009; Boyraz ve Üstündağ, 2008; Itır, 2003; Akşit, 2013). Bunun yanı sıra kırsal alanların iyileştirilmesi, köy yerleşim alanlarının korunması, yerleşim sınırlarının yeniden düzenlenmesi ve altyapı yatırımlarının geliştirilmesi yoluyla kırsal alanların sosyal, kültürel ve ekonomik açıdan desteklenmesi de arazi toplulaştırmasının kapsamı içerisinde değerlendirilmektedir (Akkaya, 1997).

Türkiye'de arazi toplulaştırması uygulamaları, başta 3083 sayılı Sulama Alanlarında Arazi Düzenlenmesine Dair Tarım Reformu Kanunu ve 5403 sayılı Toprak Koruma ve Arazi Kullanımı Kanunu olmak üzere ilgili mevzuat çerçevesinde yürütülmekte; bu kapsamda sulama alanlarında arazi düzenlemesinin yanı sıra kırsal alanların planlı bir şekilde geliştirilmesi amaçlanmaktadır (Kirmikil, 2019).

Türkiye'nin yaklaşık 78 milyon hektarlık yüzölçümünün 24 milyon hektara yakın bölümünün ekilebilir tarım arazilerinden oluşması, söz konusu kaynakların etkin ve sürdürülebilir kullanımını önemli hâle getirmektedir. Tarımsal üretimde verimliliğin artırılması ve uluslararası rekabet gücünün geliştirilmesi açısından arazi toplulaştırma çalışmalarının sistemli ve planlı biçimde yürütülmesi önem taşımaktadır. Türkiye'de ortalama tarım işletmesi büyüklüğü yaklaşık 6 hektar iken, bu değer Avrupa Birliği ülkelerinde yaklaşık 16 hektardır. Türkiye'de işletmelerin ortalama parsel sayısı 6 adet ve ortalama parsel büyüklüğü yaklaşık 1,3 hektar iken, Avrupa Birliği ülkelerinde parsel büyüklükleri yaklaşık 1,8–4 hektar arasında değişmektedir (DSİ, 2024). Bu farklılıklar, Türkiye'de tarım arazilerinin parçalı ve dağınık yapısının giderilmesi bakımından arazi toplulaştırmasının önemini ortaya koymaktadır.

DSİ (2024) verilerine göre, 2024 yılı itibarıyla Türkiye'de arazi toplulaştırması (AT) ve tarla içi geliştirme hizmetleri (TİGH) kapsamında toplam 7.586.027 hektarlık proje alanı bulunmakta olup, 2024 yılında 312.440 hektarlık alanda çalışmalar tamamlanmıştır. Aynı dönemde 2.006.641 hektarlık alanda çalışmalar devam etmektedir. Bölgesel dağılım incelendiğinde, arazi toplulaştırması ve tarla içi geliştirme hizmetlerinin farklı üst projeler kapsamında geniş bir alanda sürdürüldüğü görülmektedir. Bu durum, Türkiye'de tarımsal yapının iyileştirilmesine yönelik arazi toplulaştırma çalışmalarının uzun vadeli ve kademeli bir süreç içerisinde yürütüldüğünü göstermektedir (Tablo 1).

Tablo 1. 2024 Yılı Arazi Toplulaştırması ve Tarla İçi Geliştirme Projelerinde Tamamlanan ve Devam Eden Alanlar (Bölgesel Dağılım)

Üst Proje Alanları	2024 Yılında Biten (ha)	Toplam (ha)	
		Tamamlanan	Devam Eden
AT ve TİGH (Bölgesel olmayan)	181.258	2.304.282	817.485
AT ve TİGH (Güneydoğu Anadolu Projesi (GAP))	41.952	2.596.096	469.957
AT ve TİGH (Konya Ovası Projesi (KOP))	26.739	1.577.662	69.484
AT ve TİGH (Doğu Anadolu Projesi (DAP))	51.841	950.431	456.220
AT ve TİGH (Doğu Karadeniz Projesi (DOKAP))	10.650	157.556	193.495
Toplam	312.440	7.586.027	2.006.641

Kaynak: DSİ, 2024

Arazilerin parçalı ve dağınık yapısı, üretim faaliyetlerinin etkinliğini sınırlandırarak tarımsal verimlilik ve kârlılığın azalmasına yol açabilmektedir. Arazi toplulaştırması yoluyla parçalı arazilerin daha uygun bir yapıya kavuşturulması, yol ve sulama gibi altyapı sorunlarının giderilmesi ve tarımsal üretim koşullarının iyileştirilmesi mümkün olmakta; böylece sürdürülebilir tarımsal faaliyetlerin geliştirilmesine katkı sağlanmaktadır (Kızılaslan ve Kılıç, 2023; Gündoğdu ve ark., 2014).
Literatürde arazi toplulaştırmasının parsel büyüklüklerinin artırılması, ulaşım koşullarının iyileştirilmesi, sulama altyapısının geliştirilmesi ve üretici gelirlerinin artırılması gibi olumlu sonuçlar doğurduğu belirtilmektedir (Kızılaslan ve Kılıç, 2023; Kahramanoğlu ve Dağdelen, 2018; Erenci ve Kayalak, 2018). Bununla birlikte, üreticilerin süreç hakkında yeterince bilgilendirilmemesi, üretici katılımının sınırlı kalması, karar alma süreçlerinin yeterince şeffaf olmaması ve altyapı çalışmalarının tamamlanamaması gibi faktörler, arazi toplulaştırmasına yönelik üretici memnuniyetini olumsuz etkileyebilmektedir (İyisöz Bulut ve Unakıtan, 2023; Berk, 2015; Arslan ve Değirmenci, 2016). Uluslararası çalışmalar da arazi toplulaştırmasının arazi değerlerinde artış ve kırsal kalkınmaya katkı gibi olumlu sonuçlarının yanı sıra bazı çevresel riskleri beraberinde getirebileceğine dikkat çekmektedir (Zhou ve ark., 2020; Karakayacı ve ark., 2016). Bunun yanında, arazi sahiplerinin toplulaştırma sürecine aktif katılımının uygulamanın kabulünü ve başarısını artırdığı belirtilmektedir (Lisec ve ark., 2014). Özellikle küçük ölçekli işletmelerde mülkiyete ilişkin kaygılar ve miras yoluyla parçalanmanın devam etmesi, arazi toplulaştırma sürecinin sosyal açıdan daha karmaşık bir yapıya sahip olmasına neden olabilmektedir (Kirmikil, 2025).
Bu çerçevede, arazi toplulaştırmasının teknik ve ekonomik sonuçlarının yanı sıra üreticilerin uygulamaya ilişkin bilgi düzeylerinin, algılarının, yaklaşımlarının ve memnuniyetlerinin belirlenmesi, toplulaştırma çalışmalarının başarısı ve sürdürülebilirliği açısından önem taşımaktadır. Özellikle farklı tarımsal ve sosyo-ekonomik özelliklere sahip bölgelerde üreticilerin arazi toplulaştırmasına yönelik yaklaşımlarının ortaya konulması, uygulamaların üretici perspektifinden değerlendirilmesine katkı sağlayacaktır. Bu çalışma, Türkiye'nin Akdeniz Bölgesi'nin doğusunda yer alan Adana ve Hatay illerindeki çiftçilerin arazi toplulaştırmasına yönelik algı ve yaklaşımlarını belirlemeyi amaçlamaktadır. Bu kapsamda çiftçilerin arazi toplulaştırmasına ilişkin bilgi düzeyleri, bilgilendirilme deneyimleri, toplulaştırmayı benimseme eğilimleri, uygulamaya yönelik görüşleri ve memnuniyet düzeyleri incelenmiştir. Ayrıca çiftçilerin sosyo-ekonomik ve tarımsal işletme özellikleri ile arazi toplulaştırmasına yönelik algı ve yaklaşımları arasındaki ilişkinin ortaya konulması hedeflenmiştir.

MATERYAL VE YÖNTEM

Araştırma, Türkiye'nin Akdeniz Bölgesi'nde yer alan ve tarımsal faaliyetlerin yoğun olarak yürütüldüğü Adana ve Hatay illerinde yürütülmüştür. Araştırma alanı, Türkiye tarım ve ticaretinde önemli bir yere sahiptir. Adana, 36°59′ kuzey enlemleri ile 35°19′ doğu boylamları arasında yer almakta olup, geniş ve düz arazilere sahip verimli bir tarım bölgesidir. Alüvyonlu topraklar sayesinde buğday, mısır, pamuk, ayçiçeği, zeytin, narenciye, sebze ve baklagiller gibi çok çeşitli ürünler üretilmektedir. Hatay ise 35°52′-37°4′ kuzey enlemleri ile 35°40′-36°35′ doğu boylamları arasında yer almakta olup, verimli tarım arazilerine ve önemli limanlara sahip bir bölgedir.

Hatay il topraklarının %54,7'si tarıma elverişlidir ve başlıca ürünler arpa, buğday, patates, pamuk, narenciye, sebzeler ve baklagillerden oluşmaktadır (Anonymous, 2025a; Anonymous, 2025b).
Araştırmanın evrenini, 2024 yılı verilerine göre Adana ve Hatay illerinde Çiftçi Kayıt Sistemi'ne (ÇKS) kayıtlı üreticiler oluşturmuştur. Adana ilinde 34.955, Hatay ilinde 21.526 üretici kayıtlı olup, toplam tarım alanları sırasıyla 5.035.633 ve 5.403.000 dekar olarak belirlenmiştir (Tablo 2).

Tablo 2. Araştırmanın alanı

İl	Çiftçi sayısı	Tarım alanı (da)	Anket sayısı
Adana	34 955	5 035 633	100
Hatay	21 526	5 403 000	100
Toplam	56 481	1 438 633	200

Kaynak: TOB, 2024

Örneklem büyüklüğü, basit tesadüfi örnekleme yöntemi kullanılarak belirlenmiştir. Basit tesadüfi örnekleme, evrendeki her bir birimin eşit seçilme olasılığına sahip olduğu örnekleme yöntemidir ve yanlılığı minimuma indirir. Örneklem büyüklüğü aşağıdaki formül ile hesaplanmıştır (Bartlett ve ark., 2001):

$$n = \frac{N * Z^2 * p(1-p)}{d^2\,(N-1) + Z^2 * p(1-p)}$$

N= Evren büyüklüğü
Z=1.96 (%95 güven düzeyi)
p= 0.5 (olasılık)
d= Hata payı (0.08, %8)

Veriler, araştırmacılar tarafından hazırlanan anket formu aracılığıyla toplanmıştır. Anket formu; üreticilerin demografik ve sosyo-ekonomik özellikleri, tarımsal faaliyet ve arazi kullanım özellikleri ile arazi toplulaştırmasına ilişkin algı, bilgi ve memnuniyet düzeylerini belirlemeye yönelik sorulardan oluşmaktadır. Bu kapsamda, üreticilerin yaş, cinsiyet, medeni durum, eğitim düzeyi, aile büyüklüğü, tarımsal faaliyet deneyimi, tarım dışı iş durumu, sosyal güvence durumu, bilgisayar ve internet kullanım düzeyi ile herhangi bir üretici örgütüne üyelik durumuna ilişkin bilgiler toplanmıştır. Bunun yanı sıra, üreticilerin ürün bazında ekim alanları, verim ve üretim miktarları, arazi mülkiyet durumu (mülk/kira) ve kullanılan sulama yöntemlerine (salma, damla ve yağmurlama) ilişkin veriler elde edilmiştir. Arazi toplulaştırmasına ilişkin değerlendirmeler kapsamında ise üreticilerin toplulaştırma konusundaki bilgi düzeyi, bilgilendirilme deneyimleri, toplulaştırmayı benimseme eğilimleri, uygulamaya karşı çıkma gerekçeleri, çözüm önerileri ve memnuniyet düzeyleri belirlenmiş; söz konusu tutum ve değerlendirmeler beşli Likert ölçeği kullanılarak ölçülmüştür. Ölçeklerin güvenilirliği Cronbach's Alpha ile test edilmiş ve tüm ölçekler 0,612 ile 0,810 arasında değişen değerlerle kabul edilebilir düzeyde güvenilir bulunmuştur.
Bu çalışma için etik onay ve izin, Hatay Mustafa Kemal Üniversitesi Sosyal ve Beşeri Bilimler Bilimsel Araştırma ve Yayın Etiği Kurulundan alınmıştır (Toplantı Tarihi: 10.01.2025, Sayı: 01, Karar No: 02).

