ISSN: 2717-8439
E-ISSN: 2717-9257

Yüksek İhtisas Üniversitesi

Sağlık Bilimleri Dergisi

Yüksek İhtisas University Journal of Health Sciences

Cilt/*Volume* **5** | **Sayı**/*Issue* **1** | **Nisan**/*April* **2024**

https://dergipark.org.tr/tr/pub/yuksekihtisas

YİÜSBD'nin yer aldığı dizinler

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Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi Yüksek İhtisas Üniversitesi'nin bilimsel yayınıdır

Yüksek İhtisas University Journal of Health Sciences is a scientific publication of Yuksek Ihtisas University

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi *(Yüksek İhtisas University Journal of Health Sciences)* yılda üç sayı (Nisan, Ağustos ve Aralık) olarak yayımlanan hakemli bir dergidir

Yüksek İhtisas University Journal of Health Sciences (Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi) is a peer-reviewed journal published three times a year (April, August and December).

Yayın Türü / *Type of Publication*
Yerel Süreli / *Periodical*

Finansman / *Funding*
Yüksek İhtisas Üniversitesi / Yuksek Ihtisas Unversity

Derginin yer aldığı dizinler / *The journal is indexed in*

TÜRKİYE ATIF DİZİNİ | TÜRK MEDLINE | EBSCO

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www.bayt.com.tr

Baskı / *Print*
Miki Matbaacılık San. ve Tic. Ltd. Şti.
Matbaacılar San. Sitesi 1516/1. Sk., No: 27,
Yenimahalle, Ankara
Tel. +90 312 395 21 28
www.mikimatbaasi.com

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Yüksek İhtisas Üniversitesi
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Amaç ve Kapsam

2020 yılında yayın hayatına başlayan Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi (YIU Saglik Bil Derg), bağımsız, tarafsız ve çift-kör hakemlik ilkelerine uygun olarak yayınlanan bilimsel, açık erişimli, basılı ve aynı zamanda çevrimiçi yayınlanan süreli yayındır.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi, Yüksek İhtisas Üniversitesi'nin Nisan, Ağustos ve Aralık aylarında olmak üzere dört ayda bir yayımlanan bilimsel yayın organıdır.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi, ülkemizin ilk sağlık konseptli üniversite dergisi olma ayrıcalığı ile akademisyenlere hizmet vermek amacı yanı sıra hedef kitlesi ulusal ve uluslararası düzeyde klinik araştırmacılar, tıp/sağlık profesyonelleri, öğrenciler, hemşirelik profesyonelleri, ilgili mesleki ve akademik kurum ve kuruluşlarıdır.

Dergide sağlık bilimleri alanında orijinal makaleler, literatür gözden geçirmeleri, olgu sunumları, derleme, teknik bildiriler ve uzman görüşleri İngilizce ve Türkçe dillerinde yayımlanır. Yüksek Ihtisas Üniversitesi Sağlık Bilimleri Dergisi hakemli bir dergidir ve en yüksek etik ve editöryal standartlara uyar.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi EBSCOhost, Türkiye Atıf Dizini ve Türk Medline tarafından indekslenmektedir.

Editör

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Yazarlara Bilgiler

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi *(Yüksek İhtisas University Journal of Health Sciences)* yılda üç kez (Nisan, Ağustos ve Aralık) yayınlanan açık erişimli ve hakemli bir dergidir. Dergide sağlık bilimleri alanında İngilizce ve Türkçe dillerinde özgün makaleler, derlemeler, olgu sunumları, teknik raporlar ve yorumlar yayımlanır.

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi (Journal of Yüksek İhtisas University Health Sciences) en yüksek etik ve editörlük standartlarına uyar. Editörlük ve yayım süreci, International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE) ve National Information Standards Organization (NISO) kılavuzlarına uygun olarak yapılır. Akademik Yayıncılıkta Şeffaflık ve En İyi Uygulama (doaj.org/bestpractice) ilkeleri gözetilir.

Derginin Editörleri WAME Yöneticiler Birliğinin onaylamış olduğu editörler politikasını destekler ve Uluslararası Tıp Dergisi Editörleri Komitesi'nin yayımlamış olduğu Biyomedikal Dergilere Gönderilen Makaleler İçin Gerekli Standartlar ile tam bir uyum gösterir (**http://www.icmje.org/icmjerecommendations**).

Makale Gönderme

Yazarlar makalelerini Ulakbim- DergiPark web sitesinde bulunan Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi alanından göndermelidir. Makaleler Word dokümanı (.doc) veya zengin metin biçimi (.rtf) olarak gönderilmelidir. Her makalenin başında yazı başlığı, öz ve "medline" kurallarına göre düzenlenmiş Türkçe ve İngilizce anahtar sözcükler yazılmalıdır. Makale için iletişim kuracak tüm yazarların gerekli iletişim bilgileri olmalıdır. Tüm şekil, tablo ve gerekli görülen ek dokümanlar da gönderilmelidir. Yazarlar aynı sistem üzerinden Telif Hakkı Devri ve Finansal Durumu belirten ve yazının orijinalliğinin beyan edildiği formu da gönderilere eklemelidir.

Editoryal Politika

Tüm makaleler bilimsel katkıları, orijinallikleri ve içerikleri açısından bilimsel kurul tarafından değerlendirilir. Yazarlar verilerin doğruluğundan sorumludur. Dergi gerekli gördüğü yerlerde dil ve yazım ile ilgili uygun düzeltmeleri yapma hakkını saklı tutar. Makaleler gerekli görüldüğünde revizyon yapılmak üzere sorumlu yazara geri gönderilebilir. Dergide basılan yazılar derginin malı haline gelir ve yazıların telif hakkı Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi *(Journal of Yuksek Ihtisas University Health Sciences)* adına alınır. Daha önce herhangi bir dilde basılmış olan yazılar dergide basılmak üzere değerlendirilmez. Yazarlar, Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi'ne *(Journal of Yuksek Ihtisas University Health Sciences)* gönderdikleri bir yazıyı başka bir dergiye gönderemezler.

Makaleler, ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmjerecommendations) ile uyumlu olarak hazırlanmalıdır. Randomize çalışmalar CONSORT, gözlemsel çalışmalar STROBE, tanısal değerli çalışmalar STARD, sistematik derleme ve meta- analizler PRISMA, hayvan deneyli çalışmalar ARRIVE ve randomize olmayan davranış ve halk sağlığıyla ilgili çalışmalar TREND kılavuzlarına uyumlu olmalıdır.

Makalelerin Hazırlanması

Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi'ne (Journal of Yüksek Ihtisas University Health Science), gönderilen makaleler ICMJE'nin biyomedikal dergiler için belirlemiş olduğu standartlara göre hazırlanmış olmalıdır. Makalenin gönderilmesi sırasında yazarlar deney/araştırma tipini belirtmelidirler ve istatistik uygulamaların "Guidelines for statistical reporting in articlesfor medical journals: amplificationsand explanations" (Bailar JC III, Mosteller F, Ann InternMed 1988; 108:266 -73) kılavuzuna uygun olması gerekmektedir. Makale ile birlikte gönderilen üst yazıda makale içindeki bilgilerin herhangi bir kısmının daha önce elektronik ortam dâhil yayımlanıp yayımlanmadığı veya değerlendirilmek üzere gönderilip gönderilmediği bildirilmelidir. Çalışma için etik kurul kararı alınıp alınmadığı veya insan deneyleri ile ilgili 2018 yılında güncellenen Helsinki Bildirgesi'ne uyulup uyulmadığı belirtilmelidir, aksi durumlar açıklanmalıdır. Üst yazıda iletişim kurulacak yazarın adresi, telefonu, faks numarası ve e-posta adresi olmalıdır. Tüm başvurular benzerlik tespit yazılımı (iThenticate by CrossCheck) tarafından taranır. Yayın Kurulu, dergimize gönderilen çalışmalar hakkındaki intihal, atıf manipülasyonu ve veri sahteciliği iddia ve şüpheleri karşısında COPE kurallarına uygun olarak hareket etmektedir. Yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. ICMJE, yazarların aşağıdaki dört kriteri karşılamasını önermektedir:

1. Çalışmanın konseptine/tasarımına; ya da çalışma için verilerin toplanmasına, analiz edilmesine ve yorumlanmasına önemli katkı sağlamış olmak;
2. Yazı taslağını hazırlamış ya da önemli fikirsel içeriğin eleştirel incelemelerini yapmış olmak.
3. Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak.
4. Çalışmanın herhangi bir bölümünün geçerliliği ve doğruluğuna ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Bir yazar, çalışmada katkı sağladığı kısımların sorumluluğunu almasına ek olarak, diğer yazarların çalışmanın hangi kısımlarından sorumlu olduğunu da teşhis edebilmelidir. Ayrıca, yazarlar birbirlerinin katkılarının bütünlüğüne güven duymalıdırlar.

Makale Özellikleri

Araştırma Makalesi

Araştırma makalesi ana metni *"Giriş", "Materyal ve Metot", "Bulgular" ve "Sonuç"* alt başlıklarını içermelidir. Araştırma makaleleri için sözcük sayısı sınırları Tablo 1'dedir.

Öz: Araştırma makalelerinin özü Giriş, Materyal ve Metot, Bulgular ve Sonuç bölümlerinden oluşmalıdır. Çalışma içeriğini ve çalışmanın dayandığı zemini aktarmalı, çalışmanın amaçlarını, ana bulguları ve ana sonuçları belirtmelidir. Ayrıca çalışma ve gözlemlerin yeni ve önemli yönlerini vurgulamalıdır.

Anahtar Sözcükler: Öz bölümünün altında verilmeli ve en fazla altı adet olmalıdır. Anahtar sözcüklerin Türkiye Bilim Terimleri'nden seçilmesine özen gösterilmelidir (http://www.bilimterimleri.com).

Giriş : Bu bölümde niçin bu çalışmayı yapmaya ihtiyaç duyulduğu ve yapılma amacı sadece önemli makalelere atıfta bulunularak belirtilmelidir.

Materyal ve Metot: Bu bölümde çalışma için yapılan plan, hastalar, deney hayvanları, materyal ve kontroller, kullanılan çalışma yöntemleri ve uygulanan istatistiksel yöntem açıklanmalıdır. Etik konularla ilgili izinler yukarıda açıklandığı gibi belirtilmeli; ilaçların jenerik isimleri ile birlikte üretici adı ve üretildiği ülke ifade edilmelidir.

Bulgular: Bu bölümde istatistiksel metotlar ile desteklenen bulgular ayrıntılı olarak belirtilmelidir. Sadece en önemli bulgular vurgulanmalıdır. Şekil ve tablolar metin içinde verilen bulguları desteklemeli, tekrar etmemelidir; verinin metin, tablo veya şekil şeklindeki sunumların sadece birinde gösterilmesi yeterlidir

Tablo 1. Makale türleri için kısıtlamalar

Makale türü	Sözcük sınırı	Öz sözcük sınırı	Kaynak sınırı	Tablo sınırı	Resim sınırı
Araştırma Makalesi	4000	250 (Yapılandırılmış)	30	6	15 resim
Derleme	5000	250	50	6	20 resim
Olgu Sunumu	1500	150	15	Tablo yok	20 resim
Editöre Mektup	1000	Öz yok	5	Tablo yok	Resim yok

Tartışma /Sonuç: Bulguların önemi ve farkları vurgulanmalıdır; ancak sonuç bölümünde sunulan detaylar tekrarlanmamalıdır. Görüşler, çalışmada elde edilen gerçeklerle desteklenecek şekilde sınırlanmalıdır; araştırılmayan ya da gösterilmeyen varsayımlar tartışmaya eklenmemelidir. Bulgular başka araştırmalarla karşılaştırılmalıdır. Bu bölümde bulgular bölümünde belirtilmemiş yeni veri sunulmamalıdır.

Kaynaklar

Kaynaklar, "Uluslararası Tıp Dergisi Editörleri Komitesi (ICMJE)" tarafından geliştirilen "Biyomedikal Dergilere Gönderilen Makaleler İçin Gerekli Standartlar" kurallarına göre düzenlenmelidir. Sık kullanılan referans türleri için bazı örnekler verilmiştir. https://www.icmje.org/icmje-recommendations.pdf linki, burada sağlanmayan diğer referans türlerine ilişkin rehberlik amacıyla kullanılmalıdır. Her kaynak metindeki sırasına göre numaralandırılmalı ve listelenmelidir. Metin içerisinde cümle sonlarında parantez içinde "(....)" şeklinde belirtilmelidir. Kaynakların doğruluğundan yazar(lar) sorumludur. Dergi başlıkları Index Medicus'a uygun olarak kısaltılmalıdır. Dergi adlarının kısaltmaları için "Index Medicus'ta İndekslenen Dergilerin Listesi"ne bakınız (http://www.nlm.nih.gov/tsd/serials/lji.html). Index Medicus'ta yer almayan dergilerde kısaltma kullanılmaz. Kaynaklar'da yalnızca yayınlanmış makaleler veya "baskıda" olan makaleler kullanılabilir. Tüm yazarların isimleri yazılmalıdır, "et al" ifadesi kullanılmamalıdır.

Dergiler:

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV- infected patients. N Engl J Med. 2002;347:284-7. PMID: 12140307 DOI: 10.1056/NEJMsb020632

Çevrimiçi yayınlanmış makale:

Yalçın Çakmaklı G, Ayhan Y, Yazıcı MK, Demirci M, Şahin G. Spectral analysis of lithium tremor. Arch Neuropsychiatry, 17 Ekim 2020. https://doi.org/10.29399/npa.27378. [E-pub ahead of print]

Kitaplar:

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Kitap Bölümleri:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. 93-113.

Toplantı Sunumları:

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.l

Tablolar ve Şekiller

Tüm tablo ve şekiller "Windows" altında açılabilmelidir. Online gönderilen resimlerin çözünürlük kalitesi minimum (10x10 cm boyutunda) 300 dpi ve jpg formatında olmalıdır. Her tablo ve şekil ayrı bir sayfada sunulmalıdır. Tüm tablo ve şekiller Arabik numaralar ile belirtilmelidir. Her tablonun başlığı tablonun içeriği ve amacını belirtmelidir. Her şeklin üzerindeki işaret ve sembolleri açıklayan bir alt yazısı olmalıdır.

Derleme Yazıları

Belirli bir alanda uzmanlık potansiyeli olan yazarlar tarafından hazırlanan derlemeler memnuniyetle karşılanmaktadır. Derlemeler, klinik uygulamada bir konunun mevcut bilgi seviyesini tanımlamalı, tartışmalı, değerlendirmeli ve gelecekteki çalışmalara rehberlik etmelidir. Derleme yazılarının alt başlıkları yazarlar tarafından planlanmalıdır. Ancak, her derleme makalesi bir "Giriş" ve bir "Sonuç" bölümü içermelidir. Derleme makalelerinin sınırlamaları için Tablo 1'e bakınız.

Olgu Sunumu

Nadir görülen, yeni bir bulgunun ya da yeni bir birlikteliğin tanımlandığı, tanıda ve tedavide güçlük gösteren veya yeni bir tedavi yönteminin uygulandığı ilgi çekici ve öğretici sunular yayınlanabilir. Bu yazılar, "Giriş", "Olgu Sunumu" ve "Tartışma" alt başlıklarını içermelidir. Olgu sunumlarının sözcük sayısı sınırları Tablo 1'de belirtilmiştir.

Editöre Mektup

Dergide yayımlanmış bir makale hakkında konunun uzmanı olan veya makalenin değerlendirmesini yapmış olan hakemler görüş veya yorumlarını Editöre Mektupla bildirebilirler. Kabul edilen Mektuplar, yayımlanmalarından önce konu aldıkları makalenin yazarına gönderilir ve ek görüş bildirmek, cevap vermek isteyip istemedikleri sorulur. Bu tür yazılar mümkün oldukça ilgili yazının yazarlarının yanıtlarıyla birlikte yayımlanır.

Düzeltmeler

Düzeltme talepleri ve eleştiriler iletişim adresi belirtilen yazara gönderilir. Basımın gecikmemesi için istenen düzeltmeler en kısa zamanda cevaplandırılmalıdır. Revizyonların cevapları ile geri gönderilmesi en geç 15 gün içinde olmalıdır. Editörler kurulu 15 günden sonraya kalan revizyonlarda makaleyi reddetme hakkını saklı tutar. Tüm hakemlerin görüşlerine cevap yazılmalıdır ve yapılan düzeltmelerin sayfa numarası ile satır sırası belirtilmelidir. Yapılan tüm değişikliklerin metin üstünde koyu olarak belirtildiği bir kopya ile düzeltmeler yapıldıktan sonraki son halinin temiz bir kopyası birlikte gönderilmelidir. Sunulan kaynakların ve verilerin doğruluğundan yazarlar sorumludur. Hatalı, aldatıcı veya yanlış yönlendirici bilgilerin varlığı fark edildiğinde Baş-Editör makaleyi bilimsel literatürden çekme ve bunu duyurma hakkına sahiptir.

İletişim

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Aims and Scope

Yüksek İhtisas University Journal of Health Sciences (YIU J Health Sci), which started its publication life in 2020, is a scientific, open access, both printed and online periodical published in accordance with the principles of independent, impartial and double-blind refereeing.

Yüksek İhtisas University Journal of Health Sciences is the scientific publication of Yüksek İhtisas University, published quarterly in April, August and December.

With the privilege of being the first university journal with a health concept in our country, Yüksek İhtisas University Journal of Health Sciences aims to serve academics, and its target audience is clinical researchers, medical/health professionals, students, nursing professionals, related professional, and academic institutions and organizations at the national/international level.

In the journal; original articles, literature reviews, case reports, reviews, technical papers and expert opinions in the field of health sciences are published in English and Turkish. Yüksek İhtisas University Journal of Health Sciences is a peer-reviewed journal, and adheres to the highest ethical and editorial standards.

Yüksek İhtisas University Journal of Health Sciences is indexed by EBSCOhost, the Turkish Citation Index, and Turkish Medline.

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Instructions for Authors

Yüksek İhtisas University Journal of Health Sciences *(Yüksek İhtisas Üniversitesi Sağlık Bilimleri Dergisi)* is an open access journal, and published three times a year (April, August and December). The journal publishes original articles, reviews, case reports, technical reports and commentaries in the fields of health science in English and Turkish languages.

Journal of Yuksek İhtisas University Health Sciences is a peer- reviewed journal and adheres to the highest ethical and editorial standards. Editorial and publishing processes of the journal are in accordance with the guidelines of International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). Editorial and publishing processes of the Journal of Yüksek İhtisas University Health Science, comply with the principles of Transparency and Best Practice in Academic Publishing (doaj.org/bestpractice).