BULGULAR

Araştırma alanında, üreticilerinin arazi toplulaştırması hakkında düşüncelerine ilişkin yapılan çalışmada üreticilerin %90.5'i erkek, %9.5'i kadındır. Üreticilerin %89.5'i aktif nüfus içinde yer alan bireyler olup yaş ortalaması 45'tir. Üreticilerin %75.5'i evli ve ortalama 4 kişilik ailelere sahiptir. Ayrıca, üreticilerin büyük çoğunluğu okuma yazma bilen ve %60'ından fazlası lise ve üzeri eğitim düzeyinde eğitimli bireylerden oluşmaktadır. Üreticilerin %33.5'i tarım dışı bir işte çalışan ve neredeyse yarısına yakını özel sektörde çalışan bireyler olup tarımsal üretim konusunda tecrübeli bireylerdir. Ayrıca üreticilerin büyük çoğunluğunun sosyal güvencesinin olduğu belirlenmiştir. Üreticilerin %53'ünün bilgisayarının olduğu, %59'unun bilgisayar kullanabildiği, %73'ünün internetinin olduğu ve Tarım Kredi Kooperatifi, Sulama Birliği, Damızlık Sığır Yetiştiricileri Birliği gibi organizasyonlara üye olduğu belirlenmiştir (Tablo 3).

Tablo 3. Üreticilere ilişkin genel bilgiler

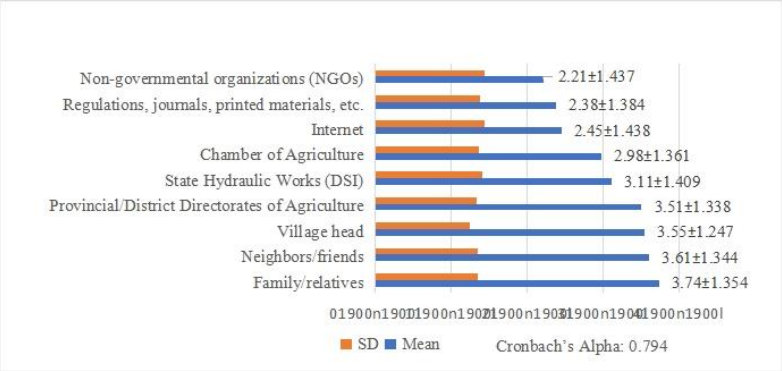
Değişken	Kategori	Frekans	%	Değişken	Kategori	Frekans	%
Yaş grupları	18-35	62	31.0	Ailedeki birey sayısı	1-3	49	24.5
	36-64	117	58.5		4-6	137	68.5
	65 ve üzeri	21	10.5		7 ve üzeri	14	7.0
Cinsiyet	Kadın	19	9.5	Medeni durum	Bekar	49	24.5
	Erkek	181	90.5		Evli	151	75.5
Eğitim durumu	Okuryazar değil	5	2.5	Tarım dışı iş	Evet	67	33.5
	İlkokul	36	18.0		Hayır	133	66.5
	Orta	38	19.0		Kamu	15	22.7
	Lise	71	35.5		Özel Sektör	30	45.5
	Önlisans	24	12.0		Esnaf	9	13.6
	Lisans	22	11.0		Serbest Meslek	9	13.6
	Lisansüstü	4	2.0		Diğer	3	4.5
Sosyal güvence	Yok	29	14.5	Bilgisayar varlığı	Evet	106	53.0
	Emekli	35	17.5		Hayır	94	47.0
	Bağkur	84	42.0	Bilgisayar kullanımı	Evet	118	59.0
	SSK	41	20.5		Hayır	82	41.0
	Emekli Sandığı	7	3.5	İnternet varlığı	Evet	146	73.0
	Diğer	4	2.0		Hayır	54	27.0
Tecrübe	1-15	89	44.5	Organizasyon üyeliği	Tarım Kredi Kooperatifi	79	100
	16-30	76	38.0		Sulama Birliği	85	100
	31 ve üzeri	35	17.5		Damızlık Sığır Yetiştiricileri Bir.	1	100

Araştırma alanının tarımsal üretim desenini, arazi mülkiyetini ve sulama uygulamaları Tablo 3'te incelenmiştir. Bölgedeki tarımda buğday ve mısır en geniş ekim alanlarına sahipken, havuç ve soya daha sınırlı alanlarda yetiştirilmektedir. Verim açısından havuç ve mısır öne çıkarken, buğday ve pamuk daha düşük verim sağlamaktadır; buna karşın, mısır ve havuç üretim miktarı bakımından da başı çekmektedir. Üreticilerin büyük çoğunluğu mülk araziler üzerinde üretim yapmakta olup, özellikle temel tahıl ve yem bitkilerinde mülk arazilerin payı yüksek (%68), değerli ve özel ürünlerde kira kullanımına da rastlanmaktadır. Sulama açısından ise salma (karık-tava) yöntemi yaygın olarak tercih edilirken, damla ve yağmurlama sulama daha çok sebze ve baklagil üretiminde kullanılmaktadır. Zeytin üretiminde sulamalı alanlar sınırlı kalmakta ve yağmurlama sulama uygulanmamaktadır (Tablo 4). Genel olarak, üretim planlaması ürün türüne göre sulama yöntemi ve arazi mülkiyetini dikkate alacak şekilde şekillenmiş olup, yüksek verimli ürünlerin sulamalı mülk arazilerde yoğunlaşması, bölgedeki tarımsal üretimin verimlilik ve arazi yönetimi dengesi gözetilerek yürütüldüğünü göstermektedir.

Tablo 4. Arazi kullanımı

Ürünler	Ekim alanı (da)	Verim (kg/da)	Üretim miktarı (ton)	N	Arazi durumu			Sulama şekli			
						Mülk	Kira	Sulu	Kuru	Salma (Karık. Tava)	Damla	Yağmurlama
Buğday	128	552	74	76	F	51	24	72	3	66	5	4
					%	68	32	96	4	88	6.7	5.3
Pamuk	95	459	44	51	F	35	16	48	3	41	8	2
					%	69	31	94	6	80	16	4
Zeytin	89	523	54	16	F	13	2	9	6	9	6	-
					%	60	40	60	40	60	40	-
Mısır	128	1240	190	62	F	42	20	62	-	58	4	-
					%	68	32	100	-	93.5	6.5	-
Havuç	93	1290	187.35	10	F	5	5	10	-	5	4	1
					%	50	50	100	-	50	40	10
Soya	71	410.5	32.09	10	F	8	2	10	-	7	2	1
					%	80	20	100	-	70	20	10

Üreticilerin yararlandıkları bilgi kaynaklarına ilişkin ortalama değerlere göre aile ve akrabalar (3.74±1.354) üreticilerin en sık başvurduğu bilgi kaynağıdır. Bunu sırasıyla komşu ve arkadaşlar (3.61±1.344) ile muhtarlar (3.55±1.247) izlemektedir. Bu sonuçlar, tarımsal bilgi ediniminde informal ve sosyal ilişkilerin belirleyici bir rol oynadığını göstermektedir. Resmî kurumsal kaynaklar arasında Tarım il/ilçe müdürlükleri (3.51±1.338) en çok başvurulan bilgi kaynağı olarak öne çıkarken, Devlet Su İşleri (3.11±1.409) ve Ziraat Odaları (2.98±1.361) daha sınırlı düzeyde tercih edilmiştir. Buna karşın, internet (2.45±1.438), mevzuat, dergi ve basılı materyaller (2.38±1.384) ile sivil toplum kuruluşları (2.21±1.437) üreticiler tarafından daha az kullanılan bilgi kaynakları olmuştur. Ayrıca, kullanılan ölçeğin Cronbach's Alpha değeri 0.794 olup, ölçeğin güvenilirliğinin kabul edilebilir düzeyde olduğunu göstermektedir (Şekil 1). Bu bulgu, üreticilerin tarımsal bilgiye erişiminde kurumsal ve dijital kanalların mevcut olmasına karşın, geleneksel ve toplumsal temelli iletişim ağlarının hâlâ baskın olduğunu ortaya koymaktadır. Bu nedenle, kurumsal yayım faaliyetlerinin güçlendirilmesi ve dijital bilgi platformlarının kullanımının teşvik edilmesi, tarımsal bilgiye erişimin etkinliğini ve kapsayıcılığını artırmada önemli katkı sağlayabilir.



Ölçek: 1= Hiç önemli değil, 2= Önemsiz, 3= Kararsız, 4= Önemli, 5= Çok önemli

Şekil 1. Çiftçilerin bilgi kaynakları

Üreticilerin arazi toplulaştırmasına yönelik bilgi düzeyi, bilgilendirme deneyimi ve benimseme eğilimlerine göre üreticilerin yaklaşık yarısı, toplulaştırma konusunda "fazla" veya "çok fazla" bilgiye sahip olduğunu belirtirken, %19,5'i sınırlı bilgiye sahiptir. Benzer şekilde, üreticilerin %59'u daha önce bilgilendirme çalışmalarına katılmıştır. Toplulaştırmaya yönelik düşüncelerde ise %40 olumlu, %39 kararsız ve %13,5 olumsuz görüş bildirmiştir. Üreticilerin %66'sı toplulaştırma çalışmalarının bölge açısından gerekli olduğunu düşünmekte, benimseme davranışları ise sosyal etkiyle yakından ilişkilidir; %20'si hemen kabul edeceğini belirtirken, %30'u tüm çiftçiler kabul ettikten sonra, %25,5'i ise önder

çiftçilerden biri kabul ettiğinde onay vereceğini ifade etmiştir (Tablo 5). Bu bulgular, üreticilerin toplulaştırmayı genel olarak olumlu karşıladığını, ancak karar verme süreçlerinde bilgilendirme ve yerel sosyal etkileşimlerin belirleyici olduğunu göstermektedir.