The Editorial Board of the Journal of Yüksek Ihtisas University Health Sciences endorses the editorial policy statements approved by the WAME Board of Directors. The journal is following the uniform requirements for manuscripts submitted to biomedical journals published by the International Committee of Medical Journal Editors (**http://www.icmje.org/icmjerecommendations**).

Submission of Manuscripts

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3 Final approval of the version to be published; and
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Research Articles

The main text of the research article should include "Introduction", "Material and Method", "Results" and "Conclusion" subheadings. Word count limits for research articles are in Table 1. Abstract; The summary of the research articles should consist of Introduction, Material and Method, Results and Conclusion sections. It should convey the content of the study and the background on which the study is based, and state the aims, main findings and results of the study. It should also highlight new and important aspects of the study and observations.

Key Words

Key Words should be given under the summary section and should not exceed six. They must be selected from MeSH (Medical Subject Headings) (https://www.nlm.nih.gov/mesh/meshhome.html).

Introduction

State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

Material and Methods

Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	30	6	15 images
Review Article	5000	250	50	6	20 images
Case Report	1500	150	15	No tables	20 images
Letter to the Editor	1000	No abstract	5	No tables	No image

Results

Present the detailed findings supported with statistical methods. Emphasize only your Important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice.

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State the importance and significance of your findings but do not repeat the details given the results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your findings with those of others'. No new data are to be presented in this section.

References

References should be arranged according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" rules developed by "International Committee of Medical Journal Editors (ICMJE)". Some examples have been provided for frequently used reference types. The http://www.nlm.nih.gov/bsd/ uniform_requirements.html site should be used for guidance on other types of references not provided here. Each reference should be numbered and listed according to their order in the text. They should be referred to in parentheses as "(....)" at the end of sentences within the text. The author(s) are responsible for the accuracy of the references. Journal titles should be abbreviated according to Index Medicus. Refer to the "List of Journals Indexed in Index Medicus" for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/ lji.html. Abbreviations are not used for journals that are not listed in the Index Medicus. Only published articles or articles "in press" can be used in references. All authors names must be written, do not use "et al".

For Journals

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV- infected patients. N Engl J Med. 2002;347:284-7. PMID: 12140307 DOI: 10.1056/NEJMsb020632

For Epub Ahead of Print Articles:

Yalçın Çakmaklı G, Ayhan Y, Yazıcı MK, Demirci M, Şahin G. Spectral analysis of lithium tremor. Arch Neuropsychiatry, 17 Ekim2020. https://doi.org/10.29399/npa.27378. [E -pub ahead of print]

Books:

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Book chapters:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. 93-113.

Meeting announcements:

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Tables and Figures

Tables and figures should work under "Windows". Color figures or grayscale images must be at least 300 dpi. Figures using ".jpg" or ".pdf" should be saved separate from the text. All tables and figures should be prepared on separate pages. They should be numbered in Arabic numerals. Each table must have a title indicating the purpose or content of each table. Each figure must have an accompanying legend defining abbreviations or symbols found in the figure.

Review Articles

Review articles by authors with potential expertise in a particular field are welcomed. Reviews should describe, discuss and evaluate the current level of knowledge of a topic in clinical practice, and be a guide for future studies. Subtitles of review articles should be planned by the authors. However, each review article must contain an "Introduction" and a "Conclusion" section. Please refer to Table1 for the limitations of the review articles.

Case Reports

There is limited space for case reports in the journal. Reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for review. The text should include the subheadings Introduction, Case Presentation, and Discussion. Please check Table1 below for wordcount specifications.

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These manuscripts include evaluation and criticisms submitted by the experts in the field or the reviewers of a manuscript regarding manuscripts previously published in the journal. The authors of manuscripts that become to pics of letters to the editor are provided with the opportunity to responds to the comments that are raised. Letters are published together with the responses of the author(s) of the manuscript concerned where possible.

Revisions

Revisions will be sent to the corresponding author. Revisions must be returned as quick as possible in order not to delay publication. Deadline for the return of revisions is 15 days. The editorial board retains the right to decline manuscripts from review if authors' response delay beyond 15 days All reviewers' comments should be addressed and revisions made should be started with page and line of the text. Send a highlighted copy indicating the revisions made and a clear copy of the revised manuscript. Authors are responsible for the truth of presented data and references. Editor-In-Chief has the right to with draw or retract the paper from the scientific literature in case of proven allegations of misconduct.

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Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of Health Sciences

ISSN 2717-8439
E-ISSN 2717-9257

Cilt / Volume 5 | **Sayı** / Number 1 | **Nisan** / April 2024

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Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of
Health Sciences
ISSN 2717-8439
E-ISSN 2717-9257

YIU Saglik Bil Derg 2024;5:1–9
https://doi.org/10.51261/yiu.2024.1383772

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Experiences of Executive Nurses during the COVID-19 Pandemic: A Qualitative Study

COVID-19 Pandemi Sürecinde Yönetici Hemşirelerin Deneyimleri

Dilek Yıldırım Tank

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ABSTRACT

Introduction: Globally, the COVID-19 pandemic has complicated the delivery of healthcare and its administration. It has been difficult for the executive nurses to handle a crisis with few resources. This study was performed to explore the experiences of executive nurses during the COVID-19 pandemic process.

Material and Method: Eight frontline nurse managers at a university hospital in Turkey were the subject of a qualitative phenomenological descriptive study. Semi-structured interviews were done between April 20 and May 24, 2022. Reporting was done using the COREQ checklist.

Results: Four interrelated themes (with sub-themes) were identified: we needed to be fast; everything has changed; tall in the saddle and safe environment for everyone.

Conclusions: During the pandemic, the aim of nurse managers was to provide nurses with knowledge, experience and psychosocial support while they were also experiencing stress, exhaustion and panic. Training and planning should be done to support compliance with new care protocols and changing treatment methods.

Keywords: COVID-19; experience; nurse manager; nursing; qualitative research.

ÖZ

Giriş: Küresel olarak, COVID-19 salgını sağlık hizmetlerinin sunumunu ve yönetimini karmaşık hale getirmiştir. Sınırlı kaynaklarla bu krizle baş edebilmek yönetici hemşireler için oldukça zor olmuştur. Bu çalışma, yönetici hemşirelerin COVID-19 pandemi sürecindeki deneyimlerini araştırmak amacıyla yapılmıştır.

Materyal ve Metod: Türkiye'de bir üniversite hastanesindeki sekiz yönetici hemşire ile yapılan bu çalışma fenomenolojik tarzda nitel çalışma tasarımına sahipti. Yarı yapılandırılmış görüşmeler 20 Nisan – 24 Mayıs 2022 tarihleri arasında yapıldı. Raporlama COREQ kontrol listesi kullanılarak yapıldı.

Bulgular: Alt temalarıyla ilişkili dört ana tema belirlendi: Hızlı olmalıyız; Her şey değişti; Ayakta durmak zorundayız; Herkes için güvenli bir ortam.

Sonuç: Pandemi sürecinde hemşire yöneticilerinin amacı, hemşirelerin yaşadığı stres, panik ve tükenmişlik ortamında onlara bilgi, deneyim ve psikososyal destek sağlamaktı. Çalışma sonucunda yeni bakım protokollerine ve değişen tedavi yöntemlerine uyumu destekleyecek eğitim ve planlamaların yapılması önerilmektedir.

Anahtar Sözcükler: COVID-19; deneyim; yönetici hemşire; hemşirelik; nitel araştırma.

Cite this article as: Yıldırım Tank D. Experiences of Executive Nurses during the COVID-19 Pandemic: A Qualitative Study. YIU Saglik Bil Derg 2024;5:1–9

Introduction

SARS COVID-19, the first case seen in December 2019, was declared a global pandemic by the WHO on March 11, 2020 (1). The healthcare system trying to manage the COVID-19 crisis has faced a challenge as disruptions, and many aspects of the care process have changed instantly. While disaster plans are in place for pandemics, preparedness for such situations is "often overlooked or only addressed in policy". The COVID-19 pandemic has both increased risks for the healthcare workforce and created an environment of chaos for healthcare systems (2). The fact that the first clinical contact for those applying to health services is usually nurses, and the majority of them are patient/clinician contact (1) shows the importance of the nursing workforce in the health system (3).

Executive nurses in a critical role in the fight against the pandemic. This role is a personal and professional responsibility

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Geliş Tarihi/Received: 31.10.2023, **Kabul Tarihi/Accepted:** 06.03.2024, **Çevrimiçi Yayın Tarihi/Available Online Date:** 31.05.2024

to ensure the safety of both the nurses they supervise and the patients cared for in their hospitals. The COVID-19 pandemic has been an unprecedented experience for nurse managers, characterized by intense stress, complex decision-making, and emotional turmoil (4, 5). It was seen whether they also described their experiences (6,7).

After the pandemic was declared, the first studies in Turkey started with the general information guide created by the scientific advisory board established by the Public Health Directorate. Afterwards, constantly updated COVID-19 outbreak management and study guides were published (8).

The capacities of the private, university and public hospitals, the number of intensive care units and the number of health personnel were determined by the Ministry of Health in Turkey. Pandemic committees were established in hospitals, and these committees restructured the hospitals, and pandemic hospitals, pandemic clinics, intensive care units, and outpatient vaccine and diagnostic laboratories were established. New hospitals were established, and the construction of hospitals under construction was accelerated. The number of personnel was increased and the continuity of the existing personnel was ensured (9).

This study, which describes the experiences of executive nurses during the COVID-19 pandemic process, focuses on human resources management, ensuring patient and employee safety, coordination of nursing care, understanding the difficulties, and helping executive nurses be more sensitive to future crises in a chaotic environment that compels crisis, decision making, problem solving and critical thinking mechanisms. These findings can be used by nurse managers to enhance organizational management strategies during health emergencies, such as the upcoming COVID-19 pandemic waves and other pandemic outbreaks of a similar sort in the future. The results will also be used as a resource for identifying teaching techniques and strategies aimed at developing the critical skills the nurse manager must master to effectively address a crisis and, in turn, improve staff biopsychosocial well-being and patient outcomes.

Material and Method

This study aims to investigate and interpret the experiences of hospital nurse managers during the COVID-19 pandemic in Turkey. A qualitative descriptive study was carried out. This design allows the study of people's experiences around a phenomenon. This study adhered to the Consolidated Criteria for Qualitative Research Reporting (COREQ) guidelines developed to evaluate qualitative research reports (10).

Participants were sampled from nursing managers of departments that were converted to COVID-19 intensive care units and clinics, working in pandemic clinics during the pandemic. A university hospital in Türkiye was chosen as the 3rd level hospital due to the priority of taking COVID-19 cases during the pandemic process as the research site. To carry out the research, written permission was obtained from the Human Research Ethics Committee of Zonguldak Bülent Ecevit University (799 / 05.06.2020) and from the Chief Physician of the institution where the research was conducted (15876 / 14.04.22).

All members were invited; informed volunteer consent forms were sent to the institution online before the study, and necessary permissions were obtained. The consent document contained the content of the survey and the assurance of confidentiality. While aiming to talk to 12 nurses, interviews were terminated when repeated, similar statements appeared, and data saturation was reached. During the interview, the conversations were recorded with a Sony Icd-Tx650 voice recorder. Using purposive sampling method eight executive-level nurse leaders were identified and included in the study. Then the interviews were transcribed, and analyzed using thematic analysis with the consent of the participants.

The interviews were completed between April 20 and May 24, 2022, after meeting with the nurses and determining the appropriate dates and time intervals. Before the interview form was applied to all participants, a pilot study, which was the preliminary application of the research, was carried out to evaluate the interviewing ability of the researcher and the audio recording process technically and to examine the relevance of the questions to the subject. A female researcher with a Ph.D. degree and training in qualitative research conducted the pilot study with a volunteer nurse who met the inclusion criteria. Alternative questions were not developed because there were no technical problems as a result of the pilot study, there were no questions that the participant did not understand, the participant answered the questions and found the questions appropriate for the research topic, and the questions in the interview form were applied to all participants. Interviews were held in a comfortable and calm environment, in the nurse's break room. Interviews were planned face-to-face with the participant, interviewer, and observer and were recorded on a voice recorder after their approval. The data were collected with a personal information form and a semi-structured interview form using an in-depth interview technique. Each interview took about 1 hour. The interviews focused on the research topic and aimed to illuminate the experience of nurse managers during the COVID-19 pandemic.

The study data were collected using a personal information form. The personal information form comprised ten questions about nurses' socio-demographic and introductory characteristics, age, gender, educational status and professional characteristics. The semi-structured interview form questions were prepared according to the research topic and purpose by scanning the literature, and the form was finalized by taking expert opinions (11,12).

Semi-structured interview form;

- How has the COVID-19 pandemic process changed the nursing management process?
- What has the COVID-19 pandemic process changed the manager nurses in workforce planning?
- How did the nurses managing the COVID-19 pandemic process provide material management?
- What kind of initiatives did nurses manage during the COVID-19 pandemic to protect physical and mental health?
- Have ethical dilemmas been experienced by nurses during patient care during the COVID-19 pandemic process?
- How did the nurses managing the COVID-19 pandemic process motivate the staff?
- How was the information flow within the team of nurses managing the COVID-19 pandemic process?
- What did the nurses managing the COVID-19 pandemic process pay attention to in terms of patient and employee safety?
- What was your leadership approach?

consists of questions.

Data Analysis

The audio recordings were converted into written text and transcribed verbatim by three researchers using the thematic analysis method, and themes and codes were created.

Data coding followed the analytical approach of Smith et al. (13): (1) reading and rereading of records; (2) at a more interpretive level, the first note of meaningful statements that make descriptive comments on what participants relate to and conceptual interpretations; (3) develop themes that emerge in each transcript; (4) looking for links between transcripts; and (5) looking for patterns at the point at which high-level themes and high-level themes are disclosed. During this step, a table can be developed for their representation.

In addition to using the COREQ criteria to evaluate qualitative research reports, the researcher adhered to the requirements outlined by Beck (14) regarding the use of phenomenological analysis: (1) the themes identified should be well represented in the analysis and supported by citations from participants; and (2) evidence, verbatim citations, must be from more than one participant.

Validity and Reliability of the Research

Lincoln and Guba criteria were used to ensure the validity and reliability of the data (15). In the study, the themes and codes were examined using the interview form by the experts in the field and method of the study subject, and the data were turned into a report by taking expert opinions. The experts consisted of 3 academics who had a Ph.D. degree in nursing and were experienced in qualitative work. More than one data collection tool was used, and the suitability of the data collection tools for the study was evaluated by making a pilot application. The pilot study was conducted with two nurse managers. Since there were no questions that were not understood after the pilot study, no changes were made to the survey form and the data from the pilot study were included in the study. A purposive sampling method was used, and the sample group suitable for the research topic and purpose was selected by confirming the participants. In addition, the research team did not direct the participants during the interview, observation did not interfere with them, and they quoted directly without adding comments. The literature supported the research findings by comparing them with other studies similar to the study. After the themes and categories were determined, they were shared with the participants and their opinions were taken and the final version was given.

Results

Eight participants were women (Table 1). Four intensive care chief nurse, two service chief nurse, and two coordinator nurse participated in the study. All participants reported that they received in-service training on COVID-19. Between the ages of 39 and 47, they have 17 to 26 years of experience in nursing. They reported working between five months and two years in services that only deal with COVID-19 patients during the pandemic process.

The four main themes and the related sub-themes from which they evolved are shown in Table 2. Each sub-themes within the overarching theme was explained with supporting text samples from the participants' transcripts. With only eight respondents, to preserve as much anonymity as possible, each of the verbatim statements reported here does not include demographic identifiers such as respondents' age or unit designation.

Four interrelated themes (with sub-themes) were identified: (1) we needed to be fast (insufficient material, providing new Information and communication, adapting to change, institutional support, partnership); (2) everything has changed (leadership approaches, flexible working hours, knowledge development and dissemination, new practices in care, workforce planning, rotations); (3) tall in the saddle (ethical dilemmas, stress, fear, cold-blooded managers, motivation) and (4) safe environment for everyone (communication, physical spaces, patient support units, away from our home).

Theme 1: We had to be Fast

In this theme, the participants reflected on the changes in creating an emergency action plan, workforce materials, and management processes as managers. There were five sub-themes: insufficient material, providing new Information and communication, keeping up with change, institutional support, and cooperation.

Insufficient Material

An inventory of protective equipment and devices used for patients was made, and correspondence was made for

Table 1. Socio-Demographic characters of participants

Degree	School	Age	Gender	Unit	Years of work as a nurse	Years of work as a nurse manager	Training in COVID-19 Management	Training style	Time of the working at COVID-19 unit
Chief Nurse	BSN	39	F	Haematology Unit	17	12	Orientation	in-service training	5 months
Chief Nurse	MSN	43	F	General Intensive Care	22	17	Orientation	in-service training	18 months
Chief Nurse	BSN	48	F	Coronary Intensive Care	27	15	Orientation	in-service training	11 months
Chief Nurse	BSN	41	F	Anesthesia Intensive Care	20	8	Orientation	in-service training	15 months
Chief Nurse	BSN	42	F	Gastroenterology Unit	20	12	Orientation	in-service training	8 months
Chief Nurse	BSN	41	F	İnfection Unit	20	8	Orientation	in-service training	24 months
Coordinator Nurse	MSN	43	F	Directorate of Nursing Services	20	6	Orientation	in-service training	24 months
Coordinator Nurse	MSN	42	F	Directorate of Nursing Services	23	15	Orientation	in-service training	24 months

Table 2. Themes

Themes	Sub-themes
We needed to be fast	• Insufficient material, • Providing new information and communication, • Adapting to change, • Institutional support, • Partnership
Everything has changed	• Leadership approaches, • Flexible working hours, • Knowledge development and dissemination, • New practices in care, • Workforce planning, • Rotations
Tall in the saddle	• Ethical dilemmas, • Stress, • Fear, • Cold-blooded managers, • Motivation
Safe environment for everyone	• Communication, • Physical spaces, • Patient support units, • Away from home

deficiencies. Material procurement was accelerated, and some companies donated.

"Because the oxygen system was used at high doses by too many patients, sometimes it was not enough." (N3)

"We had no protective shields; provided through donation." (N8)

"We did not want to share the materials in our warehouse with other services." (N4)

Providing new Information and communication

Due to the pandemic conditions, training and information sharing took place via social media, phone calls, automation systems, and one-to-one meetings were provided instead of collective events.

"We were getting new information every day." (N1)

"We had to do one-on-one visits." (N2)

"Bedside visits could not be made. We handed over in a clean area." (N5)

"The pandemic board announced a new decision Every day. We had to inform everyone." (N7)

Adapting to change

"I had to adapt everyone doctors, nurses, support staff", (N3)

"Everyone was asking me what to do." (N2)

Institutional support

A pandemic board was established at the hospital. The top management made everyday visits, and deficiencies and needs were discussed one-on-one.

"The feeling that they were with us gave me strength." (N1)

" The inadequate materials were tried to be completed quickly." (N8)

Partnership

Communication was established with institutions (All levels within the team and government supplies office, patient relatives, security units, morgue, pharmacy, etc.) for Information, material and personnel support. (N7)

Theme 2. Everything has Changed

Within the scope of this theme, the managers explained the changes they experienced. There were six sub-themes: leadership approaches, flexible working hours, knowledge development

and dissemination, new practices in care, workforce planning, and rotations.

Leadership approaches

"We got into one-on-one patient care." (N2)

"We had to be cold-blooded." (N4)

"I couldn't watch outside while they were entering the patient's side." (N6)

"We learned everything together, and I shared every piece of information with everyone one-on-one and constantly." (N6)

"A nurse said, this is my first year, I have never seen anything like this, and I told her, I have been working for 27 years, don't worry, I haven't seen it either." (N3)

"We changed together." (N8)

Flexible working hours

"All public and private employees were given administrative leave, except health workers." (N1)

"Our working hours have changed." (N2)

"Our shift breaks have been extended." (N4)

"Our 24-hour shifts have been converted to 2 shifts." (N5)

Knowledge development and dissemination;

Everything we do face-to-face with the group, including group meetings, has changed, either online or in person. "We had no information about COVID-19" (N8)

"We were always hearing different things" (N7)

"Hospital pandemic board was established, and our nurse managers shared the information from the board with us." (N6)

New practisees in care

Nurses reported that many innovations in diagnosis and treatment methods were implemented during the unknown COVID-19 pandemic.

"The prone position was not a position we routinely use. This is the first time we have used so many prone positions." (N3)

"Added new devices and many treatment protocols," (N2)

"We constantly supported their diets and even gave them food from home and herbal teas; such practices motivated them." (N1)

"We entered the patient rooms frequently for short periods, communicated constantly and realized that it accelerated their recovery." (N4)

Workforce planning

The COVID-19 pandemic has caused difficulties in workforce planning.

"It was tough to adapt to the new staff." (N8)

"We had to find personnel." (N7)

"We planned to have one nurse for two patients while a nurse was taking care of 3 patients, but we did not have enough numbers." (N4)

"New appointments were made with the coordinator nurse." (N5)

"The team members became COVID-19, or they were in contact, it was tough to find nurses and support personnel who could replace them." (N8)

" Only one of the married couples was working in the COVID-19 units." (N6)

Rotations

First, internal rotations were made, and nurses with previous intensive care experience were withdrawn from the clinics.

"There was a constant change of personnel, and this was very challenging, and we were helpless" (N4)

"New graduates were appointed to the clinics, and their adaptation was tough, and they expressed their fear". (N5)

"We kept the orientations very short, and there were rotations that lasted for sometimes one week, sometimes two months." (N8)

" Since the new nurses could not adapt, the senior ones started to be on duty more frequently." (N6)

Theme 3. Tall in the saddle

Within this theme's scope, nurse managers' experiences against emotional and spiritual reactions were formed into five sub-themes: ethical dilemmas, stress, fear, cold-blooded managers, and motivation.

Ethical dilemmas

"The biggest dilemma was experienced when the patient was suddenly arrested and intervened without wearing protective equipment." (N4)

"When the patient was arrested, we did not go inside without wearing the protective clothes; the priority was our safety, and the rule was clear." (N5)

"One of my nurses applied CPR to the patient for one and a half hours with a surgical mask. He couldn't leave the patient's head and became COVID-19." (N4)

"We are in a place where everyone is running, and we are the only ones working." (N3)

"Permits were cancelled; we couldn't even go on vacation." (N2)

"Everyone is at home except us." (N1)

Stress

"We were tired the most by the unknown." (N4)

"Something was constantly changing." (N5)

"It was a crisis, something we had not experienced before." (N8)

Fear

"Some nurses did not want to care for their COVID-19 patients." (N7)

"A nurse said, this is my first year, I have never seen anything like this, and I told her, I have been working for 27 years, don't worry, I have not seen anything like this either." (N3)

"There were those who were afraid of carrying the disease to those at home; they were afraid of carrying the virus to their elderly parents, pregnant spouses, and children at home." (N4)

"The death of young people from COVID-19 scared my nurses, especially my young nurses." (N2)

Cold-Blooded managers

"We had to be cool."(N7)

"I did not panic; it was no different from the flu; I am a former infection nurse, I approached it as droplet isolation, only protective clothing was added to the event, everything else was the same" (N6)

Motivation

"We talked every day; we had a constant dialogue with the nurses." (N7)

"We tried to open shift breaks by arranging working hours", "hospital administration and local people made the team happy by sending additional meals such as fruit and cookies"(N5)

"Nursing managers visited us daily and made us feel they were with us." (N4)

"For those who do not want to go home, shelters and services were provided in the city, and we tried to make them comfortable by organizing them." (N7)

Theme 4: Safe Environment for Everyone

Within this theme's scope, nurse managers' experiences against emotional and spiritual reactions were formed into four sub-themes: communication, physical spaces, patient support units, and away from home.

Communication

"Team communication was done one-on-one, online and via automation." (N6)

"Since patients had restrictions on visitors and companions, we enabled patients to communicate with their families online and through video calls whenever possible." (N3)

Physical Spaces

"We simplified the patient rooms and minimized the equipment in the rooms" (N5)

"We separated the physical areas as clean and dirty areas, patient files remained in the clean area and patient handovers were made in the clean area" (N8)

"We took the break rooms out of the service and used them alternately" (N2)

Patient Support Units

"Since the relatives of the patients could not come, support units were established by the hospital administration to provide missing supplies and medicines." (N1)

Away From Home

"Guest houses were provided by government institutions for healthcare workers who could not go home, and shuttles were provided at regular intervals by communicating with the city's municipal administration to provide transportation." (N4)

"I couldn't see my children for days, I couldn't go home for fear of infecting them. Everything was so hard." (N5)

Discussion

Nurse managers have a critical role in managing the nursing services provided in health institutions and creating a healthy working environment during the COVID-19 pandemic. In the study, nurse managers' experiences in the COVID-19 pandemic were examined, and some themes and codes were created. In this section, the findings of the study are discussed under different themes.

Theme 1: We had to be fast

Under this theme, defective materials, providing new information-communication, changing working relations, keeping up with change, institutional support and cooperation codes were created. Deldar et al. reported that the participants had management and equipment difficulties in their study investigating the experiences of executive nurses in the COVID-19 pandemic (11). Again in the same study, it was stated that the working environment was changed by changing the shifts of experienced nurses and assigning them to more intensive services due to the ignorance and inexperience of the new nurses. The study findings support our study (14). According to our study, many units were closed and their nurses were transferred to intensive care units. However, in this case, intensive care veterans reported that they had to stay on duty more because nurses without intensive care experience could not fully adapt.

Jackson et al. (16) emphasized that the roles and responsibilities of executive nurses have expanded during the pandemic process, and they have experienced many changes in the health system (15). Some clinics stated that they made COVID-19 clinics and experienced many new tasks and sudden changes, such as staff capacity and assignments and isolation of patients. Again in the same study, he mentioned the lack of personal protective equipment. A participant stated, 'It was decided on Tuesday night, from tomorrow everyone will wear personal protective equipment. Some buildings did not have adequate personal protective equipment, which was frightening for nurses and health '(16). In a study conducted with executive nurses during the pandemic in Spain, it was reported that urgent and continuous changes were experienced in the organization of services in terms of the management of the process and personnel in the hospital. As a result, it was emphasized that they were looking for alternatives and producing solutions to change and problems because they encountered a new and unknown situation. On the other hand, it was stated that nurse managers developed strategies such as using informal channels to communicate messages with their teams quickly and to keep the staff informed. A participant's statement was"….Information had to be given very briefly and clearly. Everything changed day by day, so we communicated via WhatsApp as quickly as possible (17). White et al. (12), in their research on nurses during the COVID-19 pandemic, encouraged the clinical nurses working during the pandemic by posting thank-you messages from the patients' families on the board by the manager nurses. It was reported that the newly graduated nurse, who was worried about care, was consoled and supported by the manager nurse. The importance of institutional support is also supported by the work done in the COVID-19 pandemic (15). In our study, they similarly mentioned the support of senior management.

Theme 2: Everything has changed

Under this theme, leadership approaches, flexible working, knowledge development-dissemination, new practices in care, number of workforce and rotations codes were created. Baykal et al. (18) reported that the number of patients coming to the emergency services and the waiting times of the patients was reduced, and the care of patients with a diagnosis or suspected COVID-19 was easier (18).

It is seen that the manager nurses pay attention to experience and performance while creating the work list; they make a work list by using the team nurse model in intensive care services, and the experienced nurses try to reduce their workload, and the rotation plans are made accordingly. The same study reported that the infection control committee gave nurses training, and video materials facilitated the training. Nurses provide collective care in order to reduce the virus load and shorten the contact time between the patient and the nurse by maintaining the nurse-patient communication in the wards, as new care practices. At the same time, it is seen that the weekly working hours of the employees in the COVID-19 services are shortened, and flexible working is applied, similar to our research finding (18). The same study reported that the infection control committee gave nurses training, and video materials facilitated the training. In their study with primary care nurse managers, Abu Mansour et al. (19) stated that shift systems have changed by the participants (19). A participant's statement on this subject said, "The nature of the shifts has changed…. For example, 8-hour shift changed to 12-hour shift...'. It was reported that various strategies, such as hiring nurses, establishing field hospitals, and opening new units, were adopted by hospitals to close the gap in terms of people and workforce. One of the highlights of the same study was that the participants appreciated the leadership skills of nurse managers. Participants; It is seen that primary care nurse managers act together in many ways, such as motivation and rewards, appreciation of hard work, logistical support, and involvement in the decision-making process in nursing (19). The results of the studies carried out support our research findings.

Theme 3: Tall in the saddle

Ethical dilemmas, stress, fear, cold-blooded managers and motivation codes were created under this theme. Nevela et al. (20), in their study investigating the experiences of executive nurses during the COVID-19 pandemic process, reported that administrative nurses adopted the ability to motivate staff as a leadership style during an unprecedented global crisis (20). It was stated that the first thing the nurses did when establishing the pandemic services was address the nurses' concerns. It was emphasized that the participants also experienced fear of the virus, hopelessness and anxiety due to the lack of personal protective equipment (20). In the study examining the difficulties experienced by nurses in Egypt during the COVID-19 pandemic, it was found that the three most considerable difficulties faced by nurses were anxiety, fear and stress. When these fears are examined, there is unpreparedness for the pandemic, a lack of personal protective equipment, and a personnel shortage (21). Abu Mansour et al. (19), it is seen that most nurse managers reported

many psychological complaints, such as fear of transmitting the COVID-19 virus from the hospital to their homes, fear of death, depression, anxiety, and distress. These feelings have been formulated in many expressions: …' I feel so overwhelmed…. It's an pandemic... It's a complicated disease... So we're afraid it's changed our lives. I am depressed because of this situation...' In the same study, the participants emphasized that they received administrative support and increased motivation. Participants stated that administrators motivated them to adapt to challenges related to the COVID-19 pandemic, and nurse managers felt safe and not alone (19). It was evident that administrative support and motivation have a positive effect on managing nursing services and psychological complaints during the pandemic process. One of our research findings was that the executive nurses were calm during the COVID-19 pandemic. It was observed that they performed health care services without becoming panicked. It was reported in the study conducted by the nurses, which had a similar finding to our research result, that they realized, they controlled the pandemic process with calmness and confidence, that they should not express their doubts and uncertainties in their daily work, and that they should not reflect their worries and fears to anyone. In our research, it is seen that one of the most significant factors that force nurses to work professionally during the pandemic process is the dilemma of self-protection and intervention for the patient. Vázquez-Calatayud et al. (17) refer to the dual challenges nurse managers face in order not to overlook the patient, who is the focus of care, and to protect themselves during the COVID-19 pandemic. The statement of the participants on this subject was"...I did not know the patients. I only knew them by their names (17). They had no family, walking in front of the service and not being able to do anything, it was hard for me...' …' It was hard for me, it was different from usual because maybe we weren't willing to take care of it...' Participants also stated that they experienced the difficulty of protective measures and the lack of closeness they showed to patients (17). In this sense, manager nurses, It has been seen that the priority of nursing studies continues to be the holistic care of the patient, and they emphasize the importance of being able to address all the patient's needs and concerns. The studies carried out support our research results.

Theme 4: Safe environment for everyone

Under this theme, communication, physical areas, patient support units and away-from-our-home codes have been created. When the studies were examined, the study by Nevela et al. (20) investigated the experiences of executive nurses during the COVID-19 pandemic process has been reported that each room was cleaned. Items were removed, clean/dirty areas were created, and separate regions for putting on/taking off personal protective equipment and entrances for COVID-19 patients (20). The research shows that physical changes were made in the hospital during the pandemic process (20). In the process, it is seen that the manager nurses are in constant communication with the team and provide strong communication by making a joint decision (18). In a study conducted with nurse managers during the COVID-19 pandemic in Spain, it was reported that the internet was used to accelerate communication and decision-making processes. A participant said,"…I always had a team that responded to me instantly, came and told us something. Sending emails made my job easier…'(17). The studies carried out are similar to our research results. During the COVID-19 pandemic, nurses provide accommodation in a different places to isolate themselves in the home environment, in a hotel, dormitory, etc., away from their homes (22). No study has been found in the literature regarding the patient support units created under the theme of our research.

Limitations

This qualitative research's limitation is that it only collects the experiences of nurse managers in a particular area. The results therefore relate to the setting in which the study was conducted and the perspectives of a small group of participants. However, the goal of this study is not to generalize the results but to provide an in-depth understanding of the reality as it is experienced by the nurse managers who participated in the study. To further our understanding of the phenomenon, it would be beneficial to do related studies in various settings.

Conclusion

Hospital operations and the healthcare sector as a whole were interrupted by the COVID-19 pandemic. Rapid decision-making and quick resource mobilization require strong and creative nursing leadership. Nurse managers are at the forefront of the pandemic as the most approachable and visible nursing leaders in acute care and many other settings. In most cases, healthcare administrators recognize the nurse manager's role as one.

During the pandemic, nurse managers throughout the country took on a lot of responsibilities at significant professional and personal costs. As a result, nurse managers encountered difficulties, moral problems, and bad feelings. Nurse managers said they are contemplating alternative professional options as their regular coping mechanisms haven't worked. This research offered data to support senior executives' plans for eliminating managerial dissonance under pressure. The researchers of this study aimed to investigate nursing managers' experiences with workforce management during the COVID-19 pandemic. To better manage nursing staff during potential rising pandemics, it is believed that the study's findings will offer public health professionals and politicians insightful information.

This study scrutinizes the experiences of nurse managers during the COVID-19 pandemic. The development of management solutions to better handle the COVID-19 problem and related pandemic outbreaks in the future can be guided by this understanding. The creating training programs for nurse managers based on the results of experiences manage uncertainty

by receiving instruction in emotional self-management and being encouraged to adopt a proactive and visionary mindset. To offer the best reaction in a crisis, it is crucial to emphasize their dual position as patient-nursing staff mediators. Finally, further qualitative research must be conducted in various contexts to investigate their contributions further.

Ethics Committee Approval: Ethical approval was obtained from Zonguldak Bulent Ecevit University, Human Research Ethics Committee (dated 05.06.2020 and numbered 799).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - DYT; Design - DYT; Supervision - DYT; Data Collection and/ or Processing - DYT; Analysis and/or Interpretation - DYT; Literature Search - DYT; Writing - DYT; Critical Reviews - DYT.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19): Situation Report - 38. 27 June 2022. Accessed online (28 June 2022): www.who.int/docs/default-source/coronaviruse/situation-reports/20200227-sitrep-38-covid-19.pdf?sfvrsn=9f98940c_2
2. Haldane V, De Foo C, Abdalla SM, Jung A-S, Tan M, Wu S, et al. Health systems resilience in managing the COVID-19 pandemic: lessons from 28 countries. Nat Med. 2021;27(6):964–980. https://doi.org/10.1038/s41591-021-01381-y
3. Halcomb E, McInnes S, Williams A, Ashley C, James S, Fernandez R, et al. The experiences of primary healthcare nurses during the COVID-19 pandemic in Australia. J Nurs Scholarsh. 2020;52(5):553–563. https://doi.org/10.1111/jnu.12589
4. Boston-Fleischhauer C. The global pandemic: should COVID-inspired care innovations continue? JONA. 2021;51(6):304–306. https://doi.org/10.1097/NNA.0000000000001017
5. Kim SC, Rankin L, Ferguson J. Nurses' mental health from early COVID-19 pandemic to vaccination. J Nurs Scholarsh. 2022;54(4):485–492. https://doi.org/10.1111/jnu.12760
6. Han L, Wong FKY, She DLM, Li SY, Yang YF, Jiang MY, et al. Anxiety and depression of nurses in a north west province in China during the period of novel coronavirus pneumonia outbreak. J Nurs Scholarsh. 2020;52(5):564–573. https://doi.org/10.1111/jnu.12590
7. Kackin O, Ciydem E, Aci OS, Kutlu FY. Experiences and psychosocial problems of nurses caring for patients diagnosed with COVID-19 in Turkey: a qualitative study. Int J Soc Psychiatry. 2021;67(2):158–167. https://doi.org/10.1177/0020764020942788
8. Sağlık Bakanlığı. COVID-19 (SARS-CoV-2 Enfeksiyonu) Genel bilgiler, epidemiyoloji ve tanı rehberi, 2021. Erişim (20.06.2022): https://covid19.saglik.gov.tr/Eklenti/39551/0/covid-19rehberigenelbilgilerepidemiyolojivetanipdf.pdf
9. Remi Gazete. COVID-19 kapsamında kamu kurum ve kuruluşlarında normalleşme ve alınacak tedbirler, 2021. Erişim (20.06.2022): https://www.resmigazete.gov.tr/eskiler/2021/06/20210630-14.pdf
10. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–357. https://doi.org/10.1093/intqhc/mzm042
11. Deldar K, Froutan R, Ebadi A. Nurse managers' perceptions and experiences during the COVID-19 crisis: a qualitative study. Iran J Nurs Midwifery Res. 2021;26(3):238–244. https://doi.org/10.4103/ijnmr.IJNMR_285_20
12. White JH. A phenomenological study of nurse managers' and assistant nurse managers' experiences during the COVID-19 pandemic in the United States. J Nurs Manag. 2021;29(6):1525–1534. https://doi.org/10.1111/jonm.13304
13. Sparkes AC, Smith B. Judging the quality of qualitative inquiry: criteriology and relativism in action. Psychol Sport Exerc. 2009;10(5):491–497. https://doi.org/10.1016/j.psychsport.2009.02.006
14. Beck CT. Introduction to Phenomenology: Focus on Methodology. Sage Publications, 2019.
15. Lincoln YS, Guba EG. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. New Dir Eval. 1986;30:73–84. https://doi.org/10.1002/ev.1427
16. Jackson J, Nowell L. The office of disaster management' nurse managers' experiences during COVID-19: a qualitative interview study using thematic analysis. J Nurs Manag. 2021;29:2392–2400. https://doi.org/10.1111/jonm.13422
17. Vázquez-Calatayud M, Regaira-Martínez E, Rumeu-Casares C, Paloma-Mora B, Esain A, Oroviogoicoechea C. Experiences of frontline nurse managers during the COVID-19: a qualitative study. J Nurs Manag. 2022;30(1):79–89. https://doi.org/10.1111/jonm.13488
18. Baykal U, Alan H, Güngör S, Tekin D, Türkmen E, Başulaş ÇY, et al. Türkiye'de COVID-19 salgını: kriz yönetiminde yönetici hemşirelerin deneyimleri ve Yönetici Hemşireler Derneği'nin faaliyetleri. Koç Üniversitesi Hemşirelikte Eğitim ve Araştırma Derg. 2020;17(3):290–293.
19. Abu Mansour SI, Abu Shosha GM. Experiences of first-line nurse managers during COVID-19: a Jordanian qualitative study. J Nurs Manag. 2022;30(2):384–392. https://doi.org/10.1111/jonm.13530
20. Nevala MS, Vuorela S. Early nurse management experiences from Finnish COVID-19 hubs: an in-action review. Int J Environ Res Public Health. 2022;19(8):4885. https://doi.org/10.3390/ijerph19084885
21. Gab Allah AR. Challenges facing nurse managers during and beyond COVID-19 pandemic in relation to perceived organizational support. Nurs Forum. 2021;56(3):539–549. https://doi.org/10.1111/nuf.12578
22. Kıraner E, Terzi B. Covid-19 pandemi sürecinde yoğun bakım hemşireliği. YBHD. 2020;24(EK-1):83–88.

Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of
Health Sciences
ISSN 2717-8439
E-ISSN 2717-9257

YIU Saglik Bil Derg 2024;5:10–15
https://doi.org/10.51261/yiu.2024.1452962

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Examining Menstrual Irregularity and Marital Adjustment in Women with COVID-19 Disease

COVID-19 Hastalığını Geçiren Kadınların Adet Düzensizliği ve Evlilik Uyumu Yönünden İncelenmesi

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ABSTRACT

Introduction: This study aims to examine the effect of COVID-19 disease on menstrual irregularity and marital adjustment of women.

Material and Method: The study was conducted with quantitative method. In the study, 147 persons were reached. The Personal Data Form and the Revised Dyadic Adjustment Scale (RDAS) were used as data collection tools.

Results: The participants reported that they had situations which caused significant difference in post-COVID-19 menstrual characteristics ($p<0.05$). Only the score of the consensus factor of the participants from the RDAS differed in terms of pre- and post-COVID-19 periods. The mean score of consensus dropped after COVID-19 and this was significant ($p<0.05$).

Conclusion: It was observed that COVID-19 disrupted the menstrual cycle and marital adjustment of women who survived the disease.

Keywords: Covid-19, woman, menstrual health, marital adjustment

ÖZ

Giriş: Çalışmanın amacı: COVID-19 hastalığını geçiren kadınların adet düzensizliği ve evlilik uyumu yönünden etkisini incelemektir.

Materyal ve Metod: Araştırma nicel yöntemdedir. Araştırmada, 147 kişiye ulaşılmıştır. Veri toplama araçları olarak; Bireysel Bilgi Formu ve Yenilenmiş Çift Uyum Ölçeği (YÇUÖ) kullanılmıştır.

Bulgular: Katılımcılar korona öncesi ve korona sonrası menstrüasyon özellikleri açısından anlamlı farklılık oluşturan durumlar yaşadıklarını bildirmişlerdir ($p<0,05$). Katılımcıların YÇUÖ'den sadece uzlaşı faktör puanı korona öncesi ve sonrası süreç açısından fark göstermiştir. Korona sonrası uzlaşı puan ortalamaları düşmüş olup bu durum anlamlı çıkmıştır ($p<0,05$).

Sonuç: COVID-19 hastalığını atlatmış kadınların menstrual siklus ve evlilik uyumu üzerinde olumsuz etki yarattığı gözlenmiştir.

Anahtar Sözcükler: Covid-19, kadın, adet sağlığı, evlilik uyumu

Cite this article as: Bulut A, Çelik G. Examining Menstrual Irregularity and Marital Adjustment in Women with COVID-19 Disease. YIU Saglik Bil Derg 2024;5:10–15

Introduction

Menstruation varies according to the person, organism, environment and climate. Stress and some exercises or changes in daily life may alter the menstrual cycle (1). Problems caused by physical, behavioural and emotional alterations associated with this process negatively affect women's lives (2–4). It is stated in the literature that menstrual irregularities are associated with age, age at menarche, body mass index (BMI), physical activity, smoking, caffeine and alcohol use, nutritional state, traumatic and permanent stressful conditions and psychological factors (5).

The COVID-19 pandemic is a state of crisis that causes global public health concern due to its medical, psychological, and socioeconomic aspects. COVID-19 infection is a pandemic that spreads rapidly, has no treatment yet, and can be fatal. The disease can be symptomatic or asymptomatic in individuals. Therefore, the most effective method is emphasised to be

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Geliş Tarihi/Received: 14.03.2024, **Kabul Tarihi/Accepted:** 22.04.2024, **Çevrimiçi Yayın Tarihi/Available Online Date:** 31.05.2024

"protection from the disease" and accordingly, such measures are taken around the world. "Social isolation – quarantine", a preventive measure, is implemented to minimise the risk of infection. Due to the "stay-at-home" policy, the quarantine conditions keep people away from their daily routine life, and lead a sedentary life, resulting in alterations in their emotional state. Also, as long as people constantly watched and listened to news about the COVID-19 pandemic and stayed at home for a prolonged time, the alterations in their emotional state increased (6). When examining the literature in general, previous studies have examined the effects of wars and some mass disasters such as earthquakes on the menstrual cycle (7).

On the other hand, this pandemic that broke out in 2019 and has spread throughout the world has led to many alterations and differences in people's lives (8). Due to many risks of infection such as droplets and contact with contaminated surfaces, the virus has turned into a disease type that necessitates severe precautions to be taken. To minimise the risk of infection, it was necessary to keep social distance between people. Social distancing has also affected spousal relations and consequently sexual intercourse. A reduction in the frequency of sexual intercourse may be observed along with sexual reluctance due to possibility of infection as a result of close contacts such as the presence of the virus in one of the spouses, kissing and physical touch (9–11).

Marriage is of primary importance for satisfying couples' biological, social and psychological needs. While social and psychological needs are taken into consideration, it contributes to the development of the sense of belonging by reinforcing the importance that spouses attach to the family institution with mutual love, respect, trust, and unity (12). The satisfaction of sexual desire constitutes a biological need and the studies have reported that sexual adjustment positively affects marital adjustment (13–15).

It can be asserted that the measures taken under quarantine during the COVID-19 pandemic negatively affect both the menstrual cycle order of women and spousal relations by causing significant psychological problems in people. A literature review revealed that menstrual cycle patterns of women and dyadic adjustment with their spouses were mostly studied during the pandemic but studies assessing menstrual cycle pattern and dyadic adjustment of women who were diagnosed with COVID-19 and suffered from this disease were not found in the literature. The contribution of the findings to the literature from this perspective is considered to be guiding in importance of evaluating the menstrual cycle pattern and dyadic adjustment in women who had this disease in negative circumstances such as the pandemic.

Objective

The aim of this study is to examine the effect of COVID-19 disease on menstrual irregularity and marital adjustment of women. This study sought answers to the following questions:

1. Does being diagnosed with COVID-19 disease affect negatively women's menstrual irregularity?
2. Does being diagnosed with COVID-19 disease affect negatively women's marital adjustment with their spouses?

Material and Method

Design of the Study

The study was conducted with quantitative method. The data were collected in an observational way, the retrospective recollection was preferred for the time relationship and it was intended to identify the society.

Population and Sample

In the study, 147 persons were reached. A post-hoc power analysis was done over the number of individuals reached. Following values were determined in the analysis; tail=one, effect size=0.2, α err prob=0.05, and the 1-β err prob=0.77. For data collection, the convenience sampling method was preferred. The data were collected by conducting face-to-face interviews with the participants between 15 November 2021 and 15 February 2022.

Ethical Considerations

The approval of the Bingol University Ethics Committee (decision no: 21/02, date: 19.08.2021) was obtained to conduct the study, followed by obtaining the permission of the institution where the study would be carried out. The women who agreed to participate in the study gave their written consent by signing an Informed Consent Form.

The participants were informed through the informative text at the top of the questionnaire in accordance with the Declaration of Helsinki, and the data were collected from voluntary female participants aged 18–49 years, who were diagnosed with COVID-19 disease and "reported no psychiatric disorder" diagnosed by a physician.

Data Collection Tools

A Personal Information Form (37 questions) and the Revised Dyadic Adjustment Scale (RDAS) were used as data collection tools.

Personal Information Form (including independent variables): This form has 37 questions about some characteristics of the participants (age, gender, education level, profession, marital status, menstrual cycle pattern, etc.).

Revised Dyadic Adjustment Scale (RDAS) (includes dependent variables): The scale was developed by Spanier (1976) to assess the quality of relationships of married or cohabiting couples in marriage or similar dyadic relationships (16). Busby et al., (1995) revised the scale (17). Gündoğdu (2007) adapted it into

Turkish (18). It consists of 14 items. It is a five-point Likert-type scale (1=never to 5=always). Items 7, 8, 9, and 10 are reversely scored. Revised dyadic adjustment scale has three sub-factors. The first factor is ***satisfaction*** and includes items 7, 9, 11, 12, and 13. The second factor is ***consensus*** and includes items 1, 2, 3, 4, 5, and 6. The third factor is ***cohesion*** and includes items 8, 10, and 14. The highest score of the scale is 70 points, and a higher score signifies that couples have a higher quality of the relationship. The Cronbach's alpha internal consistency reliability is 0.90 for the original version of the scale. In this study, the Cronbach's alpha internal consistency was determined as 0.89.

Data Assessment

The IBM Statistical Package for the Social Sciences (SPSS) program version 22 was used to analyse the data and error controls and tables were made through the program. Numbers and percentages are all provided in statistical analyses. Histogram plots were drawn for the compliance to the normal distribution, skewness and kurtosis values were evaluated, and Kolmogorov-Smirnov analyses were done. Wilcoxon test was applied between some conditions and characteristics and the total and subscale scores of the RDAS, and the value of $p < 0.05$ was accepted as statistically significant.

Results

The mean age of the participants was 32.79±6.71 years (Min: 20, Max: 47, Median: 31.00) and the mean age of their spouses was 36.09±7.54 years (Min: 24, Max: 58, Median: 35.00). 21.8% of the participants reported that they smoked. The mean year of smoking was 12.18±9.40 years (Min: 1, Max: 25, Median: 10.00). 28.6% of the participants reported that they had a chronic disease. Health problems of the participants were painful bladder syndrome (3 people), asthma (3 people), kidney disease (3 people), diabetes (3 people), FMS (3 people), Hashimoto's thyroiditis (9 people), hypertension (5 people), migraine (6 people), myasthenia gravis (3 people), and PCOS (2 people). Table 1 illustrates the socio-demographic characteristics of the participants.

The participants had a mean menarche age of 13.44±1.41 years (Min: 11, Max: 18, Median: 13.00).

The mean age of the first pregnancy was 25.72±3.81 years (Min: 18, Max: 34, Median: 26.00). The mean gravidity was 2.22±2.44 (Min: 1, Max: 19, Median: 2.00). The mean number of living children was 1.68±1.02 (Min: 0, Max: 5, Median: 1.00) Table 2 shows the reproductive characteristics.

As Table 3 shows, only the score of the consensus factor of the participants from the RDAS differed from the pre-and post-COVID-19 periods. The mean score of consensus dropped after COVID-19 and this was significant ($p<0.05$).

Table 1. Some socio-demographic characteristics of the participants (N=147)

Characteristics		n	%
Age range	30 years and below	64	43.5
	31 years and above	83	56.5
Duration of education	8 years	3	2.0
	12 years	31	21.1
	13 years and more	113	76.9
Age range of the spouse	30 years and below	38	25.9
	31 years and above	109	74.1
Duration of the spouse	8 years	6	4.1
	12 years	23	15.6
	13 years and more	118	80.3
Family Type	Nuclear	132	89.8
	Extended	15	10.2
Place of Residence	Village	3	2.0
	District	15	10.2
	Province	129	87.8
Perception of Economic status	Low	3	2.0
	Moderate	130	88.4
	High	14	9.5
Presence of a chronic disease	No	105	71.4
	Yes	42	28.6
Smoking	No	115	78.2
	Yes	32	21.8

Table 2. Reproductive characteristics of the participants (n=147)

Characteristics		n	%
Mode of last delivery (n= 118)	Normal vaginal delivery	58	49.2
	Caesarean section	60	50.8
The duration between the last two pregnancies (n=76)	Less than 2 years	18	23.7
	2 years and more	58	76.3
Unintended pregnancy (n= 138)	None	110	79.7
	Available	28	20.3
Mode of termination of unintended pregnancy (n= 40)	Abortion	5	12.5
	Curettage	6	15.0
	Birth	26	65.0
	Other	3	7.5

As Table 4 shows, the participants reported that they experienced situations causing significant differences in menstrual characteristics at the pre– and post-COVID-19 periods ($p<0.05$). The participants stated that the frequency of menstruation decreased, they complained of more pain, and their complaints such as discharge-itching-odour also increased in the post-COVID-19 period. Their requests to apply to a health institution declined based on their statements, which was significantly different ($p<0.05$).

Discussion

COVID-19 is a highly contagious virus that has caused the greatest pandemic of the last century. Since the existence of mankind, pandemics that have resulted in massive deaths have significantly affected adversely health, economic, and social life. The novel coronavirus (SARS-CoV-2) was a causative agent of a series of atypical respiratory diseases in Wuhan, Hubei Province, China in December 2019 and the World Health

Table 3. Pre- and post-COVID-19 values of the revised dyadic adjustment scale

		Consensus	Satisfaction	Cohesion	Total
Pre- COVID-19 Period	Mean ± SD Median Min-Max 95% CI	24.31 ± 5.21 25.00 6-30 23.47-25.16	18.64 ± 3.57 19.00 7-25 18.06-19.22	10.09 ± 1.85 10.00 4-13 9.79-10.39	53.06 ± 9.38 53.00 17-68 51.53-54.59
Post- COVID-19 Period	Mean ± SD Median Min-Max 95% CI	23.72 ± 5.58 25.00 6-30 22.81-24.63	18.64 ± 3.64 18.00 7-25 18.05-19.24	10.28 ± 1.95 10.00 3-14 9.96-10.60	52.65 ± 10.04 53.00 16-68 51.02-54.29
Test Values		Z= -2.013 **p = 0.044**	Z= -0.277 p = 0.782	Z= -1.733 p = 0.083	Z = -0,316 p = 0.752

Table 4. Distribution of menstrual characteristics of the participants on RDAS based on pre- and post-COVID-19 period (N=147)

Characteristics	Pre-COVID-19 Period Mean ± SD	Post-COVID-19 Period Mean ± SD	Test value
Frequency of menstruation	1.99±0.42	1.87±0.33	Z = -3.00 **p = 0.003**
Pain complaint	0.71±0.45	0.80±0.40	Z = -2.44 **p = 0.014**
Complaints of discharge, itching, odour etc.	0.24±0.43	0.46±0.50	Z = -4.58 **p = 0.001**
Applying to a health institution for the complaints	0.58±0.49	0.25±0.43	Z = -6.55 **p = 0.001**

Organisation (WHO) announced it as a pandemic on 11 March 2020 (19). Women have been reported to have a lower risk of serious illness and death due to COVID-19 infection than men. Nevertheless, existing social inequalities may impose an unequal burden of the pandemic (20). In many societies, gender-based inequalities expose women to barriers to accessing health resources and services. Due to travel restrictions, limited supplies, inadequate infection control measures, and disruption of the routine functioning of health systems during the pandemic, women have had difficulty in accessing to the healthcare system and their health have been negatively affected (21). Therefore, this study aimed to determine how COVID-19 disease affected women's menstrual irregularity and marital adjustment.

Menstruation affects a large part of the total life expectancy of women under healthy conditions, and when the existing studies are reviewed, we observe that similar to the present study, there have been a very limited number of studies on women's health since the COVID-19 pandemic broke out. It would not be wrong to suggest that the present study sets an example for future studies in this context. The mean age of the participants was 32.79±6.71 years and their mean menarche age was 13.44±1.41 years (Min: 11, Max: 18, Median: 13.00). In their study, Topatan and Kahraman reported that women had a mean age of 20.4±1.2 years and a mean menarche age of 13.32±1.36 years (22). The mean age was higher in the present study and the menarche age reported by the researchers is compatible with the results of the present study.

It was found that 21.8% of the participants reported that they smoked. The mean year of smoking was 12.18±9.40 years (Min: 1, Max: 25, Median: 10.00). 28.6% of the participants stated that they had a chronic disease. Health problems of the participants were painful bladder syndrome (3 people), asthma (3 people), kidney disease (3 people), diabetes (3 people), FMS (3 people), Hashimoto's thyroiditis (9 people), hypertension (5 people), migraine (6 people), myasthenia gravis (3 people), and PCOS (2 people). Although the cycle length varies among women and in different periods of reproductive age, it follows a regular course between the ages of 20–30. Many conditions such as smoking and chronic diseases may also affect the cycle duration, and led to changes (23). There are also studies which reported that pain, concentration, behavioural changes and negative affective problems in the premenstrual period were more common in smokers compared to non-smokers (24,25).