Tablo 5. Üreticilerin arazi toplulaştırmasına yönelik bilgi ve benimseme düzeylerinin oransal dağılımı (N=200)

Değişken	Kategori	Frekans	%
Bilgi düzeyi grupları	Hiç	11	5,5
	Az	28	14,0
	Orta	55	27,5
	Fazla	67	33,5
	Çok fazla	39	19,5
Yeterli bilgiye sahiplik	Bilgim Yok	21	10,5
	Sadece Duydum	44	22,0
	Kısmen Bilgim Var	92	46,0
	Yeterli Bilgiye Sahibim	43	21,5
Bilgilendirme çalışması	Evet	118	59,0
	Hayır	82	41,0
Toplulaştırmaya yönelik düşünce	Fikrim Yok	15	7,5
	Olumsuz	27	13,5
	Kararsız	78	39
	Olumlu	80	40
Toplulaştırma çalışmaları ihtiyacı	Evet	132	66
	Hayır	68	34
Toplulaştırma çalışmalarını benimseme durumu	Hemen kabul ederim	40	20
	Yöredeki çiftçilerin çoğunluğuna göre ederim	49	24,5
	Tüm çiftçiler kabul ettikten sonra kabul ederim	60	30
	Önder çiftçilerden biri bile kabul etse onaylarım	51	25,5

Üreticilerin arazi toplulaştırması uygulamalarına yönelik algı ve değerlendirmeleri incelendiğinde, arazi toplulaştırmasının üreticiler tarafından genel olarak olumlu karşılandığı gözlenmektedir. Özellikle "tarım arazilerine ulaşım kolaylığı ve zaman tasarrufu" (3.78±1.188) ile "dağınık ve parçalı tarım arazilerinin toplu ve düzenli hale getirilmesi" (3.77±1.147) gibi pratik faydalar, üreticiler tarafından önem düzeyi yüksek olarak değerlendirilmiştir. Benzer şekilde, "tarım arazilerinin işlenmesi, tesfiye, sulanması vb. faaliyetleri kolaylaştırması" (3.74±1.245) ve "tarımda ürün kayıplarını azaltarak üretimde sürdürülebilirliği desteklemesi" (3.70±1.215) maddeleri, toplulaştırmanın tarımsal üretime doğrudan katkı sağladığını göstermektedir. Ayrıca, "bölgede daha düzenli bir yerleşim planının oluşması" ve "arazilerde hissedarlık/miras davalarının çözülmesi" gibi sosyal ve idari faydalar da üreticiler tarafından olumlu algılanmaktadır. Öte yandan, toplulaştırmanın olumsuz algılandığı bazı yönler de bulunmaktadır. "Arazilerin yerleşim merkezlerine yakınlığı" ve "girdi maliyetlerini artırması" gibi ekonomik etkiler daha düşük ortalama değerler ile değerlendirilmiş, "tarım arazilerinde değer kaybı" ve "ara çevresindeki komşu ilişkilerinin bozulması" gibi potansiyel riskler daha az endişe uyandırmıştır. Toplulaştırmanın çevresel etkisine ilişkin algı ise en düşük puanı almış (2.62±1.479), üreticilerin çevreye yönelik olası zararları sınırlı bir endişe kaynağı olarak gördüğünü göstermektedir. Genel olarak, Cronbach's Alpha değeri (0.612) ile ölçek iç tutarlılığı orta düzeyde olup, üreticilerin toplulaştırmaya ilişkin düşüncelerinin güvenilir bir şekilde ölçüldüğünü söylemek mümkündür (Tablo 6). Bu bulgular, arazi toplulaştırmasının üreticiler nezdinde daha çok üretim ve ulaşım kolaylığı ile ekonomik ve sosyal faydaları üzerinden olumlu algılandığını, çevresel ve komşuluk ilişkileri gibi olumsuz etkilerin ise sınırlı düzeyde algılandığını ortaya koymaktadır.

Tablo 6. Üreticilerin arazi toplulaştırmasına ilişkin düşünceleri (N=200)

Düşünceler	Mean±SD	Cronbach's Alpha
Tarım arazilerine ulaşım kolaylığı ve zaman tasarrufu	3.78±1.188	
Dağınık ve parçalı tarım arazilerinin toplu ve düzenli hale getirilmesi	3.77±1.147	
Tarım arazilerinin işlenmesi, tesfiye, sulanması vb. faaliyetleri kolaylaştırması	3.74±1.245	
Tarımda ürün kayıplarını azaltarak üretimde sürdürülebilirlik	3.70±1.215	
Bölgede daha düzenli bir yerleşim planının oluşması	3.69±1.217	
Arazilerde hissedarlık/miras davalarının çözülmesi	3.54±1.356	0.612
Arazilerin yerleşim merkezlerine yakınlığı	3.35±1.314	
Girdi maliyetlerini arttırması	3.08±1.447	
Tarım arazilerinde değer kaybı	3.04±1.401	
Arazi çevresindeki komşu ilişkilerinin bozulması	3.04±1.343	
Toplulaştırma çalışmalarının çevre için zararlı olma düşüncesi	2.62±1.479	

Ölçek: 1=Kesinlikle katılmıyorum, 2= Katılmıyorum, 3= Kararsızım, 4= Kısmen katılıyorum, 5= Kesinlikle katılıyorum

Üreticilerin arazi toplulaştırma çalışmalarına karşı gösterdikleri çekinceleri ve olumsuz algıları incelendiğinde; en yüksek endişeyi "daha uzak bir yerden tarım arazisi verilme düşüncesi" (3.83±1.127), "projenin bölge içinde objektif bir şekilde yürütülmemesi" (3.82±1.152) ve "değerli arazilerin yerine daha az kıymetli tarım arazilerinin verilme düşüncesi" (3.81±1.149) konularında göstermiştir. Bu durum, üreticilerin toplulaştırmanın adil ve eşitlikçi bir biçimde yürütülmemesinden kaynaklanan endişelerinin ön planda olduğunu göstermektedir. Diğer yandan, miras yoluyla geçen arazileri verme isteksizliği (3.67±1.161), bölge çiftçilerinin görüşlerinin yeterince alınmaması (3.66±1.226), tapu işlemlerinde yaşanan sıkıntılar (3.64±1.195) ve çevredeki kişilerin olumsuz söylemleri (3.63±1.149) da üreticilerin itiraz gerekçeleri arasında önemli bir yer tutmaktadır. Bununla birlikte, arazi parçalılık durumunun yeterince yapılmaması (3.61±1.202), eski sulama kanallarının bozulması ve yeni sulama maliyetlerinin artması (3.50±1.256), yeni yolların dar olması ve ulaşımı zorlaştırması (3.43±1.380) gibi teknik ve altyapısal kaygılar nispeten daha düşük düzeyde endişe yaratmaktadır. Kullanılan ölçeğin Cronbach's Alpha değerine göre (0,706) iç tutarlılığı orta-iyi düzeyde olup, üreticilerin toplulaştırmaya karşı tepkilerinin güvenilir biçimde ölçüldüğünü göstermektedir (Tablo 7). Genel olarak, üreticilerin itirazları daha çok adalet, arazi değerleri ve kişisel mülkiyet hakları ile ilgili iken, teknik ve altyapısal sorunlar daha az ön plana çıkmaktadır.

Tablo 7. Arazi toplulaştırma çalışmalarına karşı çıkılma nedenleri (N=200)

Nedenler	Mean±SD	Cronbach's Alpha
Daha uzak bir yerden tarım arazisi verilme düşüncesi	3.83±1.127	
Arazi toplulaştırma projesinin bölge içerisinde objektif bir şekilde yürütülmemesi	3.82±1.152	0,706
Değerli arazilerin yerine daha az kıymetli tarım arazilerinin verilme düşüncesi	3.81±1.149	

Miras yoluyla geçen arazileri vermek istememeleri	3.67±1.161
Bölge çiftçilerinin görüşlerinin alınması	3.66±1.226
Tapu işlemlerinde yaşanan sıkıntıların oluşması	3.64±1.195
Çevredeki kişilerin olumsuz söylemleri	3.63±1.149
Arazi parçalılık durumunun yeterince yapılması	3.61±1.202
Eski sulama kanalları bozulması ve yeni yapılan sulama kanallarında maliyet artışı	3.50±1.256
Yeni yolların dar olması, ulaşımı zorlaştırması ve arazi kaybı düşüncesi	3.43±1.380

Ölçek: 1=Kesinlikle katılmıyorum, 2= Katılmıyorum, 3= Kararsızım, 4= Kısmen katılıyorum, 5= Kesinlikle katılıyorum

Üreticilerin arazi toplulaştırma sürecinde karşılaşılan sorunlara yönelik çözüm önerilerini ve önceliklerine göre; en yüksek önemi "hisseli tapu sorunlarının tamamen ortadan kaldırılması" (3.91±1.204) ve "devlet kuruluşları tarafından toplulaştırma işlemlerinin yürütülmesi" (3.91±1.110) önerilerine vermektedir. Bu durum, üreticilerin süreçte hukuki güvence ve resmi otoritenin rolünü kritik bir faktör olarak gördüğünü göstermektedir. Bunun yanı sıra, "toplulaştırma öncesi bilgilendirme toplantılarının düzenlenmesi" (3.82±1.240) ve "tarım arazilerinin daha doğru ve eşit bir şekilde dağıtılması" (3.79±1.160) gibi öneriler de yüksek öncelikli olarak değerlendirilmiş, sürecin şeffaf ve adil bir şekilde yürütülmesi gerektiği vurgulanmıştır. Üreticiler ayrıca "yeni arazi sahiplerinin çevresindeki komşuların doğru belirlenmesi" (3.74±1.241), "çiftçi görüşlerinin alınması" (3.74±1.364) ve "parsel listelerinin SMS, posta gibi iletişim yollarıyla bildirilmesi" (3.74±1.234) gibi iletişim ve katılıma dayalı önlemleri de önemli bulmaktadır. Diğer yandan, "parsel listelerinin askıda kalma süresi ve çiftçi itiraz sürelerinin uzun olması" (3.49±1.232) daha düşük öncelikli görülmüştür. Cronbach's Alpha değeri (0,787) ile ölçek yüksek düzeyde iç tutarlılığa sahip olup, önerilerin güvenilir bir şekilde ölçüldüğünü göstermektedir (Tablo 8). Genel olarak, üreticiler arazi toplulaştırma sürecinde hukuki güvence, resmi otorite desteği, adil dağıtım ve etkin bilgilendirme mekanizmalarını öncelikli çözüm yolları olarak görmektedir.

Tablo 8. Arazi toplulaştırma çalışmalarına ilişkin çözüm önerileri (N=200)

Öneri	Mean±SD	Cronbach's Alpha
Hisseli tapu sorunlarının tamamen ortadan kaldırılması	3.91±1.204	0,787
Devlet kuruluşları tarafından toplulaştırma işlemlerinin yapılması	3.91±1.110	
Arazi toplulaştırma çalışması öncesi bir bilgilendirme toplantısının düzenlenmesi	3.82±1.240	
Tarım arazilerinin daha doğru ve eşit bir şekilde dağıtılması	3.79±1.160	
Toplulaştırma sonrası yeni arazi sahiplerinin çevresindeki komşu arazi sahiplerinin iyi belirlenmesi	3.74±1.241	
Arazi toplulaştırma işlemlerinde çiftçi görüşleri alınarak yapılması	3.74±1.364	
Yeni belirlenen parsel listelerinin üreticiye sms, posta vb. iletişim yollarıyla bilgilendirilmeleri	3.74±1.234	
Yeni belirlenen parsel listelerinin askıda kalma ve çiftçi itiraz sürelerinin uzun olması	3.49±1.232	

Ölçek: 1=Kesinlikle katılmıyorum, 2= Katılmıyorum, 3= Kararsızım, 4= Kısmen katılıyorum, 5= Kesinlikle katılıyorum

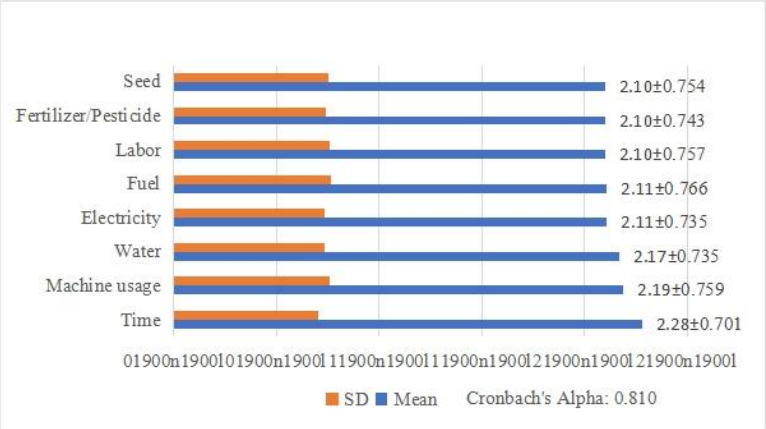
Tablo 9'deki veriler, üreticilerin bölgelerindeki arazi toplulaştırma çalışmalarına ilişkin memnuniyet düzeylerini göstermektedir. Üreticiler en yüksek memnuniyeti "tarla yollarının yeterliliği ve iyileşmesi" (3.75±1.088) ve "işgücü maliyetlerinde azalma" (3.73±1.056) maddelerinde göstermiştir; bu durum, toplulaştırmanın üretim süreçlerini kolaylaştırıcı ve ekonomik açıdan faydalı olduğunu işaret etmektedir. Sürdürülebilir tarımsal üretim (3.64±0.988), daha yüksek verim ve ürün kalitesi (3.61±1.203) ile yeni parsellerin köy merkezine yakınlığı (3.60±1.126) gibi etkiler de üreticiler tarafından olumlu değerlendirilmiştir. Bununla birlikte, "tarımda girdi kullanımında azalma" (3.53±1.102) ve "arazilerde makine kullanım kolaylığı" (3.46±1.202) gibi faydalar orta düzeyde memnuniyet yaratmıştır. "Yine arazi toplulaştırma çalışması yapılsa onay verme" (3.44±1.132) maddesi, üreticilerin sürece genel olarak olumlu yaklaşmakla birlikte bazı çekinceler taşıdığını göstermektedir. En düşük memnuniyet ise "kırdan kente göçün engellenmesi" (3.04±1.079) maddesinde görülmekte, toplulaştırmanın sosyo-demografik etkilerinin sınırlı algılandığını ortaya koymaktadır. Cronbach's Alpha değeri (0,749) ile ölçek iç tutarlılığı yüksek olup, üreticilerin memnuniyet düzeylerinin güvenilir biçimde ölçüldüğünü göstermektedir (Tablo 9). Genel olarak, üreticiler toplulaştırma çalışmalarını özellikle üretim kolaylığı, maliyet azalması ve verimlilik açısından olumlu değerlendirmekte, sosyo-demografik etkiler ve gelecekteki uygulamalar konusunda ise daha temkinli bir yaklaşım sergilemektedir.