The participants reported that they had situations which caused significant difference in post-COVID-19 menstrual characteristics ($p<0.05$). The participants reported that the frequency of menstruation decreased, they complained of more pain, and their complaints such as discharge-itching-odour also increased in the post-COVID-19 period. Their requests to apply to a health institution also declined based on their statements, which was significantly different ($p<0.05$). When the studies on how natural disasters or other epidemics that have taken place in the world affected women's health are examined, it is observed that the number of such studies in the literature is very limited. When the literature has been examined, it has been found that stress and anxiety in women led to menstrual irregularities and problems. The results of the study by Hong-Li et al. on menstrual irregularity rates during the earthquake in Wenchuan reported that approximately 21% of the participants stated that their menstrual cycles became irregular after the Wenchuan

earthquake and that rate was significantly higher compared to the pre-earthquake period (6%, p <0.05) (26). In another study examining the effect of a 16-day war on the menstrual cycle, menstrual data of women just before the war and 3 and 6 months after the war were gathered and analysed in comparison with women who were not exposed to war. Consequently, it was found that women who perceived war as an acute stressor and were more exposed to war suffered from menstrual irregularities (7). Apart from these, the effects of natural disasters have not been analysed in the literature in terms of women's health, and it appears that menstrual health or reproductive system health has not been examined in the studies where general effects have been analysed and all studies have mostly focused on conditions related to pregnancy (27–31). Unfortunately, it appears that the articles only addressed the effects of COVID-19 disease on women's health in terms of maternal or pregnant women's health, and no details about menstrual health are available in the articles. Especially women's menstrual cycle pattern and dyadic adjustment with their spouses during the pandemic have been analysed in the literature, but studies that evaluated the menstrual cycle patterns of women who were diagnosed with COVID-19 and suffered from this disease have not been found (32,33). Contribution of the findings to the literature from this perspective is considered to be guiding in importance of evaluating the menstrual cycle pattern in negative circumstances such as pandemic and in women who had this disease.

Despite recent studies suggesting that stress can propagate into relationships and is associated with lower-quality relationships, some couples are able to maintain the quality of their relationships under stressful experiences. For example, while unfavourable experiences such as cancer, the death of a child, and natural disasters disrupt the relationship and adjustment of some couples, they improve the relational attachment of some couples (34–36). It was determined in the present study that the dyadic adjustment of women in the stressful atmosphere brought about by the COVID-19 isolation process was negatively affected. It is reported that pandemic-related alterations disrupt the functioning of the whole family and the stress that disturbs one person may also have negative effects on the spouse (37).

Only the score of the consensus factor of the participants from the RDAS differed in terms of pre– and post-COVID-19 periods. The mean score of consensus dropped after COVID-19 and this was found to be significant (p<0.05). Pietromonaco and Overall's model indicated that extrinsic stress may lead to maladaptive dyadic relationship processes such as negativity and hostility (38). The COVID-19 pandemic and lockdown compelled couples into social isolation and they had to come to grips with their daily lives (such as childcare). The propagation of stress can disrupt the dyadic adjustment of couples by making the time spent together shorter, weakening mutual feelings, diminishing communication, or increasing the appearance of certain disorders (anxiety, depression, rigidity) (39). Therefore, we believe that an online relationship training programme may be beneficial to increase and support their satisfaction with their relationship and dyadic adjustment.

Conclusion

In conclusion, it was observed that COVID-19 disrupted the menstrual cycle and marital adjustment of women who survived the disease. During the pandemic, the participants reported a drop in the frequency of menstruation in the post-COVID-19 period, an uptick in pain complaints, and an increase in complaints such as discharge-itching-odour. With these multifaceted conclusions about menstrual health, the present study, which is believed to shed light on future studies, has been a study that is almost a review in assessing the effects of the pandemic period we are going through from the standpoint of women's health. Moreover, the findings of the study indicated that dyadic adjustment was negatively affected in women with COVID-19 and in the stressful atmosphere brought about by the COVID-19 isolation process. The process we are going through should prioritise introducing marriage counselling programmes for individuals who have marital conflicts, encouraging them to receive couple and family therapy, and improving marital adjustment. Given the effect of monthly earnings on stress, it is important for these intervention programmes to be free of charge or affordable. Accordingly, it would be beneficial for postgraduate students of clinical psychology to engage in group intervention either as part of their internship or their thesis programmes, both academically and in terms of public health.

Etik Kurul Onayı: Bingöl Üniversitesi Sağlık Bilimleri Bilimsel Araştırma ve Yayın Etik Kurulun'dan (19.08.2021 tarihli ve 21/02 sayılı) etik onay alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - AB; Tasarım - AB, GÇ; Denetleme - AB, GÇ; Veri Toplanması ve/veya İşlemesi -AB, GÇ; Analiz ve Yorum - AB, GÇ; Literatür Taraması - AB; Yazıyı Yazan - AB, GÇ; Eleştirel İnceleme - AB.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Ethics Committee Approval: Ethical approval was obtained from Bingöl University Health Sciences Scientific Research and Publication Ethics Committee (dated 19.08.2021 and numbered 21/02).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AB; Design - AB, GÇ; Supervision - AB, GÇ; Data Collection and/ or Processing - AB, GÇ; Analysis and/or Interpretation - AB, GÇ; Literature Search - AB; Writing - AB, GÇ; Critical Reviews - AB.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Güney E, Unver H, Aksoy Derya Y, Ucar T. Effects of physical exercise levels on menstrual cycle. JDU Health Sci Inst. 2017;7(3):137–142.
2. Tanrıverdi G, Selcuk E, Okanlı A. Prevelance of premenstrual syndrome in university students. J Anatolia Nurs Health Sci. 2010;13(1):52–57.

3. Hachul H, Andersen ML, Tufik S. Sleep quality based on the use of different sanitary pads during menstruation. Int J Gynaecol Obstet. 2011;115(1):57–60. https://doi.org/10.1016/j.ijgo.2011.05.015
4. Arıoz A, Ege E. Effectiveness of education in increasing the quality of life and the control of premenstrual syndrome on university students who have premenstrual syndrome problem. J Gen Med (Dover). 2013;23(3):63–9.
5. Ucar T, Aksoy YD, Timur ST. A study on the status of and factors in irregular menstruation in university students. Turk Silahlı Kuvvetleri Koruyucu Hekim Bul. 2015;14(3):215–221. https://doi.org/10.5455/pmb.1-1413184900
6. Aydın Kartal Y, Kaykisiz EY. Investigation of the relationship between eating behaviors and premenstrual syndrome symptoms of midwifery students in the covid-19 outbreak. Med Sci. 2020;15(4):133–143.
7. Hannoun AB, Nassar AH, Usta IM, Zreik TG, Abu Musa AA. Effect of war on the menstrual cycle. Obstet Gynecol. 2007;109(4):929–932. https://doi.org/10.1097/01.AOG.0000257170.83920.de
8. Ünal E, Atik D, Gözüyeşil E. COVID-19 pandemic and women. Halic Uni J Health Sci. 2021;4(1)1–8. https://doi.org/10.48124/husagbilder.825346
9. National Health Service. Advice for everyone - Coronavirus (COVID-19), 2020. Available online (July 3, 2022): https://www.nhs.uk/covid-19-advice-and-services/
10. Jacob L, Smith L, Butler L, Barnett Y, Grabovac I, McDermott D, et al. Challenges in the practice of sexual medicine in the time of COVID-19 in the United Kingdom. J Sex Med. 2020;17(7):1229–1236. https://doi.org/10.1016/j.jsxm.2020.05.001
11. Şahin E, Satılmış İG. Sexuality and sexual health in the COVID-19 pandemic. Androl Bul. 2020;22(4):249–253. https://doi.org/10.24898/tandro.2020.24392
12. Türkseven A, Söylemez İ, Dursun P. Relationship between sexual dysfunctions and marital adjustment. Crisis Magazine. 2020;28(1):9–20.
13. Çolak AM, Cin FM. The effect of women's sexual satisfaction on their hapiness in relationships. Istanbul Commerce University J Social Sci. 2019;18(35):745–754.
14. Brezsnyak M, Whisman MA. Sexual desire and relationship functioning: the effects of marital satisfaction and power. J Sex Marital Ther. 2004;30(3):199–217. https://doi.org/10.1080/00926230490262393
15. Ojo AAE. Personality traits and sexual satisfaction as determinants of marital satisfaction among couples in Ibadan. AJOL. 2017;15(1):8421–8441.
16. Spanier GB. Measuring dyadic adjustment: new scales for assessing the quality of marriage and similar dyads. J Marriage Fam. 1976;38(1):15–28. https://doi.org/10.2307/350547
17. Busby DM, Christensen C, Crane DR, Larson JH. A revision of the dyadic adjustment scale for use with distressed and non distressed couples: construct hierarchy and multidimensional scales. J Marital Fam Ther. 1995;21(3):289–308. https://doi.org/10.1111/j.1752-0606.1995.tb00163.x
18. Gundogdu A. Relationships between self-construals and marital quality. PhD Thesis. Ankara: Middle East Technical University; 2007.
19. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52(11):549–57. https://doi.org/10.1152/physiolgenomics.00089.2020
20. Lindberg LD, VandeVusse A, Mueller J, Kirstein M. Early impacts of the COVID-19 pandemic: findings from the 2020 Guttmacher survey of reproductive health experiences. Guttmacher Institute, 2020. Accessed: December 13, 2022). https://doi.org/10.1363/2020.31482
21. Stein D, Ward K, Cantelmo C. Estimating the potential impact of COVID-19 on mothers and newborns in low-and middle-income countries. Heal Policy Plus Available online (December 18, 2022): https://scholar.harvard.edu/doritstein/publications/estimating-potential-impact-covid-19-mothers-and-newborns-low-and-middle
22. Topatan S, Kahraman Ş. The methods they applied for coping and the quality of life of university students living the premenstrual syndrome. J Anatolia Nurs Health Sci. 2020;23(1):35–44. https://doi.org/10.17049/ataunihem.481238
23. Rebar RW. The normal menstrual cycle, 2nd ed. Philadelphia, PA: W. B. Saunders Company; 1995. pp. 85–97.
24. Hirokawa K. Premenstrual symptoms in youngs Japanese women: agency, communion and lifestyle habits. Sex Roles. 2011;65(1):56–68. https://doi.org/10.1007/s11199-011-9992-6
25. Pınar A, Öncel S. Prevalance of premenstrual syndrome in women in between 15-49 ages (Antalya/Turkey). Turkiye Klinikleri J Gynecol Obst. 2011;21(4):227–237.
26. Li XH, Qin L, Hu H. Influence of the Wenchuan Earthquake on self-reported irregular menstrual cycles in surviving women. Gynecol Endocrinol. 2011;27:706–10. https://doi.org/10.3109/09513590.2010.526663
27. Sato K, Oikawa M, Hiwatashi M, Sato M, Oyamada N. Factors relating to the mental health of women who were pregnant at the time of the Great East Japan Earthquake: analysis from month 10 to month 48 after the earthquake. Biopsychosoc Med. 2016;10(22):1–6. https://doi.org/10.1186/s13030-016-0072-6
28. Fatem SR, Islam S, East L, Usher K. Women's health-related vulnerabilities in natural disasters: a systematic review protocol. BMJ Open 2019;9:e032079. https://doi.org/10.1136/bmjopen-2019-032079
29. Isaranuwatchai W, Coyte PC, McKenzie K, Noh S. Impact of the 2004 Tsunami on self-reported physical health in Thailand for the subsequent 2 years. Am J Public Health. 2013;103(11):2063–2070. https://doi.org/10.2105/AJPH.2013.301248
30. World Health Organization (WHO). Preventing unsafe abortion. Available online (December 28, 2022): https://iris.who.int/bitstream/handle/10665/112321/WHO_RHR_14.09_eng.pdf?sequence=9&isAllowed=y
31. Aly J, Haeger KO, Christy AY, Johnson AM. Contraception access during the COVID-19 pandemic. Contracept Reprod Med. 2020;5(17):1–9. https://doi.org/10.1186/s40834-020-00114-9
32. Connor J, Madhavan S, Mokashi M, Amanuel H, Johnson NR, Pace LE, et al. Health risks and outcomes that disproportionately affect women during the Covid-19 pandemic: a review. Soc Sci Med. 2020;266:113364. https://doi.org/10.1016/j.socscimed.2020.113364
33. Chattu VK, Yaya S. Emerging infectious diseases and outbreaks: implications for women's reproductive health and rights in resource-poor settings. Reprod Health. 2020;17(1):43. https://doi.org/10.1186/s12978-020-0899-y
34. Manne S, Badr H. Intimacy and relationship processes in couples' psychosocial adaptation to cancer. Cancer Suppl. 2008;112(11):2541–55. https://doi.org/10.1002/cncr.23450
35. Cohan CL, Cole SW. Life course transitions and natural disaster: marriage, birth, and divorce following hurricane hugo. J Fam Psychol. 2002;16(1):14–25. https://doi.org/10.1037/0893-3200.16.1.14
36. Gritz ER, Wellisch DK, Siau J, Wang HJ. Long-term effects of testicular cancer on marital relationships. Psychosomatics. 1990;31(3):301–312. https://doi.org/10.1016/S0033-3182(90)72168-8
37. Prime H, Wade M, Browne DT. Risk and resilience in family well-being during the COVID-19 pandemic. Am Psychol. 2020;75(5):631–643. https://doi.org/10.1037/amp0000660
38. Pietromonaco PR, Overall NC. Applying relationship science to evaluate how the Covid-19 pandemic may impact couples' relationships. Am Psychol. 2021;76(3):438–450. https://doi.org/10.1037/amp0000714
39. Bodenmann G. Dyadic coping and its significance for marital functioning. In: Revenson TA, Kayser K, Bodenmann G, editors. Couples Coping with Stress: Emerging Perspectives on Dyadic Coping. American Psychological Association; 2005. pp. 33–49. https://doi.org/10.1037/11031-002

Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of Health Sciences
ISSN 2717-8439
E-ISSN 2717-9257

YIU Saglik Bil Derg 2024;5:16–23
https://doi.org/10.51261/yiu.2024.1443870

ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Morphometric Changes in Liver and Pancreas in Experimental Colitis Model and Examination of the Effects of Vagal Stimulation on These Changes in Chronic Period

Deneysel Kolit Modelinde Karaciğer ve Pankreasta Görülen Morfometrik Değişiklikler ve Vagal Stimulasyonun Kronik Dönemde Bu Değişiklikler Üzerine Olan Etkilerinin İncelenmesi

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ABSTRACT

Introduction: Inflammatory bowel disease is a chronic and idiopathic disease of the digestive tract. The disease also affects the liver and pancreas. Our aim in the study was to examine the effect of transcutaneous auricular vagal nerve stimulation (TAVNS) on the healing of liver and pancreas damage.

Material and Method: 36 rats in 4 groups were included in this study. The Sham group was intracolonic injected with saline and TAVNS was not applied. The Sham+ TAVNS group was injected intracolonically with saline and TAVNS was applied. The TNBS+Sham group was injected with TNBS (trinitrobenzene sulfonic acid) intracolonically and TAVNS was not applied. In TNBS+ TAVNS group, both TNBS was injected and TAVNS was applied. Liver tissue and pancreas tissue were examined histologically and histomorphometrically.

Results: In our study, the final body weights of TNBS+Sham and TNBS+ TAVNS groups were found to be significantly lower than Sham and Sham+TAVNS groups. The liver and pancreas histopathological scores of the TNBS injected groups were significantly higher. In the liver hepatocytes of rats in TNBS+Sham group, necrotic areas, vacuolar degeneration, and sinusoidal congestion were observed in some regions. Degenerative findings in liver sections of group TNBS+ TAVNS group were also partially reduced. The number and area of Langerhans islets in the pancreas of the animals in TNBS+Sham and TNBS+ TAVNS groups were found to be lower than in Sham and Sham+ TAVNS groups.

Conclusion: In this study, we found that TNBS-induced colitis in rats caused histopathological and histomorphometric changes in the liver and pancreas, causing weight loss, and that TAVNS had therapeutic effects on these changes.

Keywords: Colitis, vagal nerve stimulation, liver, pancreas

ÖZ

Giriş: İnflamatuvar bağırsak hastalığı, sindirim sisteminin kronik ve idiyopatik bir hastalığıdır. Hastalık ayrıca karaciğeri ve pankreası da etkilemektedir. Çalışmadaki amacımız transkutanoz aurikular vagal sinir stimulasyonunun (TAVNS) karaciğer ve pankreas hasarının iyileşmesi üzerindeki etkisini incelemektir.

Materyal ve Metod: Çalışmamız 4 grup halinde 36 sıçanla yapılmıştır. Sham grubuna intrakolonik salin enjeksiyonu yapılmış ve TAVNS uygulanmamıştır. Sham+ TAVNS grubuna intrakolonik olarak salin enjekte edilmiş ve TAVNS uygulanmıştır. TNBS+Sham grubuna intrakolonik olarak TNBS (trinitrobenzen sülfonik asit) enjekte edilmiş ve TAVNS uygulanmamıştır. TNBS+TAVNS grubuna hem TNBS enjekte edilmiş hem de TAVNS uygulanmıştır. Karaciğer dokusu ve pankreas dokusu histolojik ve histomorfometrik olarak incelenmiştir.

Bulgular: Çalışmamızda TNBS+Sham ve TNBS+TAVNS gruplarının son vücut ağırlıkları Sham ve Sham+TAVNS gruplarına göre anlamlı olarak düşük bulundu. TNBS uygulanan grupların karaciğer ve pankreas histopatolojik skorları anlamlı olarak yüksekti. TNBS+Sham grubundaki sıçanların karaciğer hepatositlerinde bazı bölgelerde nekrotik alanlar, vakuolar dejenerasyon ve sinüzoidal konjesyon gözlendi. Grup TNBS+TAVNS grubunun karaciğer kesitlerindeki dejeneratif bulgular kısmen azaldı. TNBS+Sham ve TNBS+TAVNS gruplarındaki hayvanların pankreasındaki Langerhans adacıklarının sayısı ve alanı, Sham ve Sham+ TAVNS gruplarına göre daha düşük bulundu.

Sonuç: Bu çalışmada sıçanlarda TNBS kaynaklı kolitin karaciğer ve pankreasta histopatolojik ve histomorfometrik değişikliklere neden olarak kilo kaybına yol açtığı ve TAVNS'nun bu değişiklikler üzerinde terapötik etkilerinin olduğu tespit edilmiştir.