Tablo 9. Bölgenizdeki toplulaştırma çalışmalarına karşı memnuniyetiniz (N=200)

Memnuniyet	Mean±SD	Cronbach's Alpha
Tarla yollarının yeterliliği ve iyileşmesi	3.75±1.088	
İşgücü maliyetlerinde azalma	3.73±1.056	
Sürdürülebilir tarımsal üretim açısından	3.64±0.988	
Daha yüksek verim ve ürün kalitesi	3.61±1.203	
Yeni parsellerin köy merkezine yakınlaşması	3.60±1.126	0,749
Tarımda girdi kullanımında (ilaç, gübre, tohum, yakıt, elektrik vb.) azalma	3.53±1.102	
Arazilerde makine kullanım kolaylığı	3.46±1.202	
Yine arazi toplulaştırma çalışması yapılsa onay verme	3.44±1.132	
Kırdan kente göçün engellenmesi	3.04±1.079	

Ölçek: 1= Hiç memnun değilim, 2= Memnun değilim, 3= Kararsızım, 4= Memnunum, 5= Çok memnunum

Arazi toplulaştırması sonrasında çiftçilerin girdi kullanımında genel olarak belirgin bir değişim bulunmamaktadır. Ortalama değerler, zaman, makine kullanımı ve su gibi girdilerde sınırlı bir azalma eğilimi sergilemekle birlikte, çoğu girdi için değişim minimal düzeydedir. Ölçek iç tutarlılığı yüksek (Cronbach's Alpha= 0,810) olup, ölçümün güvenilir olduğunu ortaya koymaktadır (Şekil 2). Bu sonuçlar, arazi toplulaştırmasının çiftçilerin girdi kullanım alışkanlıkları üzerinde köklü bir etki yaratmadığını, ancak bazı girdilerde verimlilik ve kullanım kolaylığı açısından küçük iyileşmeler sağladığını göstermektedir.



Şekil 2. Arazi toplulaştırması sonrası çiftçilerin girdi kullanımındaki değişimi (N=200)
Ölçek: 1= Arttı, 2= Değişmedi, 3= Azaldı

SONUÇ VE ÖNERİLER

Bu araştırmada, üreticilerin arazi toplulaştırması hakkındaki bilgi düzeyleri, görüşleri ve uygulamaya yönelik değerlendirmeleri incelenmiştir. Sonuçlar, üreticilerin çoğunun toplulaştırmayı genel olarak olumlu karşıladığını göstermektedir. Üreticiler; ulaşım kolaylığı, zaman tasarrufu, arazi düzeninin iyileşmesi, miras kaynaklı sorunların azalması ve verim artışı gibi alanlarda toplulaştırmanın fayda sağladığını ifade etmiştir. Bununla birlikte, bazı üreticilerin arazilerin adil dağıtılmadığı, daha uzak bölgelere parsel verildiği ve değer açısından kayıplar yaşandığı yönünde endişeleri bulunmaktadır. Toplulaştırma sürecinde bilgi eksikliği yaşayan üreticiler, uygulamanın her aşamasında yeterince bilgilendirilmek istediklerini belirtmiştir. Ayrıca, üreticilerin toplulaştırma hakkında en çok sosyal çevresinden bilgi aldığını, resmi kaynaklardan yararlanmanın ise sınırlı olduğunu ortaya koymuştur. Toplulaştırma sonrası memnuniyet, özellikle makine kullanım kolaylığı, tarla yollarının düzelmesi ve iş gücü maliyetlerinin azalması konularında yüksek bulunmuştur. Buna karşın, toplulaştırmanın kırsaldan kente göçü engellemede etkisinin düşük olduğu belirlenmiştir. Sonuç olarak, arazi toplulaştırması tarımsal üretimde düzen, verimlilik ve zaman yönetimi açısından önemli katkılar sağlamaktadır. Ancak adalet algısı ve bilgilendirme eksikliği bazı üreticilerin memnuniyetini olumsuz etkilemektedir. Elde edilen bulgular doğrultusunda, arazi toplulaştırması sürecinde bilgilendirme ve tarımsal yayım faaliyetlerine daha fazla önem verilmesi, toplulaştırma öncesi ve sonrasında üreticilere yönelik seminer, eğitim ve bilgilendirme toplantılarının sıklığının ve kapsamının artırılması önerilmektedir. Parsel dağıtımı ve değerleme süreçlerinde adil ve şeffaf mekanizmaların oluşturulması, objektif kriterlerin uygulanması ve böylece üreticilerin eşitlik ve hakkaniyet algısının güçlendirilmesi önem taşımaktadır. Hisseli tapu sorunlarının ve miras kaynaklı ihtilafların azaltılması amacıyla mülkiyet yapısının netleştirilmesine yönelik hukuki ve idari düzenlemelerin geliştirilmesi gerekmektedir. Ayrıca devlet kurumları, kooperatifler ve sulama birlikleri arasındaki iş birliğinin güçlendirilerek kurumsal koordinasyonun geliştirilmesi, toplulaştırma uygulamalarının etkinliğini artıracaktır. Üreticilerin internet ve tarımsal bilgi sistemlerinden daha etkin yararlanmalarının teşvik edilmesi ve dijital bilgi platformlarının yaygınlaştırılması da bilgiye erişimin kolaylaştırılması açısından önemlidir. Bunun yanında, yeni açılan tarla yollarının genişliği, sulama kanallarının kapasitesi ve parsel geometrileri gibi unsurların teknik standartlara uygun biçimde planlanması ve altyapının iyileştirilmesi gerekmektedir. Üreticilerin toplulaştırma sürecindeki gelişmelerden zamanında haberdar edilmesi amacıyla SMS, e-posta ve dijital platformlar gibi iletişim araçlarının daha etkin kullanılması; özellikle askı ve itiraz sürelerine ilişkin bilgilendirmelerin zamanında yapılması sağlanmalıdır. Son olarak, arazi toplulaştırmasının göç, gelir ve istihdam üzerindeki etkilerinin uzun dönemli olarak izlenmesi, elde edilen sonuçlar doğrultusunda gerektiğinde bölgesel teşvik politikalarının geliştirilmesi ve toplulaştırmanın sosyo-demografik etkilerinin düzenli olarak değerlendirilmesi önerilmektedir. Sonuç olarak, arazi toplulaştırması bölgedeki tarımsal üretim sisteminin daha verimli, ekonomik ve düzenli bir hale gelmesine katkı sağlamaktadır. Ancak uygulamanın başarısı, bilgilendirme düzeyi, adalet algısı, kurumsal koordinasyon ve teknik altyapının etkinliğine bağlıdır. Bu doğrultuda geliştirilecek politika ve uygulamalar, arazi toplulaştırmasının sürdürülebilir tarıma katkısını önemli ölçüde artıracaktır.

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TÜRKİYEDE TARIMSAL İŞGÜCÜ ÜCRET YAPISININ DEĞERLENDİRİLMESİ

EVALUATION OF THE AGRICULTURAL LABOR WAGE STRUCTURE IN TÜRKİYE

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ÖZET

Tarım sektörü, Türkiye ekonomisinde istihdam, gıda güvenliği ve kırsal kalkınma açısından stratejik bir öneme sahiptir. Bununla birlikte tarım işgücü piyasası; düşük ücret düzeyleri, mevsimlik çalışma yapısı, kayıt dışı istihdamın yaygınlığı, toplumsal cinsiyete dayalı ücret farklılıkları ve sınırlı sosyal güvence gibi yapısal sorunlarla karşı karşıyadır. Bu sorunlar, tarımsal üretimin sürdürülebilirliği ile sektörde çalışanların ekonomik ve sosyal refahını olumsuz yönde etkilemektedir. Bu çalışmanın amacı, Türkiye'de tarımsal işgücü ücret yapısını ikincil veriler ışığında değerlendirerek mevsimlik ve sürekli tarım işçilerinin ücret düzeylerini, cinsiyete göre ücret farklılıklarını, bölgesel ücret dağılımlarını ve son yıllardaki değişim eğilimlerini ortaya koymaktır. Çalışmada, Türkiye İstatistik Kurumu (TÜİK) tarafından yayımlanan Tarımsal İşletme İşgücü Ücret Yapısı bültenlerindeki resmî veriler kullanılmıştır. Araştırma bulguları, 2021–2025 döneminde mevsimlik ve sürekli tarım işçilerinin ücretlerinde belirgin nominal artışlar yaşandığını, ancak kadın işçilerin ücretlerinin tüm dönemlerde erkek işçilere kıyasla daha düşük seviyede kaldığını göstermektedir. 2025 yılında mevsimlik tarım işçilerinin günlük ücreti bir önceki yıla göre %37,8 artarak 1.299 TL'ye, sürekli tarım işçilerinin aylık ücreti ise %42,1 artarak 37.305 TL'ye yükselmiştir. Aynı dönemde mevsimlik kadın işçilerin ücreti %34,1, erkek işçilerin ücreti ise %40,6 oranında artmıştır. Ayrıca ücretlerin iller arasında önemli farklılıklar gösterdiği; 2025 yılında en yüksek mevsimlik günlük ücretin Rize'de, en düşük ücretin erkek işçiler için Ankara'da ve kadın işçiler için Hatay'da gerçekleştiği belirlenmiştir. Elde edilen bulgular, tarım işgücü piyasasında ücret farklılıklarının yalnızca ekonomik değil, aynı zamanda toplumsal cinsiyet ve bölgesel eşitsizliklerle ilişkili yapısal bir sorun olduğunu ortaya koymaktadır. Sonuç olarak, tarımsal işgücü piyasasında daha adil ve sürdürülebilir bir ücret yapısının oluşturulabilmesi için kayıt dışı istihdamın azaltılmasına yönelik politikaların güçlendirilmesi, toplumsal cinsiyet temelli ücret eşitsizliklerinin giderilmesi, sosyal güvenlik kapsamının genişletilmesi ve mevsimlik tarım işçilerinin çalışma koşullarının iyileştirilmesi büyük önem taşımaktadır.

Anahtar Kelimeler: Tarımsal işgücü, ücret yapısı, mevsimlik tarım işçileri, toplumsal cinsiyet, kayıt dışı istihdam.

ABSTRACT

The agricultural sector plays a strategic role in the Turkish economy in terms of employment, food security, and rural development. However, the agricultural labor market faces several structural challenges, including low wage levels, the seasonal nature of employment, widespread informal employment, gender-based wage disparities, and limited social security coverage. The aim of this study is to evaluate the wage structure of agricultural labor in Türkiye using secondary data published by the Turkish Statistical Institute (TurkStat). The findings indicate that in 2025 the average daily wage of seasonal agricultural workers rose by 37.8% year-on-year to TL 1,299, while the monthly wage of permanent agricultural workers rose by 42.1% to TL 37,305. Over the same period, women's seasonal daily wages increased by 34.1% and men's by 40.6%; women's wages remained consistently lower than men's throughout 2021–2025. Substantial regional disparities were also identified: in 2025 the highest seasonal daily wages were paid in Rize, while the lowest were recorded in Ankara (male workers) and Hatay (female workers). The results demonstrate that wage disparities in the agricultural labor market represent not only an economic issue but also a structural problem associated with gender inequality and regional disparities.

Keywords: Agricultural labor, wage structure, seasonal agricultural workers, gender, informal employment.

GİRİŞ

Türkiye'de tarım sektörü; istihdam, gıda güvenliği, kırsal kalkınma, ihracat ve ulusal gelire sağladığı katkılar bakımından stratejik bir öneme sahiptir. Artan nüfusun gıda ihtiyacının karşılanması, gıda arz güvenliğinin sağlanması ve doğal kaynakların korunması gibi hususlar, tarım sektörünün ekonomik ve sosyal açıdan önemini artırmaktadır. Bu durum, tarımsal arz güvenliğinin garanti altına alınmasını ve tarım sektörünün uygun politikalarla desteklenmesini gerekli kılmaktadır (Yıldırım & Karakoyun, 2023). Türkiye'de tarım sektörü, tarihsel süreç içerisinde ekonominin temel unsurlarından biri olmuş; günümüzde sektörün istihdam ve milli gelir içerisindeki payı geçmiş dönemlere kıyasla azalmış olmakla birlikte, çok sayıda hanenin temel gelir kaynaklarından biri olma özelliğini sürdürmüştür (Anonim, 2025a).

Türkiye'de yaşanan ekonomik ve demografik dönüşüm, tarım sektörünün istihdam yapısını da önemli ölçüde değiştirmiştir. Cumhuriyetin ilk yıllarında yaklaşık %75 olan kırsal nüfus oranının 2020 yılında %7 seviyelerine gerilemesi, kırdan kente yönelik göç sürecinin boyutunu ortaya koymaktadır. Kırdan kente göç eden nüfusun sanayi sektöründen ziyade ağırlıklı olarak hizmet sektöründe istihdam edildiği görülmektedir. Bu süreçte tarımda istihdam edilenlerin oranı %67,7'den %16'ya düşerken, sektörün GSYH içindeki payı da %6,7 seviyelerine gerilemiştir (Demir ve ark., 2023). Benzer şekilde, tarım sektörünün milli gelir içerisindeki payı 1980 yılında %25,8 iken, 2022 yılında %4,8'e düşmüştür. Bununla birlikte sektör, 2022 yılında %0,6 oranında büyüme kaydetmiştir (TAGEM, 2023). Tarım sektörü ihracat açısından da Türkiye ekonomisinde önemli bir yere sahiptir. 2022 yılında 34,2 milyar dolarlık tarım ihracatı gerçekleştirilmiş ve 2023 yılı itibarıyla 213 ülke ve serbest bölgeye hububat, bakliyat, yağlı tohumlar ve mamulleri ihraç edilmiştir. Tarımsal istihdamın toplam istihdam içerisindeki payı ise 2022 yılında %15,8 olarak gerçekleşmiştir (Ticaret Bakanlığı, 2022). Dünya Bankası verilerine göre, 2021 yılında küresel tarımsal katma değer yaklaşık 3,26 trilyon dolar düzeyinde gerçekleşmiş ve dünya genelinde 891 milyon kişi tarım sektöründe istihdam edilmiştir.

Tarım sektörünün ekonomik öneminin yanı sıra işgücü piyasasının kendine özgü yapısı da sektörün değerlendirilmesini gerekli kılmaktadır. Tarım işgücü piyasasında kendi hesabına çalışanlar, mevsimlik ve geçici tarım işçileri, sürekli çalışan tarım işçileri ile aile fertlerinin önemli bir bölümü kayıt dışı istihdam kapsamında yer almaktadır (Akbıyık, 2008). Türkiye'de işgücü piyasası ve istihdamın yapısı, çalışma çağındaki nüfusun artışı ve ekonomik dönüşümle birlikte zaman içerisinde değişmiştir. Genç nüfusa sahip olan Türkiye'de son on yılda çalışma çağındaki kurumsal olmayan nüfusun sürekli arttığı, ekonomik dönüşümün ise temel işgücü göstergelerini etkileyerek işgücü piyasasının yapısal sorunlarını daha görünür hâle getirdiği belirtilmektedir (Şentürk, 2015). Bu yapısal özellikler içerisinde mevsimlik tarım işçiliği, ekonomik ve sosyal politika açısından çözüm bekleyen alanlardan biri olarak öne çıkmaktadır. Tarım işgücünün önemli bir bölümü mevsimlik özellik taşımakta; düşük ücret düzeyleri, kayıt dışılık, göç hareketleri, barınma ve çalışma koşullarına ilişkin sorunlar gibi çok boyutlu sorunlarla karşı karşıya kalmaktadır (Topal, 2010). Tarım işgücü içerisinde aile işgücü de önemli bir yere sahiptir. Tarım işletmesinin veya aile şirketinin üretimine katkıda bulunan ancak para veya pazarlanabilir ürün şeklinde herhangi bir ücret almayan kişiler bu kapsamda değerlendirilmektedir. Kadınlar, çoğu zaman gerçek anlamda ortak olmalarına, işi, karar alma süreçlerini ve riskleri işletme sahibiyle (eş, erkek kardeş, oğul veya baba) eşit olarak paylaşmalarına rağmen bu kategoriye dâhil edilme eğilimindedir (FAO, 1992).Türk iş hukuku literatüründe tarım işçisine ilişkin özel bir tanım bulunmamakla birlikte, tarım işçisi; tarımsal faaliyetlerde bir işverene bağlı olarak, iş sözleşmesi çerçevesinde bitkisel veya hayvansal üretime yönelik dikim, söküm, bakım, yetiştirme ve hasat gibi işleri yerine getiren kişi olarak tanımlanmaktadır. Tarım işçileri, yapılan işin niteliğine bağlı olarak belirsiz süreli veya belirli süreli iş sözleşmeleriyle çalışabilmektedir (Anonim, 2025b). Türkiye İstatistik Kurumu tarafından her yıl yayımlanan Tarımsal İşletme İşgücü Ücret Yapısı Araştırması kapsamında, tarımsal işletmelerde çalışan mevsimlik işçilere ilişkin ücret ve çalışma bilgileri derlenmekte; mevsimlik işçilerin faaliyet, dönem, ürün, ödeme şekli ve cinsiyet ayrımında çalıştıkları gün sayısı ile işletme tarafından ödenen toplam ücretleri değerlendirilmektedir. Sürekli çalışan işçilere ilişkin olarak da ödeme şekillerine göre işçi sayıları, çalışılan ay sayısı ve ödenen toplam ücret bilgileri derlenmektedir (TÜİK, 2026).

Bu çalışma, Türkiye'de tarımsal işgücü ücret yapısını ikincil veriler üzerinden değerlendirmeyi amaçlamaktadır. Bu doğrultuda mevsimlik ve sürekli tarım işçilerinin ücret düzeyleri; cinsiyet, istihdam türü ve bölgesel farklılıklar açısından ele alınarak 2021–2025 dönemindeki değişim eğilimleri ortaya konulmaktadır.

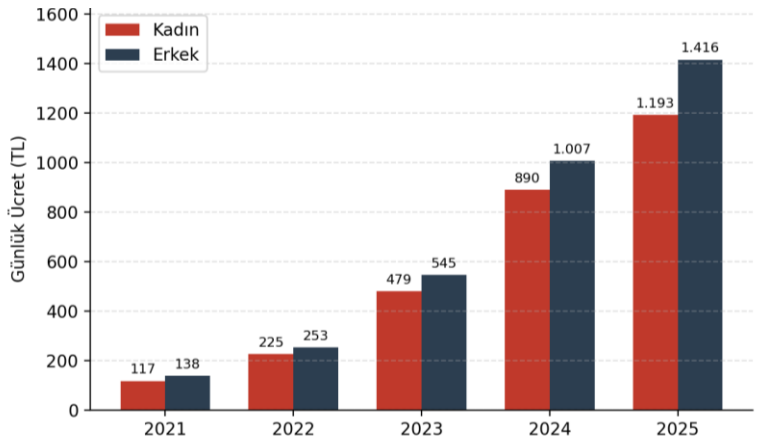
MATERYAL VE YÖNTEM

Bu araştırmanın ana materyalini, Türkiye'de tarımsal işgücünün ücret yapısına ilişkin Türkiye İstatistik Kurumu (TÜİK) tarafından yayımlanan Tarımsal İşletme İşgücü Ücret Yapısı bültenlerindeki resmî ikincil veriler oluşturmaktadır. TÜİK, bu istatistikleri, verinin ait olduğu üretim yılında ve tarım işlerinin en yoğun olduğu dönemde, tarımsal amaçla en az beş mevsimlik işçi ya da en az bir sürekli işçi çalıştıran illerdeki tarımsal işletmelerden derlediği verilere dayanarak üretmektedir; 2025 yılı bülteni 35 ildeki 4.397 tarımsal işletmeden elde edilen verilere dayanmaktadır (TÜİK, 2026). Araştırmada, tarımsal işletmelerde çalışan mevsimlik ve sürekli işçilerin ücretleri kadın ve erkek işçiler ayrımında ele alınmıştır. Araştırmanın zaman boyutunu 2021–2025 dönemi oluşturmakta olup, bu kapsamda mevsimlik işçilerin günlük, sürekli işçilerin ise aylık ücretlerindeki nominal değişim incelenmiştir; çalışmada kullanılan tüm yüzdesel değişim oranları TÜİK bültenlerinde doğrudan açıklanan, deflatöre tabi tutulmamış nominal artış oranlarıdır. Ayrıca, 2025 yılına ait il düzeyindeki veriler kullanılarak tarımsal işgücü ücretlerinin illere göre gösterdiği en yüksek ve en düşük değerler değerlendirilmiştir.

BULGULAR

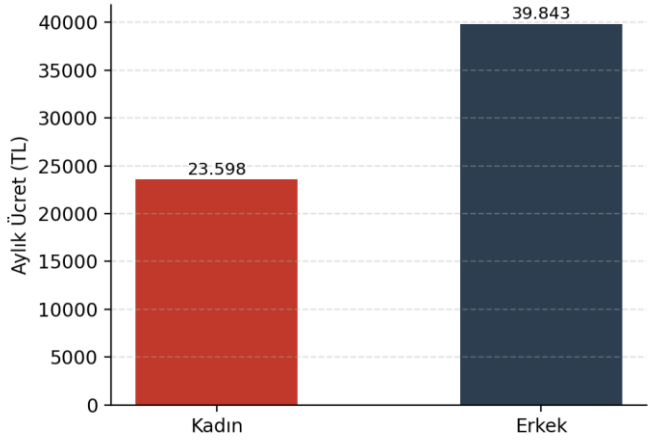
1. Tarımsal işletmelerin işgücü ücret yapısı

Tarımsal işletmelerde 2025 yılında mevsimlik tarım işçilerinin günlük ücretleri bir önceki yıla göre %37,8 artarak 1.299 TL olarak gerçekleşmiştir. Mevsimlik erkek işçi ücretleri %40,6 artış göstererek 1.007 TL'den 1.416 TL'ye yükselirken, kadın işçilerin günlük ücretleri %34,1 artış göstererek 890 TL'den 1.193 TL'ye yükselmiştir (TÜİK, 2026) (Şekil 1).