Anahtar Sözcükler: Kolit, vagal sinir stimulasyonu, karaciğer, pankreas

Cite this article as: Koçak Ö, Gözil R, Atalar K, Akarca Dizakar SÖ, Alim E, Soylu A, Bahçelioğlu M. Morphometric Changes in Liver and Pancreas in Experimental Colitis Model and Examination of the Effects of Vagal Stimulation on These Changes in Chronic Period. YIU Saglik Bil Derg 2024;5:16–23

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Geliş Tarihi/Received: 03.05.2024, **Kabul Tarihi/Accepted:** 14.05.2024, **Çevrimiçi Yayın Tarihi/Available Online Date:** 31.05.2024

Introduction

Inflammatory bowel disease (IBD) is a chronic autoimmune condition whose exact cause remains unknown. It encompasses two primary types: ulcerative colitis and Crohn's disease. IBD is quite common in the world, and its incidence is increasing (1). While the exact cause remains incompletely understood, it is recognized that both genetic predisposition and environmental influences play significant roles in the development of the disease (2-4). Ulcerative colitis is characterized by inflammation restricted to the colon, whereas Crohn's disease can affect any segment of the gastrointestinal tract, often manifesting in the small and large intestines (5). Most of the clinical findings are similar in both types of IBD. Some of those are abdominal pain, diarrhea, and weight loss (6). Although this disease is predominant, especially in the intestines, extraintestinal findings are also seen in a significant part of the patients. Studies have reported that IBD also affects the liver and pancreas (7, 8). In treatment, medical and surgical methods keep the disease in remission for a while and suppress the symptoms, but side effects and long-term recurrence are common. For all these reasons, non-invasive, side-effect-free, easily applicable methods are needed in the treatment of IBD (9, 10). The experimental colitis model induced by TNBS (trinitrobenzene sulfonic acid), which we used in our study, is similar to human ulcerative colitis and is used in IBD research (11).

The vagus nerve holds the distinction of being the longest cranial nerve in the human body, coming out of the brain stem and extending to the thorax and abdomen, providing parasympathetic innervation to the organs here. It has special importance because it connects with both the central nervous system and the enteric nervous system. Recent research has stated that the vagus nerve provides an anti-inflammatory effect in cases of chronic inflammation through its wide neuronal network in the brain and afferent and efferent fibers extending to the body (12,13). The curative effect of the vagus nerve has been known since ancient times, and many methods have been used to stimulate the vagus nerve until today (14). Transcutaneous auricular vagal nerve stimulation (TAVNS) is a method based on stimulating the auricular branch, the only cutaneous branch of the vagus nerve, with electrical impulses over the skin. This method has received US Food and Drug Administration (FDA) approval for resistant epilepsy. Furthermore, the effectiveness of TAVNS method in treating many diseases such as depression, migraine, rheumatoid arthritis, and cardiac insufficiency is still being investigated. The fact that it is non-invasive, easily applicable, portable, and has minimal side effects makes this method advantageous (15).

In this research, our aim was to assess alterations in the liver and pancreas within a rat model of experimental colitis, as well as investigate the impacts of TAVNS on these changes during the chronic phase using histomorphometric and histopathological analysis.

Material and Methods

This research was carried out at Gazi University Experimental Research and Animal Laboratory. Ethical approval of the study was obtained from Animal Research Committee at Gazi University (G.Ü.ET 21.041). The study received support from the Gazi University Scientific Research Projects Unit under project number TTU-2021-7301. 36 adult male Sprague-Dawley rats, weighing between 180-200 g, were utilized for the study and maintained under controlled conditions. The temperature was maintained at 22±1°C, with humidity levels between 60-70%. The animals were subjected to a 12-hour light and 12-hour dark cycle. Adequate provisions were made to ensure that the rats had ad libitum access to food and water. They were housed in groups of three in cages. Prior to the commencement of the experiments, the rats were allowed to acclimate to these conditions for 7 days.

Experimental Groups

Four major groups of 9 rats each were created randomly from the total population of the rats. Animals in the Sham group received an intracolonic saline injection and TAVNS was not performed. Animals in Sham+TAVNS group received an intracolonic saline injection and TAVNS. Animals in Group TNBS+Sham group were injected with intracolonic TNBS and not TAVNS. Animals in TNBS+TAVNS group received intracolonic TNBS injection and TAVNS.

Colitis induction in TNBS+Sham and TNBS+TAVNS groups was applied according to the classical TNBS (trinitrobenzene sulfonic acid) colitis model developed by Morris et al. (11). The rats, after 12 hours of food deprivation, were anesthetized using a combination of 50 mg/kg ketamine and 0.05 mg/kg acepromazine. An 8 cm long cannula was inserted through the anus into the colon and TNBS was dripped in 50% ethanol (total volume, 0.25 ml) at 10 mg per rat (Figure 1). The rats were kept in an upside-down position so that TNBS could remain in the colon after intracolonic administration (Figure 2)

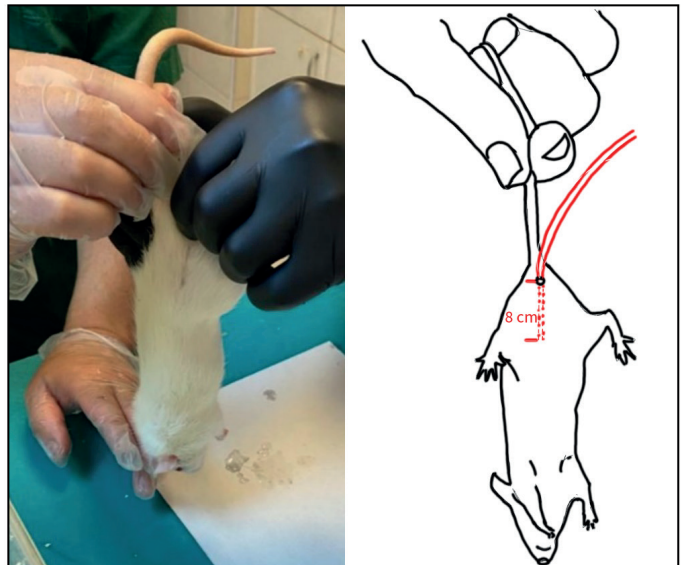

Figure 1. Colitis induction

Transcutaneous Auricular Vagal Nerve Stimulation (TAVNS)

The Vagustim® device, created for use in animal trials, was used to apply TAVNS. Vagustim was developed to non-invasively and bilaterally stimulate the auricular branch of the vagus nerve. It consists of two units, the stimulator, and the ear electrodes. While the stimulator generates electrical impulses, the ear electrode transfers the stimulus through the skin to the vagus nerve in both ears (16).

TAVNS was applied to the rats in Sham+TAVNS group and TNBS+TAVNS group under anesthesia for 30 minutes twice a day for 10 days. The ear electrodes of the device were placed in the tragus of the rats bilaterally, including the cavum concha, and stimulation was applied (Figure 3 and Figure 4). The same procedure was applied to Sham group and TNBS+Sham group but no stimulation. In our study, TAVNS current intensity was 1 mA, pulse duration was 500 µs, the frequency was 10 Hz, the voltage was 5 V, and the application was made accordingly. The application time continued for 30 minutes. Stimulation was conducted in cycles consisting of 30 seconds of stimulation followed by 30 seconds of rest. Consequently, each session involved a total of 15 minutes of vagal nerve stimulation.

Surgical Procedure

Rats were weighed before colitis induction and after 10 days of vagal nerve stimulation. On the 10th day after colitis induction, rats were deeply anesthetized using intramuscularly (ketamine 150 mg/kg and acepromazine 0.15 mg/kg). Then, rats were transcardially perfused with saline. Liver and pancreas tissues were removed. The liver and pancreas were weighed.

Histological Method

The liver and pancreas tissues of the experimental groups were fixed with 4% paraformaldehyde for light microscopic examination. Sections of 4 µm thickness were taken with a microtome (RM 2245, Germany) from paraffin blocks obtained after histological follow-up procedures. Tissues were stained with Hematoxylin-Eosin and Masson's Trichrome.

Liver and pancreas sections were stained in Harris Hematoxylin solution. Histopathological scoring was performed in the liver and pancreas tissues, and the area of the central vein in the liver and the area of Langerhans islets, and the number of Langerhans islets in the pancreas tissues were determined. According to the liver inflammation score, 0 points were given if there was no inflammation, score 1 if there was mild lobular/mild portal inflammation, score 2 if there was moderate lobular/portal inflammation, and score 3 if there was severe lobular/portal inflammation (17). According to the liver necrosis score, 0 points if there is no necrosis, score 1 if there is hepatic parenchymal necrosis below 10%, score 2 if 10-25% liver parenchymal necrosis is present, and score 3 if there is liver parenchymal

Figure 2. Upside-down position

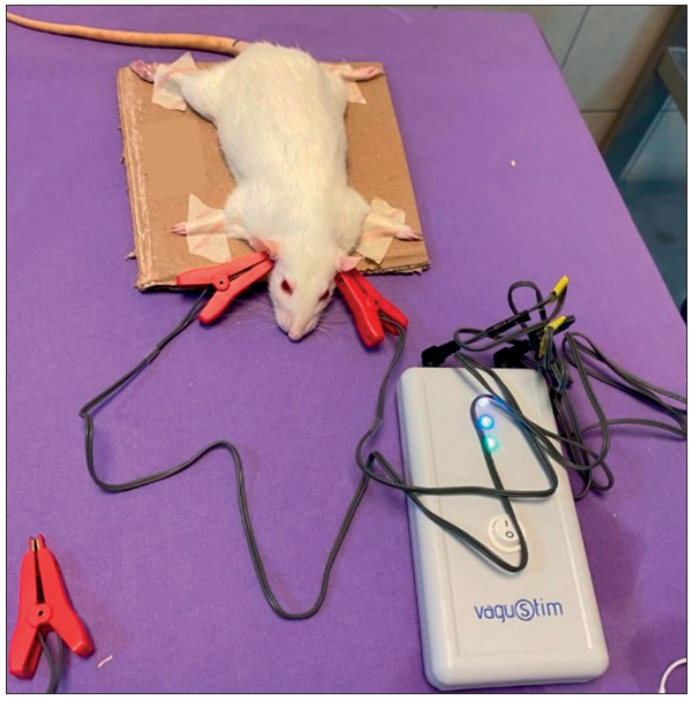

Figure 3. Transcutaneous auricular vagal nerve stimulation

Figure 4. Placement of the ear electrode

Table 1. Weight averages of the experimental groups

Mean±SD (standard deviation)	Sham Group Saline / TAVNS (-)	Sham+TAVNS Group Saline / TAVNS (+)	TNBS+Sham Group TNBS / TAVNS (-)	TNBS+TAVNS Group TNBS / TAVNS (+)
Final body weight (kg)	196.789±5.17	200.125±30.32	161.667±24.56	167.333±18.83
Liver weight (g)	7.397±0.61	9.446±1.20	6.583±0.87	9.030±1.36
Pancreas weight (g)	0.804±0.22	0.665±0.14	0.730±0.21	0.620±0.35

Table 2. Liver histological findings of the experimental groups.

Mean±SD	Sham Group Saline / TAVNS (-)	Sham+TAVNS Group Saline / TAVNS (+)	TNBS+Sham Group TNBS / TAVNS (-)	TNBS+TAVNS Group TNBS / TAVNS (+)
Liver Histopathological Score	0.4±0.50	0.7±0.57	2.45±0.82	2.05±0.60
Central vein diameter (μ)	55149±109	58325±132	53747±166	54134±135
Percentage of collagen fiber area (%)	2.79±2.6	3.19±2.3	10.28±6.9	7.27±5.7
Number of islets of Langerhans	13.71±5.02	12±4.69	5±1.86	6.83±3.18
Langerhans islet area (μ)	0.043±0.002	0.052±0.004	0.034±0.004	0.048±0.006
Pancreas histopathological score	0.5±0.51	0.5±0.51	2.3±1.03	2.05±0.60

necrosis above 25% (18). Pancreas histopathological scoring was conducted using parameters such as edema (rated on a scale of 0-4 points), acinar necrosis (0-4 points), hemorrhage and fat necrosis (0-4 points), as well as inflammation and perivascular infiltration (0-4 points), as outlined in a previous study (19). The mean scores of the rats were determined according to the groups.

Collagen fiber distribution was evaluated by performing Masson's Trichrome staining (Code: RRSK20-100, Atom Scientific, United Kingdom) on liver tissue sections of the experimental groups. The images captured using the Leica DM 4000B microscope from Germany were analyzed using the Leica LAS V4.9 program. The percentage of liver collagen fiber area was calculated utilizing Image J, a Java-based software program developed by the National Institutes of Health.

Statistical Analysis

SPSS (Statistical Package for Social Science, 22nd version) package program was used for statistical analysis of the obtained data. The normality of the data distribution was assessed using the Shapiro-Wilk test. A one-way analysis of variance (ANOVA) followed by the Tukey test was conducted. Results were deemed significant if the p-value was less than 0.05. In addition, the mean±standard deviation value was calculated.

Results

Weight Findings

At the end of the experiment, the final body weights of the rats were measured, and the average weight for each group was calculated. The mean weight of Sham group was found to be significantly higher than group TNBS+Sham group ($p<0.01$). The mean body weight of Sham+TAVNS group was higher than TNBS+TAVNS group ($p<0.05$). The mean liver weight of Sham group was found to be significantly lower than Sham+TAVNS group ($p<0.01$). The mean liver weight of TNBS+Sham group was significantly lower than TNBS+TAVNS group ($p<0.001$). Considering the mean pancreas weights of the rats; the mean pancreas weight of Sham group was higher than TNBS+Sham group, but the difference was not statistically significant ($p>0.05$), (Table 1).

Liver Histological Findings

In the liver sections examined after hematoxylin-eosin staining, cords consisting of polygonal hepatocytes extending radially from the central vein to the periphery and sinusoids between the cords were observed in the saline-injected groups (Sham and Sham+TAVNS groups). Hepatocytes with acidophilic staining had normal histological structure, some hepatocytes were observed to be binucleated. Liver sinusoidal spaces were in normal arrangement (Figure 5 A and B). In the group that received TNBS injection but did not receive TAVNS (TNBS+Sham group), inflammation in some lobular and portal areas was noted, as well as deterioration in hepatocyte structures and radial arrangement. Vacuolar degeneration and sinusoidal congestion were detected in certain areas of the hepatocytes. Localized necrotic areas were detected in the liver parenchyma (Figures 5 C and D). In the sections of both TNBS injection and TAVNS groups, as a result of histopathological scoring, it was observed that degenerative findings continued to exist even though they were partially reduced (Figure 5 E and F).

According to the histopathological scoring that determines the level of necrosis and inflammation in the livers of rats; the score of TNBS+TAVNS group was lower than TNBS+Sham group, but it was not statistically significant ($p>0.05$). The histopathological score of TNBS+Sham group was significantly higher than Sham group ($p<0.001$). The histopathological score of TNBS+TAVNS group was significantly higher than Sham+TAVNS group ($p<0.001$). There was no statistically significant difference between all groups in terms of liver central vein diameters of rats ($p>0.05$), (Table 2).

Following Masson's Trichrome staining, the percentage of collagen fiber area was determined. Subsequently, the collagen fiber area percentage was calculated for each group. Liver tissues were evaluated between groups, and no statistical significance was observed between the saline-injected groups (Sham and Sham+TAVNS groups). In the non-TAVNS treated groups, the collagen fiber distribution of those injected with TNBS was significantly lower than those injected with saline ($p<0.0001$). It was found that in the TNBS-injected groups, the percentage of collagen fiber area decreased in the non-TAVNS group compared to the TAVNS group, but this decrease was not statistically significant. In the TNBS-injected groups, the fibrotic changes observed in the livers of the non-TAVNS group (TNBS+Sham) were also partially reduced compared to the TNBS-injected and TAVNS-treated (TNBS+TAVNS) groups (Figure 6 A-F).

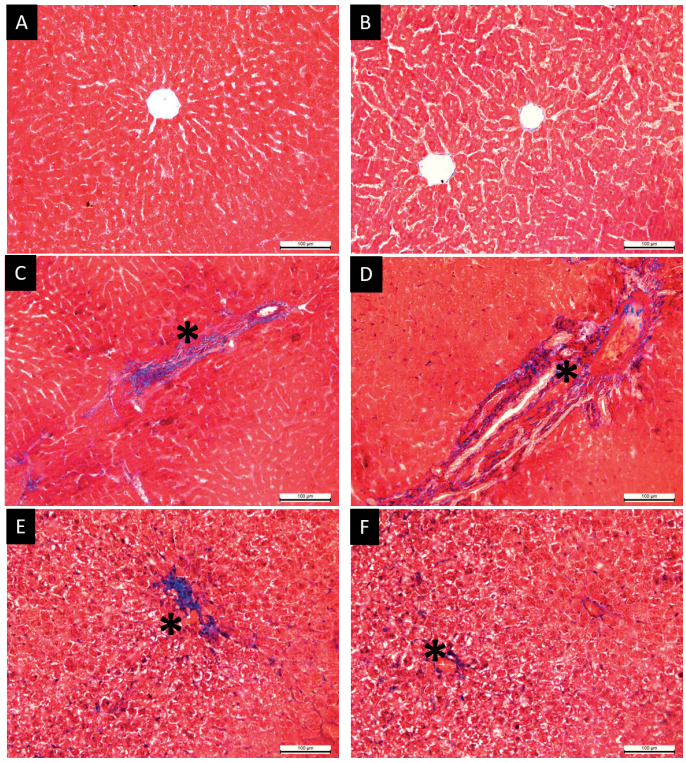

Figure 6. Liver tissue sections of the experimental groups were stained with Masson's Trichrome (MT). (A) Sham group; (B) Sham+TAVNS group, (C, D) TNBS+Sham group; (E, F) TNBS+TAVNS group, Collagen fibers (*) are seen as blue areas (MT, X200)

Pancreas Histological Findings

The exocrine section containing pancreas acini structures and endocrine areas including islets of Langerhans were observed in normal histological structure in pancreas sections stained with Hematoxylin-Eosin belonging to Sham group and Sham+TAVNS group. Interlobular connective tissue areas, intralobular canal structures, and vascularized formations had normal histological structures. While the islets of Langerhans were arranged as cords, the acini structures contained cells with basophilic cytoplasm at the base and eosinophilic cytoplasm at the apical (Figure 7 A and B).

In the exocrine pancreas tissue of TNBS+Sham group, acinar necrosis, hemorrhage, and perivascular infiltration were observed in some areas. In some islets of Langerhans, congestion between cells was noted. Lymphocytic infiltration was detected in interlobular areas, and atrophy was observed in some acinar cells in exocrine pancreas sections (Figures 7 C and D). It was noted that a decrease in acinar atrophy and lymphocytic infiltration was observed in sections belonging to TNBS+TAVNS group, and pancreas histopathological changes continued in some sections (Figure 7 E and F).

The average number of islets of Langerhans in the rat pancreas was calculated for each group. In the groups that did not undergo TAVNS, the saline-injected group exhibited significantly higher numbers of Langerhans islets compared to the TNBS-injected group ($p<0.01$). Within the TNBS-injected groups, although the TAVNS group showed a higher number of islets of Langerhans, the difference was not statistically significant ($p>0.05$). Regarding the average area of Langerhans islets in the rat pancreas, among the TAVNS groups, the TNBS-injected group displayed smaller islet areas compared to the non-TNBS-injected group.

Among the saline-injected groups, the islet areas in the group without TAVNS were observed to be lower than the group where TAVNS was applied. However, these differences

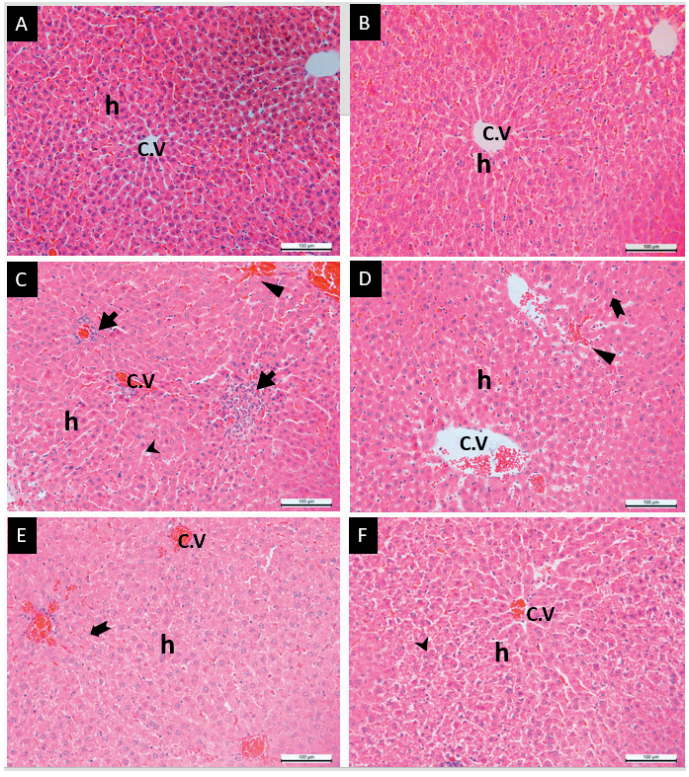

Figure 5. Liver tissue sections of the experimental groups stained with Hematoxylin-Eosin (HE); (A) Sham Group; (B) Sham+TAVNS Group, (C, D) TNBS+Sham Group; (E, F) TNBS+TAVNS Group, central vein (c.v), hepatocyte (h), inflammatory areas (➔), vacuolar degeneration (➤), necrosis (➡), congestion (▶) (HE, x200)

were not statistically significant (p>0.05). Regarding the histopathological scoring of pancreas tissues in rats, among the groups not subjected to TAVNS, the histopathological score of the TNBS injection group was markedly higher than that of the saline injection group (p<0.001). Similarly, among the TAVNS groups, the histopathological score of the TNBS injection group was significantly elevated compared to the saline injection group (p<0.001). (Table 2).

Discussion

Inflammatory bowel disease (IBD) is a prevalent, chronic disorder affecting the gastrointestinal tract, the exact cause of which remains uncertain. It encompasses two main types: ulcerative colitis and Crohn's disease, both of which can significantly impair quality of life and occasionally contribute to the development of depression and anxiety (20). There are many studies on the epidemiological, immunological, biochemical, and microbiological features of IBD (21). However, liver and pancreas involvement, which is one of the extraintestinal manifestations of the disease, has not been adequately studied although it is common.

Duan et al. (17) investigated the effects of a substance called vitexin on liver damage due to IBD in a study on mice. In the study, the colitis model induced by dextran sodium sulfate was used and the histopathology of the liver damage of the subjects was examined by Hematoxylin-Eosin staining. As a result of the study, it was stated that colitis causes inflammation and hepatocyte necrosis in the liver (22). In the study conducted by Lunder et al. (23), the researchers investigated the incidence of primary sclerosing cholangitis in patients with IBD. They examined the findings of primary sclerosing cholangitis 20 years later in 470 people diagnosed with IBD in Norway between 1990 and 1993. They stated that they detected primary sclerosing cholangitis in 7% of the patients, and they found biochemical markers indicating primary sclerosing cholangitis in 65% (23). In the research conducted by Değer et al. (24), the investigation centered around oxidative damage and apoptosis in rats with TNBS-induced colitis. The study also delved into the therapeutic potential of glutamine in mitigating damage to the colon and pancreas during colitis. A cohort of 28 male rats was randomly divided into four groups for the experiment. Group 1 received TNBS injection exclusively, Group 2 received TNBS injection along with glutamine supplementation, Group 3 received glutamine alone, and Group 4 received saline. It has been reported that interstitial edema and acinar vacuolization are observed in pancreas sections stained with Hematoxylin-Eosin and that glutamine treatment may have a protective effect on pancreas degeneration (24).

Today, IBD is tried to be treated with medical and surgical methods. However, both drug side effects and the recurrence of the disease create problems for patients and physicians.

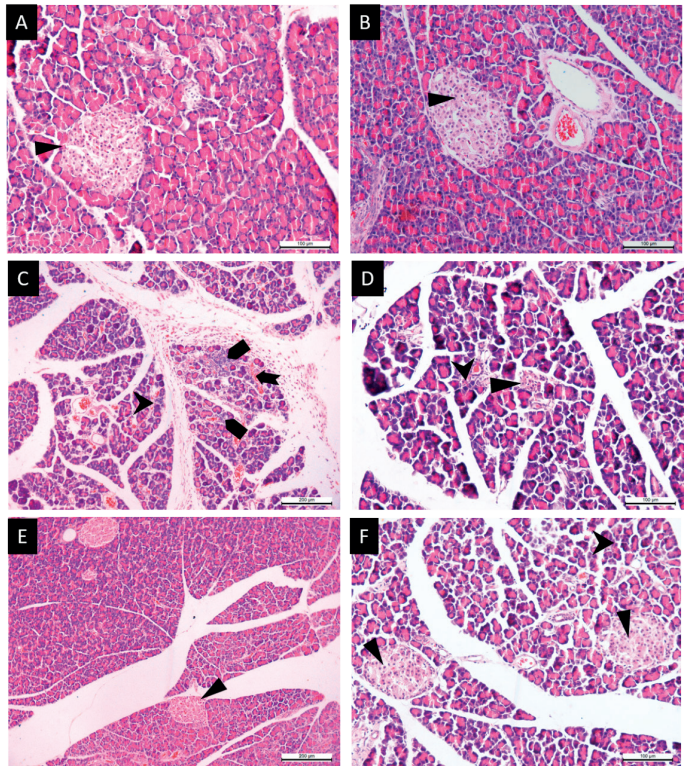

Figure 7. Images of the sections of the pancreas tissue stained with Hematoxylin-Eosin. (A) Sham group; (B) Sham+TAVNS group, (C, D) TNBS+Sham group; (E, F) TNBS+TAVNS group, Islets of Langerhans (►), atrophic acini (➤), perivascular infiltration (➡) and hemorrhage (➥) (HE, A, B, D, F: X200; C and E: X100)

Sympathetic system dominance is observed in 35% of people with Crohn's disease as a result of impaired parasympathetic activity (25). Recently, the focus has been on the vagus nerve's role in modulating inflammatory responses.

A study on mice by Ghia et al. (26) investigated the anti-inflammatory effect of the vagus nerve on colitis that persisted for several weeks. Using the dextran sodium sulfate-induced colitis model, vagotomy was performed in one group and not in the other group. When inflammatory markers and cytokine profiles were examined between groups, inflammation in vagotomized mice was more severe than in the control group. This indicates that the vagus nerve may have a protective role in IBD (26). Meregnani et al (27) investigated the effect of vagal nerve stimulation on IBD in TNBS-induced experimental colitis model in rats. Vagal nerve stimulation was performed with a stimulator surgically placed in the cervical region, and stimulation was performed 3 hours a day for 5 consecutive days. It has been reported that weight loss improved, and inflammatory markers were positively affected in rats that received vagal nerve stimulation (27). Rawat et al. (28), in a study on rats, investigated the effectiveness of TAVNS in 2-Dimethylhydrazine-induced colon cancer. In conclusion, it has been reported that vagal nerve stimulation of the transcutaneous auricular nerve improves autonomic function, reduces oxidative damage, and increases the activation of the

cholinergic anti-inflammatory pathway. TAVNS prevented the carcinogenic effects of 2-Dimethylhydrazine by increasing mitochondrial apoptosis (28).

Conclusion

In this study, it was observed that TNBS-induced colitis led to a reduction in body weight and an elevation in stress levels in rats. Examination of tissue sections stained with hematoxylin-eosin revealed inflammation in liver tissue, structural deterioration in hepatocytes, and necrosis in certain parenchymal areas due to colitis. While TAVNS was found to mitigate these degenerative changes, it did not completely prevent them. In the sections stained with Masson's Trichrome, fibrotic changes, and inflammatory areas were observed with the increase of collagen tissue in the liver tissue. Although not statistically significant, TAVNS reduced fibrotic changes in the liver. In the pancreas tissue, it has been observed that colitis reduces the number and area of Langerhans islets. This result suggested the deterioration in the endocrine functions of the pancreas. As a result of the histopathological scoring of the exocrine pancreas; exocrine pancreas degeneration was noted in the TNBS-injected groups. TAVNS reduced exocrine pancreas degeneration, but this effect was not statistically significant.

As a result, it is determined that TAVNS has a healing effect on the alterations that the IBD causes in the liver and pancreas. This research will support the treatment of IBD.

We predict that TAVNS is promising in IBD because it is easy to apply, non-invasive, has minimal side effects; and reveals an anti-inflammatory effect on the vagus nerve, but it should be supported by further experimental research.

Etik Kurul Onayı: Gazi Üniversitesi Hayvan Deneyleri Yerel Etik Kurulu'ndan (G.Ü.ET 21.041 kodu ile) etik onay alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - MB, ÖK, RG, EA; Tasarım - ÖK, KA, SÖAD, EA; Denetleme - MB, RG; Veri Toplanması ve/veya İşlemesi -ÖK, EA, AS; Analiz ve Yorum - MB, RG, SÖAD; Literatür Taraması - ÖK, AS; Yazıyı Yazan - ÖK, KA, AS; Eleştirel İnceleme - MB, EA.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.

Finansal Destek: Bu çalışma Gazi Üniversitesi Bilimsel Araştırma Projeleri Birimi (BAP) tarafından (TTU-2021-7301 proje numarası ile) desteklenmiştir.

Ethics Committee Approval: Ethical approval of the study was obtained from the Animal Research Committee at Ankara Gazi University (G.Ü.ET 21.041).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - MB, ÖK, RG, EA; Design - ÖK, KA, SÖAD, EA; Supervision - MB, RG; Data Collection and/ or Processing - ÖK, EA, AS; Analysis and/or Interpretation - MB, RG, SÖAD; Literature Search - ÖK, AS; Writing - ÖK, KA, AS; Critical Reviews - MB, EA.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The study was supported by Gazi University Scientific Research Projects Unit with project number TTU-2021-7301.

References

1. Baron JH. Inflammatory bowel disease up to 1932. The Mount Sinai Journal of Medicine, New York. 2000;67(3):174-89.
2. Jowett S, Seal C, Pearce M, Phillips E, Gregory W, Barton J, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut. 2004;53(10):1479-84.
3. Higuchi LM, Khalili H, Chan AT, Richter JM, Bousvaros A, Fuchs CS. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. The American journal of gastroenterology. 2012;107(9):1399.
4. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, et al. Sleep duration affects risk for ulcerative colitis: a prospective cohort study. Clinical Gastroenterology and Hepatology. 2014;12(11):1879-86.
5. Cosnes J, Gower–Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785-94. e4.
6. Ballester Ferré MP, Bosca-Watts MM, Minguez Pérez M. Enfermedad de Crohn. Medicina Clínica. 2018:26-33.
7. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. Up to date [online]. 2011.
8. Park SH, Kim D, Ye BD, Yang S-K, Kim J-H, Yang D-H, et al. The Characteristics of Ulcerative Colitis Associated With Autoimmune Pancreatitis. Journal of Clinical Gastroenterology. 2013;47(6):520-5.
9. Chaparro M, Ordás I, Cabré E, Garcia-Sanchez V, Bastida G, Peñalva M, et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. Inflammatory bowel diseases. 2013;19(7):1404-10.
10. Benjamin I, Griggs RC, Fitz JG. Andreoli and Carpenter's Cecil Essentials of Medicine E-Book: Elsevier Health Sciences; 2015.
11. Morris GP, Beck PL, Herridge MS, Depew WT, Szewczuk MR, Wallace JL. Hapten-induced model of chronic inflammation and ulceration in the rat colon. Gastroenterology. 1989;96(2):795-803.
12. Cheng J, Shen H, Chowdhury R, Abdi T, Selaru F, Chen JDZ. Potential of Electrical Neuromodulation for Inflammatory Bowel Disease. Inflammatory Bowel Diseases. 2019;26(8):1119-30.
13. Briand M-M, Gosseries O, Staumont B, Laureys S, Thibaut A. Transcutaneous Auricular Vagal Nerve Stimulation and Disorders of Consciousness: A Hypothesis for Mechanisms of Action. Frontiers in Neurology. 2020;11(933).
14. Hou PW, Hsu HC, Lin YW, Tang NY, Cheng CY, Hsieh CL. The History, Mechanism, and Clinical Application of Auricular Therapy in Traditional Chinese Medicine. Evid Based Complement Alternat Med. 2015;2015:495684.
15. Mertens A, Raedt R, Gadeyne S, Carrette E, Boon P, Vonck K. Recent advances in devices for vagus nerve stimulation. Expert review of medical devices. 2018;15(8):527- 39.
16. Vagus Nerve Stimulation (VNS) Device For Animal Research. https://vagustim.io/vagus-nerve-stimulation-animal-research-2/ (01.01.2022).
17. Duan S, Du X, Chen S, Liang J, Huang S, Hou S, et al. Effect of vitexin on alleviating liver inflammation in a dextran sulfate sodium (DSS)-induced colitis model. Biomedicine & Pharmacotherapy. 2020;121:109683.
18. Zhang L, Zhao Y, Fan L, Xu K, Ji F, Xie Z, et al. Tectorigenin protects against experimental fulminant hepatic failure by regulating the TLR4/mitogen-activated protein kinase and TLR4/nuclear factor-κB pathways and autophagy. Phytotherapy Research. 2019;33(4):1055-64.
19. Fusco R, Cordaro M, Siracusa R, D'Amico R, Genovese T, Gugliandolo E, et al. Biochemical evaluation of the antioxidant effects of hydroxytyrosol on pancreatitis-associated gut injury. Antioxidants. 2020;9(9):781.
20. Fusco R, Cordaro M, Siracusa R, D'Amico R, Genovese T, Gugliandolo E, et al. Biochemical evaluation of the antioxidant effects of hydroxytyrosol on pancreatitis-associated gut injury. Antioxidants. 2020;9(9):781.
21. Kim H-S, Berstad A. Experimental colitis in animal models. Scandinavian journal of gastroenterology. 1992;27(7):529-37.
22. Duan S, Du X, Chen S, Liang J, Huang S, Hou S, et al. Effect of vitexin on alleviating liver inflammation in a dextran sulfate sodium (DSS)-induced colitis model. Biomedicine & Pharmacotherapy. 2020;121:109683.
23. Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, et al. Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease. Gastroenterology. 2016;151(4):660-9.e4.
24. Değer C, Erbil Y, Giriş M, Yanik BT, Tunca F, Olgaç V, et al. The Effect of Glutamine on Pancreatic Damage in TNBS-Induced Colitis. Digestive Diseases and Sciences. 2006;51(10):1841-6.

25. Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn's disease. Scandinavian journal of gastroenterology. 1991;26(4):361- 6.
26. Ghia J-E, Blennerhassett P, El-Sharkawy RT, Collins SM. The protective effect of the vagus nerve in a murine model of chronic relapsing colitis. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2007;293(4):G711-G8.
27. Meregnani J, Clarençon D, Vivier M, Peinnequin A, Mouret C, Sinniger V, et al. Anti-inflammatory effect of vagus nerve stimulation in a rat model of inflammatory bowel disease. Autonomic Neuroscience. 2011;160(1):82-9.
28. Rawat JK, Roy S, Singh M, Guatam S, Yadav RK, Ansari MN, et al. Transcutaneous vagus nerve stimulation regulates the cholinergic anti-inflammatory pathway to counteract 1, 2-dimethylhydrazine induced colon carcinogenesis in albino wistar rats. Frontiers in pharmacology. 2019;10:353.

Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of Health Sciences
ISSN 2717-8439
E-ISSN 2717-9257

YIU Saglik Bil Derg 2024;5:24–30
https://doi.org/10.51261/yiu.2024.1358528

DERLEME / REVIEW

Contemporary Advancements in the Early Detection of Melanoma and the Horizon of Home- Based Diagnostic Approaches

Melanomun Erken Teşhisindeki Güncel İlerlemeler ve Ev Tabanlı Tanısal Yaklaşımların Geleceği

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ABSTRACT

Melanoma remains a significant health concern, given its escalating incidence and associated mortality rates. In recent years, there have been noteworthy advancements in early detection methods in this domain. While the literature corroborates the effectiveness of these methods in enhancing early detection potential, there exists pronounced skepticism regarding their broader implications on overall survival outcomes. In this exhaustive review, we delve into the cutting-edge diagnostic methodologies developed for melanoma detection that transcend the need for direct dermatological intervention. Our nuanced analysis highlights the existence of several home-based and non-specialized techniques offering commendable precision in melanoma detection. However, deeper investigations are warranted regarding their efficacy in clinical practice, reliability, and cost-effectiveness. The review also encompasses discussions about the transformative potential artificial intelligence-centric diagnostic methods might hold as the paramount tools for future prognosis.