Şekil 1. Mevsimlik tarım işçilerinin ortalama günlük ücretleri (TL), 2021-2025 (TÜİK, 2026)

Sürekli tarım işçilerine ödenen aylık ücret, erkek işçiler için %43,4 oranında artarak 27.788 TL'den 39.843 TL'ye, kadın işçiler için %22,1 artarak 19.328 TL'den 23.598 TL'ye yükselmiştir (TÜİK, 2026) (Şekil 2).



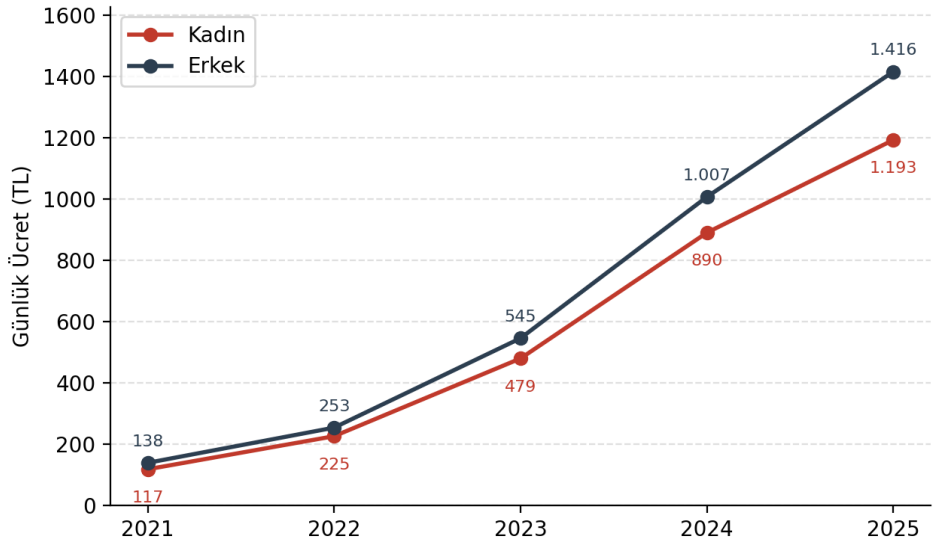
Şekil 2. Sürekli tarım işçilerinin ortalama aylık ücretleri, 2025 (TÜİK, 2026)

Türkiye'de mevsimlik işçilerin ücretlerinin son 5 yılı incelendiğinde, ücret artışlarının belirgin oranda arttığı ancak cinsiyete dayalı ücret farkının tüm dönem boyunca korunduğu görülmektedir. Ücret artışlarının, yüksek enflasyon, asgari ücrete gelen zamlar ve tarım işgücü arzında meydana gelen daralmalarla ilgili olduğu düşünülmektedir (Tablo 1).

Tablo 1. Yıllar itibarıyla cinsiyete göre mevsimlik tarım işçilerinin günlük ücretleri (TL)

Yıl	Kadın (TL)	Erkek (TL)
2025	1.193	1.416
2024	890	1.007
2023	479	545
2022	225	253
2021	117	138

Kaynak: TÜİK, 2022; TÜİK, 2024; TÜİK, 2026



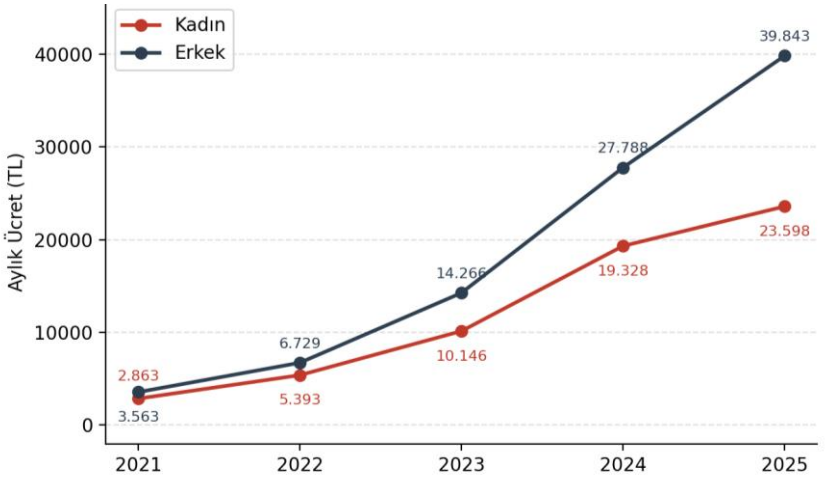
Şekil 3. Mevsimlik işçilerin günlük ücretleri (TL), 2021-2025

Tablo 2, 2021–2025 yılları arasında sürekli tarım işçilerinin aylık ücretlerini cinsiyete göre göstermektedir. Tablo incelendiğinde, ilgili dönemde hem kadın işçilerin hem de erkek işçilerin aylık ücretlerinde belirgin bir artış eğilimi görülmektedir. Bu artış, genel ekonomik koşullar, enflasyonist ortam ve asgari ücret düzenlemeleriyle paralel bir seyir izlemektedir. Tüm yıllar itibarıyla erkek işçilerin aylık ücretlerinin kadın işçilere kıyasla daha yüksek olduğu dikkat çekmektedir. Cinsiyete dayalı ücret farkı, yıllar içinde mutlak değer olarak artmakta; bu durum tarım sektöründe ücret eşitsizliğinin süreklilik arz ettiğini göstermektedir. Özellikle 2025 yılı verileri, hem ücret düzeylerindeki artışı hem de kadın ve erkek işçiler arasındaki ücret farkının belirginleştiğini ortaya koymaktadır.

Tablo 2. Sürekli tarım işçilerinin aylık ücretleri (TL)

Yıl	Kadın (TL)	Erkek (TL)
2025	23.598	39.843
2024	19.328	27.788
2023	10.146	14.266
2022	5.393	6.729
2021	2.863	3.563

Kaynak: TÜİK, 2022; TÜİK, 2024; TÜİK, 2026



Şekil 4. Son 5 yılın sürekli işçi ücret karşılaştırması (TL)

2. İllere göre ücret dağılımı

2025 yılı il düzeyindeki veriler incelendiğinde, tarım işgücü ücretlerinin iller arasında belirgin farklılıklar gösterdiği görülmektedir. Mevsimlik tarım işçilerine ödenen en yüksek günlük ücret, çay hasadının etkisiyle hem erkek hem de kadın işçiler için Rize ilinde gerçekleşmiştir. En düşük günlük ücret ise erkek işçiler için Ankara'da, kadın işçiler için Hatay'da kaydedilmiştir (TÜİK, 2026) (Tablo 3).

Tablo 3. Mevsimlik tarım işçilerinin illere göre en yüksek ve en düşük günlük ücretleri, 2025

Kategori	İl	Günlük Ücret (TL)
En yüksek (erkek)	Rize	3.283
En yüksek (kadın)	Rize	3.075
En düşük (erkek)	Ankara	1.037
En düşük (kadın)	Hatay	976

Kaynak: TÜİK, 2026

Sürekli tarım işçilerinde ise en yüksek aylık ücret erkek işçiler için Niğde'de, kadın işçiler için İzmir'de gerçekleşmiş; en düşük ücretler ise hem erkek hem de kadın işçiler için Antalya ilinde kaydedilmiştir (TÜİK, 2026) (Tablo 4).

Tablo 4. Sürekli tarım işçilerinin illere göre en yüksek ve en düşük aylık ücretleri, 2025

Kategori	İl	Aylık Ücret (TL)
En yüksek (erkek)	Niğde	53.927
En yüksek (kadın)	İzmir	25.521
En düşük (erkek)	Antalya	26.186
En düşük (kadın)	Antalya	23.040

Kaynak: TÜİK, 2026

SONUÇ VE ÖNERİLER

Bu çalışmada Türkiye'de mevsimlik ve sürekli tarım işçilerinin ücret yapısı; yıllar itibarıyla değişimi, cinsiyet farklılıkları ve illere göre dağılımı çerçevesinde incelenmiştir. TÜİK'in resmî verilerine göre, 2021–2025 döneminde hem mevsimlik hem de sürekli tarım işçilerinin ücretlerinde belirgin nominal artışlar yaşanmıştır. Ancak bu artışlar, yüksek enflasyon ve yükselen yaşam maliyetleri birlikte değerlendirildiğinde reel gelirde kalıcı bir iyileşmeye işaret etmemektedir. Ayrıca bulgular, cinsiyete dayalı ücret eşitsizliğinin süreklilik arz ettiğini göstermektedir: 2025'te mevsimlik kadın işçilerin ücreti erkeklerin yaklaşık %84'üne, sürekli kadın işçilerinki ise yaklaşık %59'una karşılık gelmektedir. Bu fark; kadın emeğinin daha düşük nitelikli işlerde yoğunlaşması, kayıt dışılığa daha fazla maruz kalınması ve ücretsiz aile işçiliğinin yaygınlığıyla ilişkilendirilebilir. Sonuç olarak, ücretlerdeki artışa rağmen kayıt dışılık, bölgesel eşitsizlik ve cinsiyete dayalı ayrım yapısal sorunlar olmaya devam etmektedir. Bu çerçevede; kayıt dışı istihdamı azaltacak esnek sigorta modellerinin geliştirilmesi, eşit işe eşit ücret ilkesinin denetim mekanizmalarıyla güçlendirilmesi, düşük ücretli illerde (örn. Hatay) hedefli destek

programları uygulanması ve mevsimlik işçiler için kooperatifleşmenin teşvik edilmesi önerilmektedir. Ayrıca barınma, sağlık ve eğitime erişim gibi yaşam koşullarını kapsayan bütüncül politikalar ile cinsiyet, bölge ve istihdam türü ayrımında daha kapsamlı veri üretimi, sektörün adil ve sürdürülebilir bir yapıya kavuşması için büyük önem taşımaktadır.

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YAŞLANMA SÜRECİ: EPİGENETİK YAKLAŞIMLAR

AGING PROCESS: EPIGENETIC APPROACHES

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Özet
Yaşlanma; genom bütünlüğü, hücresel enerji üretimi, protein dengesi, bağışıklık işlevleri ve doku yenilenmesinde zamanla ortaya çıkan değişimlerin birikimiyle şekillenen çok boyutlu bir süreçtir. Gen dizisi büyük ölçüde sabit kalmasına rağmen genlerin hangi hücrede, ne zaman ve ne ölçüde ifade edildiğini belirleyen epigenetik düzenekler yaş boyunca yeniden yapılanır. DNA metilasyonu, histon modifikasyonları, kromatin organizasyonu, kodlamayan RNA'lar ve epigenetik enzimlerdeki değişiklikler hücresel kimliğin kararlılığını azaltabilir; inflamasyon, metabolik bozukluk ve hücresel yaşlanma gibi süreçleri güçlendirebilir. Bu çalışma, yaşlanmanın epigenetik temellerini bütüncül biçimde inceleyen anlatısal bir derlemedir. Epigenetik sürüklenme, DNA metilasyon saatleri, heterokromatin kaybı, histon değişimleri, kromatin mimarisi ve çevresel etkenlerin epigenom üzerindeki etkileri değerlendirilmiştir. Bulgular, epigenetik yaş göstergelerinin kronolojik yaştan farklı olarak biyolojik yaşlanmanın bazı boyutlarını yansıtabildiğini; ancak doku özgüllüğü, hücre bileşimi, nedensellik ve ölçüm standardizasyonu sorunlarının sürdüğünü göstermektedir. Beslenme, fiziksel aktivite, farmakolojik epigenetik düzenleyiciler ve kısmi hücresel yeniden programlama umut verici olmakla birlikte, güvenlilik ve uzun dönem sonuçları açıklığa kavuşmadan yaşlanmayı tersine çeviren klinik uygulamalar olarak değerlendirilmemelidir.
Anahtar kelimeler: Yaşlanma; epigenetik; DNA metilasyonu; epigenetik saat; biyolojik yaş.

Abstract
Aging is a multidimensional process shaped by the gradual accumulation of changes in genome maintenance, cellular bioenergetics, proteostasis, immune function, and tissue renewal. Although the DNA sequence remains largely stable, epigenetic systems that determine when, where, and to what extent genes are expressed are remodeled across the life course. Alterations in DNA methylation, histone modifications, chromatin organization, non-coding RNAs, and epigenetic enzymes may weaken cellular identity and reinforce inflammation, metabolic dysfunction, and cellular senescence. This narrative review evaluates the epigenetic foundations of aging, with emphasis on epigenetic drift, DNA methylation clocks, heterochromatin loss, histone alterations, chromatin architecture, and environmental influences on the epigenome. Current evidence indicates that epigenetic age measures can capture aspects of biological aging beyond chronological age; however, tissue specificity, cell composition, causal interpretation, and assay standardization remain important limitations. Nutrition, physical activity, pharmacological epigenetic modulators, and partial cellular reprogramming are promising research areas, but they should not be interpreted as clinically established age-reversal strategies before long-term safety and efficacy are demonstrated.
Keywords: Aging, Epigenetics, Epigenetic Clock, Biological Age

1 Giriş

Yaşlanma, yalnızca geçen zamanın sonucu değil; moleküler hasar, onarım kapasitesi, metabolik sinyaller, çevresel maruziyetler ve hücresel yanıtların yaşam boyunca karşılıklı etkileşimidir. Güncel yaşlanma biyolojisi genomik kararsızlık, telomer aşınması, epigenetik değişiklikler, proteostaz kaybı, bozulmuş otofaji, düzensiz besin algılama, mitokondri işlev bozukluğu, hücresel yaşlanma, kök hücre tükenmesi, hücreler arası iletişim bozukluğu, kronik inflamasyon ve mikrobiyom değişikliklerini birbirine bağlı temel özellikler olarak ele almaktadır (López-Otín et al., 2023). Epigenetik değişiklikler bu ağın merkezinde yer alır; çünkü genom ile çevre arasında dinamik bir ara yüz oluşturur ve hücre kimliğini belirleyen gen ifade programlarını düzenler.

Epigenetik, DNA dizisinde değişiklik olmaksızın gen işlevinde ortaya çıkan, hücre bölünmeleri boyunca kısmen korunabilen fakat çevresel ve fizyolojik uyaranlara yanıt verebilen düzenlemeleri kapsar. DNA metilasyonu, histonların kimyasal modifikasyonları, nükleozom yerleşimi, ATP bağımlı kromatin

yeniden düzenleme kompleksleri, üç boyutlu genom mimarisi ve kodlamayan RNA ağları bu düzenlemelerin başlıca bileşenleridir. Yaş ilerledikçe bazı bölgelerde öngörülebilir metilasyon değişiklikleri görülürken genom genelinde epigenetik gürültü ve bireyler arası değişkenlik artar. Bu durum "epigenetik sürüklenme" olarak adlandırılır.

Bu çalışmanın amacı, yaşlanma sürecinde ortaya çıkan temel epigenetik değişiklikleri mekanistik bir çerçevede açıklamak; epigenetik saatlerin biyolojik yaş ölçümündeki yerini değerlendirmek ve yaşam biçimi ile deneysel müdahalelerin epigenom üzerindeki olası etkilerini bilimsel sınırlılıklarıyla tartışmaktır.

2 Yöntem

Bu çalışma anlatısal derleme niteliğindedir. Yaşlanma biyolojisi, DNA metilasyonu, histon modifikasyonları, kromatin organizasyonu, kodlamayan RNA'lar, epigenetik saatler ve hücresel yeniden programlama alanındaki temel araştırmalar ile yüksek etkili derlemeler kavramsal bütünlük içinde incelenmiştir. Kaynak seçiminde mekanistik katkı, insan verisiyle ilişki, yöntemsel yenilik ve alandaki kurucu nitelik dikkate alınmıştır. Çalışma sistematik derleme veya meta-analiz değildir; bu nedenle yayınların nicel etki büyüklüklerini birleştirme amacı taşımamaktadır. Bulgular nedensellik, doku özgüllüğü ve klinik uygulanabilirlik açısından eleştirel olarak değerlendirilmiştir.

3 Epigenetik Düzenlemenin Temel Bileşenleri

3.1 DNA metilasyonu

Memelilerde DNA metilasyonu çoğunlukla CpG dinükleotitlerindeki sitozinin 5-metilsitozine dönüştürülmesiyle gerçekleşir. DNMT1 replikasyon sonrasında mevcut metilasyon örüntüsünü korurken DNMT3A ve DNMT3B yeni metilasyon işaretlerinin kurulmasında görev alır. TET proteinleri 5-metilsitozini ardışık oksidasyon ürünlerine dönüştürerek aktif veya pasif demetilasyon süreçlerine katkı verir. Promotör ve güçlendirici bölgelerdeki metilasyon değişimleri transkripsiyon faktörü bağlanmasını ve kromatin erişilebilirliğini etkileyebilir; ancak metilasyonun işlevi genomik bağlama göre değişir.

Yaşlanmada genom genelinde hafif hipometilasyon eğilimi ile belirli CpG adalarında ve gelişimsel gen bölgelerinde bölgesel hipermetilasyon birlikte görülebilir. Tekrarlayan dizilerde metilasyon kaybı genom kararlılığını azaltabilir; promotör hipermetilasyonu ise bazı koruyucu genlerin ifadesini baskılayabilir. Bununla birlikte yaşla ilişkili her metilasyon değişikliği işlevsel değildir. Bir kısmı hücre bileşiminin değişmesini, klonal genişlemeyi veya yaşam boyu maruziyetlerin birikimini yansıtabilir.

3.2 Histon modifikasyonları ve kromatin erişilebilirliği

DNA, histon proteinleri etrafında paketlenerek nükleozomları oluşturur. Histon kuyruklarındaki asetilasyon, metilasyon, fosforilasyon, ubiquitinasyon ve diğer kimyasal işaretler kromatinin erişilebilirliğini ve düzenleyici proteinlerin bağlanmasını değiştirir. Histon asetiltransferazlar asetil grubu ekleyerek çoğunlukla açık kromatini destekler; histon deasetilazlar bu işareti kaldırır. Histon metilasyonunun etkisi ise kalıntıya göre farklıdır: H3K4me3 aktif promotörlerle, H3K27ac aktif düzenleyici bölgelerle; H3K9me3 ve H3K27me3 baskılayıcı kromatinle ilişkilidir.

Yaşlanmayla histon miktarında azalma, baskılayıcı heterokromatin işaretlerinde düzensizlik ve genomun bazı bölgelerinde erişilebilirlik artışı bildirilmiştir. Bu değişiklikler transpozonların baskılanmasını zayıflatabilir, hücre tipine özgü gen ifade sınırlarını bulanıklaştırabilir ve inflamatuvar programları etkinleştirebilir. Sirtuinler gibi NAD^+ bağımlı deasetilazlar metabolik durum ile kromatin düzenlemesini bağlar; NAD^+ düzeyindeki yaşa bağlı azalma bu nedenle epigenetik ve metabolik yaşlanmayı kesiştiren bir mekanizma olarak değerlendirilmektedir (Sen et al., 2016).

.3 Kromatin mimarisi ve nükleer organizasyon

Genom çekirdek içinde rastgele yerleşmez. Topolojik olarak ilişkili bölgeler, kromatin döngüleri ve nükleer lamina bağlantıları uzak DNA bölgeleri arasındaki düzenleyici iletişimi belirler. Lamin proteinlerindeki bozuklukların erken yaşlanma sendromlarına yol açması, nükleer mimarinin yaşlanmadaki önemini göstermektedir. Normal yaşlanmada lamina ilişkili bölgelerin düzeni, heterokromatin dağılımı ve kromatin sıkılığı değişebilir. Bunun sonucu olarak genomun bazı bölgeleri uygunsuz biçimde erişilebilir hâle gelebilir ve hücresel kimlik programlarında sapmalar gelişebilir.

3.4 Kodlamayan RNA'lar

MikroRNA'lar, uzun kodlamayan RNA'lar ve dairesel RNA'lar transkriptlerin kararlılığını, çeviriyi ve kromatin düzenleyici komplekslerin hedeflenmesini etkiler. Yaşla birlikte miR-34a, miR-146a ve inflamasyonla ilişkili diğer mikroRNA ağlarında değişiklikler bildirilmiştir. Uzun kodlamayan RNA'lar telomer bakımı, heterokromatin oluşumu ve hücresel yaşlanma yanıtlarına katılır. Ancak bu moleküllerin etkileri dokuya özgüdür ve tek bir RNA'nın tüm organizma yaşlanmasını açıklaması beklenmemelidir.

Epigenetik katman	Yaşla ilişkili eğilim	Olası biyolojik sonuç	Temel sınırlılık
DNA metilasyonu	Genel hipometilasyon ve bölgesel hipermetilasyon	Gen ifadesi, genom kararlılığı ve hücre kimliğinde değişim	Hücre bileşimi ve doku farklılığı
Histon işaretleri	Aktif ve baskılayıcı işaretlerin yeniden dağılımı	Kromatin erişilebilirliği ve transpozon kontrolünde bozulma	İşaretlerin bağlama göre farklı işlevi
Kromatin mimarisi	Heterokromatin ve lamina bağlantılarında kayıp	Uzak düzenleyici iletişim ve nükleer bütünlükte bozulma	İnsan dokusunda ölçüm güçlüğü
Kodlamayan RNA	Dokuya özgü ifade değişimleri	mRNA kararlılığı, çeviri ve kromatin düzenlenmesi	Nedensellik ve hedef özgüllüğü

4 Yaşlanmada Epigenetik Değişim Modelleri

4.1 Epigenetik sürüklenme ve hücresel kimlik kaybı

Genç dokularda hücre tipine özgü epigenetik örüntüler görece kararlıdır. Zaman içinde replikasyon hataları, onarım süreçleri, metabolik dalgalanmalar ve çevresel maruziyetler nedeniyle bu örüntülerde küçük sapmalar birikir. Tek yumurta ikizleri yaşamın erken döneminde benzer epigenetik profillere sahipken yaşla ve farklı yaşam koşullarıyla birlikte profillerinin ayrışması, epigenomun çevre ve zamanla değişebildiğini göstermiştir (Fraga et al., 2005). Sürüklenme, hücreler arası heterojenliği artırarak doku işlevinin eşgüdümünü zayıflatabilir.

Epigenetik bilgi kaybı hipotezi, DNA hasarına verilen yanıt sırasında kromatin düzenleyici proteinlerin geçici olarak yer değiştirmesinin ve özgün konumlarına tam olarak dönememesinin hücresel kimliği aşındırabileceğini öne sürer. Hayvan modellerindeki bulgular ilgi çekici olmakla birlikte, bu mekanizmanın normal insan yaşlanmasındaki payı ve geri döndürülebilirliği henüz kesin değildir.

Salgı fenotipi

Hücresel yaşlanma, çoğalma yeteneğinin kalıcı biçimde durduğu fakat metabolik etkinliğin sürdüğü bir durumdur. Yaşlanmış hücrelerde DNA hasar yanıtı, p16 ve p21 yolları, lamin B1 kaybı, senesansla ilişkili heterokromatin odakları ve geniş kapsamlı enhanser yeniden yapılanması görülebilir. Bu hücrelerin salgıladığı sitokin, kemokin, büyüme faktörü ve proteazlardan oluşan senesansla ilişkili salgı fenotipi komşu hücrelerin epigenomunu ve doku mikroçevresini değiştirebilir. Kısa süreli senesans yara onarımı ve tümör baskılanması için yararlı iken, yaşla biriken senesan hücreler kronik inflamasyonu artırabilir.

5 Epigenetik Saatler ve Biyolojik Yaş

Belirli CpG bölgelerindeki metilasyon düzeylerinin kronolojik yaşla güçlü ilişki göstermesi, DNA metilasyon saatlerinin geliştirilmesini sağlamıştır. Horvath'ın çoklu doku saati farklı dokularda yaş tahmini yapmayı amaçlarken Hannum saati ağırlıklı olarak kan verisine dayanmıştır (Hannum et al., 2013; Horvath, 2013). İkinci nesil saatler yalnızca kronolojik yaşı tahmin etmek yerine morbidite ve mortaliteyle ilişkili klinik özellikleri yakalamayı hedeflemiştir. PhenoAge klinik fenotipik yaşla ilişkili metilasyon örüntülerini, GrimAge ise plazma proteinleri ve sigara maruziyeti vekillerini kullanır (Levine et al., 2018; Lu et al., 2019).

Takvim yaşından daha yüksek epigenetik yaş tahmini "yaş hızlanması" olarak yorumlanır ve bazı çalışmalarda mortalite, kardiyometabolik risk, bilişsel gerileme ve kırılganlıkla ilişkilendirilmiştir. Bununla birlikte epigenetik saat tek başına yaşlanmanın mekanik ölçeri değildir. Farklı saatler farklı biyolojik alanları yakalar; kan hücrelerinin dağılımı, örnekleme, teknik platform, etnik ve

sosyoekonomik çeşitlilik sonuçları etkileyebilir. Bir müdahalenin epigenetik yaşı azaltması, klinik işlevi veya yaşam süresini mutlaka iyileştirdiği anlamına gelmez.

Saat yaklaşımı	Temel hedef	Güçlü yön	Dikkat edilmesi gereken nokta
Birinci nesil	Kronolojik yaş tahmini	Yüksek yaş korelasyonu	Klinik risk ve mekanizma sınırlı
PhenoAge	Fenotipik yaş ve hastalık yükü	Klinik biyobelirteçlerle bağlantı	Popülasyon ve doku bağımlılığı
GrimAge	Mortalite ve risk göstergeleri	Sağlık sonuçlarıyla güçlü ilişki	Vekil değişkenlere dayanması
DunedinPACE	Yaşlanma hızının boylamsal tahmini	Süreç hızına odaklanma	Kohort ve uygulama standardizasyonu

6 Çevre Yaşam Biçimi ve Epigenetik Yaşlanma

Epigenom, yaşam boyunca beslenme, fiziksel aktivite, tütün kullanımı, hava kirliliği, psikososyal stres, uyku ve sosyoekonomik koşullardan etkilenebilir. Sigara kullanımı AHRR gibi belirli lokuslarda güçlü ve tekrarlanabilir metilasyon izleri bırakır. Obezite, insülin direnci ve kronik inflamasyon metabolik dokuların kromatin yapısını değiştirebilir. Buna karşılık düzenli fiziksel aktivite kas, yağ dokusu ve bağışıklık hücrelerinde metabolik esnekliği destekleyen gen ağlarıyla ilişkilidir.

Besinlerden sağlanan folat, B12 vitamini, kolin ve metiyonin tek karbon metabolizması üzerinden S-adenozilmetiyonin üretimini etkileyerek metilasyon kapasitesine katkıda bulunur. Ancak daha fazla metil vericinin her zaman daha sağlıklı bir epigenom oluşturacağı söylenemez; etki doz, yaşam dönemi, genotip ve dokuya bağlıdır. Polifenoller ve kısa zincirli yağ asitleri bazı epigenetik enzimleri etkileyebilir, fakat hücre kültürü dozlarının beslenmeyle erişilebilir düzeylerle karıştırılmaması gerekir. Epigenetik değişikliklerin çevresel maruziyet ile hastalık arasındaki aracı mı, maruziyetin biyolojik kaydı mı, yoksa hastalığın sonucu mu olduğu her çalışmada ayrı değerlendirilmelidir. Boylamsal tasarımlar, Mendelci randomizasyon, hücre ve hayvan modelleri ile hedeflenmiş deneyler nedenselliği güçlendirebilir; kesitsel ilişki tek başına nedensellik göstermez.

7 Epigenetik Müdahale Yaklaşımları

7.1 Yaşam biçimi müdahaleleri

Fiziksel aktivite, enerji dengesi, yeterli uyku ve sigaradan kaçınma, yaşlanmayla ilişkili metabolik ve inflamatuvar yolları etkileyen en uygulanabilir yaklaşımlardır. Bazı küçük çalışmalar yaşam biçimi programlarının epigenetik yaş göstergelerinde değişim oluşturabileceğini bildirmiştir; ancak örneklem büyüklüğü, kontrol grubu, takip süresi ve çoklu karşılaştırma sorunları nedeniyle sonuçlar temkinli yorumlanmalıdır. Klinik amaç epigenetik saati düşürmekten çok işlevsel kapasiteyi ve hastalıksız yaşam süresini artırmaktır.

7.2 Epigenetik enzimleri hedefleyen ilaçlar

DNA metiltransferaz ve histon deasetilaz inhibitörleri bazı kanserlerde kullanılmaktadır; fakat geniş etkileri nedeniyle sağlıklı yaşlanma amacıyla kullanımları uygun değildir. Sirtuin aktivitesi, NAD^+ metabolizması, histon asetilasyonu ve kromatin düzenleyiciler deneysel hedeflerdir. Yaşlanan organizmada epigenetik bir enzimin sistemik olarak uyarılması tüm dokularda aynı sonucu doğurmayabilir; kanserleşme, bağışıklık bozukluğu veya hücre kimliği kaybı gibi riskler değerlendirilmelidir.

7.3 Kısmi hücresel yeniden programlama

Oct4, Sox2, Klf4 ve c-Myc gibi faktörlerin sürekli ifadesi somatik hücreleri pluripotent duruma taşıyabilir; ancak hücre kimliğini kaybettirir ve tümör riski oluşturur. Kısmi yeniden programlama yaklaşımı, faktörleri sınırlı süre ve düzeyde kullanarak yaşla ilişkili epigenetik işaretleri azaltmayı, hücre kimliğini ise korumayı amaçlar. Hayvan ve hücre modellerinde rejenerasyon, epigenetik yaş ve doku işlevi açısından umut verici sonuçlar bildirilmiştir (Ocampo et al., 2016; Lu et al., 2020). Buna rağmen uygun doz, hedef doku, uzun dönem genom kararlılığı ve tümör güvenliği çözülmeden insanlarda genel bir gençleştirme yöntemi olarak kabul edilemez.

8 Epigenetik Yaşlanma ve Hastalıklar

Kanserde global hipometilasyon, tümör baskılayıcı genlerde bölgesel hipermetilasyon ve enhancer yeniden yapılanması sık görülür. Yaşla ortaya çıkan epigenetik sürüklenme, klonal hematopoez ve doku mikroçevresi değişimleri kanser gelişimine elverişli bir zemin oluşturabilir. Bununla birlikte kanser epigenomu normal yaşlanmanın basitçe hızlanmış biçimi değildir; seçilim ve somatik mutasyonlarla şekillenir.

Alzheimer ve diğer nörodejeneratif hastalıklarda sinaptik işlev, mikroglial aktivasyon ve protein kalite kontrolüyle ilişkili bölgelerde epigenetik değişiklikler saptanmıştır. Beyin dokusunun hücresel çeşitliliği ve hastalığın ileri evresinde alınabilmesi, neden ve sonucu ayırmayı güçleştirir. Kardiyometabolik hastalıklarda hiperglisemi, lipid fazlalığı ve inflamasyon uzun süreli kromatin izleri bırakarak "metabolik hafıza" oluşturabilir. Bağışıklık hücrelerindeki yaşa bağlı kromatin değişimleri ise inflamatuvar yanıtın kalıcılığına katkı sağlayabilir.

9 Tartışma

Epigenetik araştırmalar, aynı genomu taşıyan hücrelerin neden farklı işlevler kazandığını ve yaşla bu işlevsel sınırların nasıl aşındığını açıklamak için güçlü bir çerçeve sunmaktadır. DNA metilasyonu ve kromatin örüntülerindeki değişiklikler hem yaşlanmanın kaydı hem de bazı durumlarda işlevsel sürücüsü olabilir. Bu çift yönlü ilişki, epigenetik belirteçlerin yorumunu güçleştirir: yaşla ilişkili bir değişiklik neden, telafi yanıtı veya hasarın sonucu olabilir.

Epigenetik saatler biyolojik yaş araştırmalarını hızlandırmış, fakat tek bir evrensel biyolojik yaş ölçümü oluşturmamıştır. Saatin eğitim aldığı doku ve sonuç değişkeni neyi ölçtüğünü belirler. Bu nedenle farklı saatler arasındaki uyumsuzluk hata olmaktan çok farklı biyolojik boyutların yakalanması anlamına gelebilir. Klinik kullanımdan önce analitik tekrarlanabilirlik, referans aralıkları, farklı nüfuslarda doğrulama ve değişimin anlamlı klinik sonlanımlarla ilişkisi gösterilmelidir.

Epigenetik düzeneklerin geri dönüşebilir olması tedavi açısından çekicidir; ancak geri dönüşebilirlik güvenli ve kolay müdahale edilebilirlik anlamına gelmez. Hücre kimliğini koruyan aynı mekanizmalar yanlış hedeflendiğinde tümörleşmeye veya işlev kaybına yol açabilir. Gelecek araştırmaların tekil işaretlerden çok hücre tipine özgü, zamansal ve çok katmanlı epigenom modellerine; ayrıca epigenetik değişim ile organ işlevi arasındaki nedensel bağlara odaklanması gerekmektedir.

10 Sonuç ve Öneriler

Yaşlanmada epigenetik değişiklikler DNA metilasyonu, histon işaretleri, kromatin mimarisi ve kodlamayan RNA ağlarının birlikte yeniden yapılanmasıyla ortaya çıkar. Epigenetik sürüklenme ve heterokromatin kaybı hücre kimliğini zayıflatırken, belirli metilasyon örüntüleri biyolojik yaşın tahmininde kullanılabilir. Bununla birlikte epigenetik yaş, yaşlanmanın tamamını temsil eden tek bir ölçüt değildir ve doku bileşimi ile yöntemsel özelliklerden etkilenir.

Araştırmalarda boylamsal tasarımların, tek hücreli ve mekânsal epigenom yöntemlerinin, çoklu omik verilerin ve işlevsel doğrulamanın birlikte kullanılması önerilmektedir. Müdahale çalışmalarında epigenetik belirteç değişiminin yanı sıra fiziksel işlev, hastalık insidansı, yaşam kalitesi ve güvenlilik sonlanımları değerlendirilmelidir. Güncel kanıtlar sağlıklı yaşam davranışlarını desteklemekte; farmakolojik epigenetik düzenleme ve kısmi yeniden programlamayı ise dikkatli translasyonel araştırma gerektiren deneysel alanlar olarak konumlandırmaktadır.

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Veteriner Fakültesi Dekanlığı
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İlgi : 18.06.2026 tarihli ve 183922 sayılı yazı.

İlgi yazınız ile Bölümünüz personeli Prof. Dr. Mahire BAYRAMOĞLU AKKOYUN için talep etmiş olduğunuz olur alınmış olup yazımız ekinde sunulmuştur. İlgiliye tebliği hususunda;

Bilginize rica ederim.

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Üniversitemizin, İktisadi Kalkınma ve Sosyal Araştırmalar Enstitüsü iş birliğinde 23 Ağustos-1 Eylül 2026 tarihleri arasında Japonya'da düzenlenecek olan Ispec 12.Uluslararası Tıp Ve Sağlık Bilimleri Kongresi'nin iş ve işleyişinin yürütülmesi için **Kongre Başkanı** olarak Fakültemiz akademik personelinden Prof. Dr. Mahire BAYRAMOĞLU AKKOYUN'un kurulda yer alması hususunu;

Olurlarınıza arz ederim.

Prof. Dr. Kıvanç İRAK
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__.__.____
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