Keywords: Melanoma, early-detection, self-assessment, primary healthcare, artificial intelligence, clinical application

ÖZ

Melanom, yükselen insidansı ve buna bağlı mortalite oranları nedeniyle ciddi bir sağlık endişesi olarak kalmaya devam etmektedir. Son yıllarda, bu alanda erken teşhis yöntemlerinde kayda değer gelişmeler yaşanmıştır. Literatürde, bu yöntemlerin erken teşhis potansiyelini artırmada etkili olduğu belgelense de, genel yaşam süresi sonuçları üzerindeki etkileri hakkında ciddi şüpheler bulunmaktadır. Bu detaylı incelemede, melanom teşhisi için doğrudan dermatolojik müdahalenin ötesinde geliştirilen güncel tanısal yöntemleri ele almaktayız. Yaptığımız analiz, melanoma teşhisinde yüksek hassasiyet sunan bir dizi ev tabanlı ve uzmanlık-dışı tekniklerin varlığını ortaya koymaktadır. Ancak bu tekniklerin klinik uygulamadaki etkinlikleri, güvenilirlikleri ve maliyet-etkinlikleri gibi konularda daha derinlemesine araştırmalara ihtiyaç vardır. Ayrıca, yapay zekâ odaklı teşhis yöntemlerinin geleceğin tanı araçları olarak nasıl bir dönüşüm potansiyeli taşıdığına dair tartışmaları da içermektedir.

Anahtar Sözcükler: Melanom, erken teşhis, öz-muayene, birinci basamak sağlık hizmeti, yapay zekâ, klinik uygulama

Cite this article as: Gençoğlu Ş. Contemporary Advancements in the Early Detection of Melanoma and the Horizon of Home- Based Diagnostic Approaches. YIU Saglik Bil Derg 2024;5:24–30

Introduction

In recent decades, melanoma's incidence has witnessed a pronounced escalation in the U. S., with an increase of 320% since 1975 (1). This trend in melanoma is not just restricted to the U. S.; globally, there's a discernible rise in its incidence (2). Interestingly, this rise presents a stark contrast to the overall cancer rates, which have either plateaued or experienced a modest decline (3). As melanoma takes its place as the fifth most frequently diagnosed cancer in the U. S., there's a concerted push towards enhancing its diagnostic methodologies, especially targeting its nascent stages. The literature suggests that direct dermatological evaluations (in contrast to assessments by non-specialized physicians) are associated with prompt melanoma detection, which in turn aligns with improved survival outcomes (4). A comprehensive study conducted within the German populace revealed that individuals who had been screened dermatologically exhibited superior survival rates than those who hadn't (5). However, overarching analyses spanning large datasets have indicated that the recent strategic measures may not have sufficiently mitigated melanoma-associated mortality (6).

While specialized dermatological evaluations remain the cornerstone for melanoma diagnosis, an over-reliance on such specialist interventions can inadvertently become an impediment, especially for populations grappling with access challenges, culminating in potential therapeutic delays. Empirical evidence underscores the salient fact that early-stage melanoma identification, irrespective of the disease's severity,

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Geliş Tarihi/Received: 12.09.2023, **Kabul Tarihi/Accepted:** 22.04.2024, **Çevrimiçi Yayın Tarihi/Available Online Date:** 31.05.2024

Table 1. Comprehensive overview of melanoma identification techniques

Method	Target audience	Advantages	Challenges
Personal skin checks (ABCDE/Seven-point Glasgow/ Ugly duckling criteria)	General populace	– Free of charge – Immediate – Doesn't need expert equipment or guidance – Can be done frequently	– Variable efficiency findings – Public may misinterpret skin variations – Potential for unwarranted medical visits
Dermatoscope review	Healthcare providers in primary settings	– Established benefit compared to unaided inspection – Limited training for efficient use by non-experts	– Equipment costs – Necessitates skill acquisition
Mobile applications	General populace & primary healthcare providers	– User-friendly – Universally accessible with a smartphone	– Potentially high cost – Infrequent software enhancements
AI-driven image assessment	General populace & primary healthcare providers	– Continuously advancing technology identifies at risk areas – Updates can integrate newer evaluation criteria	– AI's operations are often not transparent – Potential cultural biases in software algorithms
Periodic digital skin analysis	General populace & primary healthcare providers	– User-friendly tracking of concerning skin areas – Facilitates specialist contact if necessary	-
Remote dermatology services	General populace	– Direct feedback system for prompt expert advice – Gains from expert evaluation without clinic visits – Elevates early detection chances	– Extensive use may burden specialists – Not universally insurance-supported

invariably correlates with enhanced survival trajectories (7). Such critical insights have galvanized the development of alternative, non-specialist-dependent diagnostic paradigms for melanoma's early detection. There's a prevailing emphasis on promoting self-examinatory practices; however, a subset of studies articulates potential challenges in aptly disseminating the nuances of melanoma recognition to the layperson (8,9). Notably, these self-assessment initiatives are pivotal in intercepting the initial manifestations of melanoma (10). From an economic vantage point, the early detection of melanoma doesn't just portend survival advantages but also translates to substantial fiscal efficiencies (11,12). A recent study highlighted the significant cost differential in treating T1a and T4b tumors, pointing to an expenditure that's 1000–2000% higher in contrast to the management of early-stage melanomas (13). While there have been reservations suggesting that the financial outlay linked to evaluating additional suspicious lesions might surpass the savings derived from bypassing the treatment of advanced-stage diseases, prevailing research establishes the cost-effectiveness of early detection interventions, notably screening initiatives and direct dermatological evaluations (14–16).

Notably, efforts geared towards amplifying melanoma screenings spearheaded by dermatologists have predominantly culminated in enhanced screening prevalence among younger females (17,18). Despite the increased susceptibility of this demographic to melanoma (19,20), it stands in juxtaposition to the demographic data pointing towards elderly males as the primary risk cohort for melanoma (21,22). Such paradoxes underline the imperativeness of an exhaustive deliberation of these melanoma detection modalities.

In this comprehensive review, we delve into an assortment of early melanoma detection techniques, transcending just self-assessment modalities (Table 1). Noticing the lacuna in literary discussions, our analysis pivots towards methodologies accessible to patients beyond traditional dermatological setups. This encompasses the embrace of avant-garde technological instruments and the integration of profound learning artificial intelligence algorithms. Given their pivotal roles in melanoma detection at nascent stages, we further elucidate the instrumental roles general practitioners and primary care physicians can play in channeling melanoma diagnostics.

Methodology

For this review, our objective was to explore melanoma detection techniques that eliminate the need for direct dermatologist interaction. We selected articles based on their relevance to self-testing and primary care melanoma detection procedures. Directly pertinent articles then guided our search for additional resources and enriched our understanding of specific techniques. Preference was given to articles from the past 5–7 years to ensure contemporary insights. Some exceptions were made for especially pertinent older articles when no recent alternatives were available.

Home-Based Early Detection

Advancing strategies to address the gaps left by previous efforts is pivotal to ameliorating melanoma prognoses. Studies indicate that men face a graver prognosis for melanoma (23), are at higher risk (22), but often postpone medical consultations for symptoms (24). This reluctance presents a challenge to timely detection in healthcare systems. Given this hurdle and the significance of early intervention, strategies targeting these high-risk groups should prioritize home-based accessibility.

Recognizing the observable nature of most melanomas, self-examination remains a cornerstone of numerous early detection initiatives. Entities like the Melanoma Research Alliance (25), AIM Foundation (26), Melanoma Research Foundation (27),

and the American Melanoma Foundation (28) offer resources guiding the public in self-assessing their skin.

Visual Self-Examinations

Skin self-examinations (SSEs) are a broadly endorsed tactic that empowers individuals in melanoma prevention. Research indicates their potential in identifying preliminary melanoma manifestations (23). A popular tool for these examinations is the "ABCDE Method" (29), a mnemonic highlighting potential malignant mole indicators:

- Asymmetry: Healthy moles generally have symmetrical appearances, while malign ones may be irregular.
- Border: Healthy moles feature clear, rounded borders, whereas malignant ones may present jagged edges.
- Color: A uniform color is typical of benign moles, while malign ones may exhibit varied shades.
- Diameter: Malign moles often exceed six millimeters, roughly the diameter of a pencil.
- Evolving: Malign moles tend to evolve in dimensions, contour, and hue.

Originally conceptualized at New York University in 1985, the ABCDE method aimed at educating both medical professionals and the public in distinguishing between regular and malign moles (30). Though there are concerns regarding its consistent application by laypersons (31), it remains valuable for professionals (32,33).

A key advantage of SSE is its flexibility regarding location and time. Evidence supports its efficacy in enhancing melanoma detection with frequent annual assessments (34). The modular nature of the ABCDE framework allows future augmentations (35). Moreover, individuals are often more attuned to their skin anomalies than annual-visiting clinicians.

However, the absence of a standardized SSE procedure can lead to varied thoroughness. Statistics show that only a minority fully adhere to the recommended examination areas, with most covering just two-thirds (36). Concerningly, melanomas detected through self-examination often tend to be advanced and risk-laden (37). Such findings suggest self-examinations, without prior melanoma experience, might not be as effective in early detection.

Despite its imperfections, the ABCDE framework serves as a foundational tool for public health initiatives, warranting further refinement for more consistent public application. Parallel to this is the seven-point Glasgow checklist (7PCL), endorsed by institutions like The National Institute for Health and Care Excellence (38), and widely adopted, especially in the UK (39). The 7CPL delineates seven distinguishing mole characteristics and advises specialist consultation for scores of ≥3 (40):

- Change in lesion size: 2 points
- Lesion shape irregularity: 2 points
- Lesion color irregularity: 2 points
- Inflammation at or around the lesion: 1 point
- Alteration in lesion sensation: 1 point
- Large lesion size (>7 mm in diameter): 1 point
- Oozing or crusting at or around the lesion: 1 point

The weighted 7PCL, another SSE tool for the general public, has demonstrated greater sensitivity than the ABCDE method when used by physicians (41). It has been the focal point of several awareness and self-screening campaigns, especially in the UK (42,43). However, there's a need to assess its efficacy as a self-screening tool.

The Ugly Duckling Method

Individuals can identify "ugly duckling signs" –moles differing from others on their body (44). Typically, benign nevi share similar visual traits (45), and comparing all nevi can decrease biopsies by a factor of seven (46). This straightforward tool is easily communicated to patients, but its simplicity might cause some to overlook cancer symptoms. It should be used in conjunction with other tools, like modifying the ABCDE method into the ABCDEF approach, where F represents "funny looking moles" (47-50).

Naked-eye SSEs have yet to consistently prove their effectiveness in improving outcomes. Elements like skin awareness after melanoma diagnosis, family history, and interest in SSE are pivotal (51). While some argue that SSEs lead to more overdiagnosis than improved outcomes (52), others believe that overdiagnosis isn't the sole metric for early-detection (53). Studies indicate that women at melanoma risk, when trained online and given telehealth dermatologist access, schedule fewer benign mole checks (54-58).

The inconsistency in SSE performance and quality poses challenges in establishing its usefulness for early detection. Research has shown that educational aids can enhance SSE quality and performance. Online tools, like game-based training on ABCD or UDS methods, have boosted accurate melanoma identification (59).

Primary Care Physician and General Practitioner Methods

While self-examination aids melanoma early detection, primary care physicians (PCPs) and general practitioners play a pivotal role. Given melanoma's swift referral time after initial observation (60,61), these professionals must adeptly recognize melanoma symptoms. Thus, the tools and their referral success rate warrant analysis.

A dermatoscope, introduced in 1989 (59), magnifies skin areas, enabling detailed observation. Its use significantly improved

melanoma identification among dermatologists and generalists alike (62-65). Studies highlight its importance, suggesting brief training can make PCPs proficient dermatoscope users (66,67).

Electronic tools, like Sequential Digital Dermoscopy Imaging (SDDI), assist in tracking lesion changes. Coupling SDDI with dermatoscopes achieved >97% accuracy in managing pigmented lesions and melanoma by general practitioners (68).

Other tools like Spectrophotometric Intracutaneous Analysis (SIAscopy) provide non-invasive image assessments of pigmented skin lesions (69), proving effective in primary care settings (70).

Teledermatology enables PCPs to quickly consult specialists, reducing in-person appointment wait times by 78% (71,72). The store-and-forward teledermatology approach, which compiles images for future analysis, has improved detection rates and reduced in-person visits (73,74). However, concerns like image quality, potential for errors, and collaboration challenges persist (75), and insurance coverage remains limited in the US (76).

Efficacy Controversy: Contemporary Approaches to Melanoma Detection and Overdiagnosis Concerns

Contemporary advancements in melanoma detection techniques have incited debate regarding their true efficacy, especially when it comes to influencing long-term survival outcomes. Some contest that increasing melanoma detection initiatives have yet to produce a notable impact on survival rates or melanoma occurrence (77,78). Notably, incidences of less aggressive melanoma manifestations have surged, yet mortality linked to melanoma remains elevated (79,80). Questions have arisen about the effectiveness of certain imaging tools, like MoleMate – a tool developed using SIAscopy technology. Observations indicate that MoleMate led to a surge in referrals, however, these often misaligned with expert evaluations (81).

Conversely, substantial evidence suggests non-specialists can efficiently manage suspicious lesion cases, directing appropriate referrals. An insightful study contrasting rural and urban melanoma incidences revealed that rural regions, with fewer specialists, presented no amplified harm or survival risk, even when more lesions were biopsied (82). This implies that apprehensions about non-specialists may be unfounded, suggesting primary care providers' (PCPs) involvement can be beneficial. Further studies comparing melanoma detection across specialist and non-specialist clinics reveal that general practitioners effectively identify melanoma. A pivotal metric here is the number needed to biopsy (NNB), indicative of how efficiently suspicious lesions are identified. Interestingly, a 2020 study unveiled negligible differences in NNB between dermatologists and non-dermatology practitioners (83).

Horizon of Melanoma Detection: Embracing Emerging Technologies

The trajectory of melanoma detection research has been evolving at an unprecedented pace. A burgeoning approach, evident in contemporary literature, revolves around harnessing artificial intelligence (AI) and deep learning for melanoma diagnosis via dermatoscope images (84–88). Primary providers acquire these images and software subsequently analyses them against a database of healthy and afflicted skin representations (89). A particular mobile-based computer-aided diagnosis (CAD) tool, validated within PCP settings, boasts an accuracy rate exceeding 80% and nearly 90% sensitivity (90). Another investigation involving PCPs and nurse practitioners highlighted AI's potential to augment diagnostic accuracy in alignment with dermatologist panels (91). The intricacies of AI in skin cancer detection were elaborated by Dildar et al. (92).

Yet, these AI technologies remain nascent. Several shortcomings persist, including their 'black-box' characteristic, where decision-making remains opaque (93). The static nature of many diagnostic apps, not reflecting the evolving melanoma diagnostic criteria, raises concerns. Financial constraints, particularly for lower socio-economic groups, also limit technology access (94). Programs like Sklip® from Oregon Health and Science University are attempting to bridge this gap (95). Furthermore, AI's inherent biases, as evidenced by its training data predominantly originating from three states, restrict its efficacy for diverse populations (96,97).

Conclusion and Recommendations

The preceding decades witnessed pivotal strides in melanoma detection methodologies, emphasizing self-screenings, non-specialist interventions, and innovative diagnostic techniques. While these endeavors are commendable, the accuracy issues, emanating from expertise dearth and internal biases, cannot be overlooked. Some critics argue that these only lead to overdiagnoses, escalating costs without discernible survival benefits.

However, to hastily discredit such advancements may overlook the nuances of melanoma biology, yet to be fully understood. It's essential to strategize for equitable access, ensuring the inclusion of those deprived of resources. Emphasizing rural healthcare and cost-effective strategies is paramount.

The ongoing debate on overdiagnosis necessitates more studies to gauge if early detection truly offers survival advantages. It is imperative to fortify training modules for the public and PCPs, targeting high-risk, low-access groups. A paradigm shift, empowering PCPs in melanoma diagnosis, can expedite early detection and unburden the already overburdened dermatologists.

Simultaneously, AI's potential is undeniable but mandates transparency and unbiased data inputs to ensure widespread,

equitable effectiveness. Addressing AI's inherent biases can pivot the landscape of melanoma diagnosis, catalyzing a future where early, accurate detection is the norm, not the exception.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - ŞG; Tasarım - ŞG; Denetleme - ŞG; Analiz ve Yorum - ŞG; Literatür Taraması - ŞG; Yazıyı Yazan - ŞG.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - ŞG; Design - ŞG; Analysis and/or Interpretation - ŞG; Literature Search - ŞG; Writing - ŞG.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Saginala K, Barsouk A, Aluru JS, Rawla P, Barsouk A. Epidemiology of melanoma. Med Sci. 2021;9(3):63. https://doi.org/10.3390/medsci9040063
2. Carr S, Smith C, Wernberg J. Epidemiology and risk factors of melanoma. Surg Clin N Am. 2020;100:1–12. https://doi.org/10.1016/j.suc.2019.09.005
3. Tripp MK, Watson M, Balk SJ, Swetter SM, Gershenwald JE. State of the science on prevention and screening to reduce melanoma incidence and mortality: The time is now. CA Cancer J Clin. 2016;66:460–480. https://doi.org/10.3322/caac.21352
4. Pennie ML, Soon SL, Risser JB, Veledar E, Culler S, Chen SC. Melanoma outcomes for Medicare patients: association of stage and survival with detection by a dermatologist vs a nondermatologist. Arch Derm. 2007;143:488–494. https://doi.org/10.1001/archderm.143.4.488
5. Datzmann T, Schoffer O, Meier F, Seidler A, Schmitt J. Are patients benefiting from participation in the German skin cancer screening programme? A large cohort study based on administrative data. Br J Derm. 2022;186:69–77. https://doi.org/10.1111/bjd.20658
6. Stang A, Jöckel KH. Does skin cancer screening save lives? A detailed analysis of mortality time trends in Schleswig-Holstein and Germany. Cancer. 2016;122:432–437. https://doi.org/10.1002/cncr.29755
7. Leiter U, Buettner PG, Eigentler TK, Forschner A, Meier F, Garbe C. Is detection of melanoma metastasis during surveillance in an early phase of development associated with a survival benefit? Melanoma Res. 2010;20:240–246. https://doi.org/10.1097/CMR.0b013e32833716f9
8. Borland R, Marks R, Noy S. Public knowledge about characteristics of moles and melanomas. Aust J Public Health. 1992;16:370–375. https://doi.org/10.1111/j.1753-6405.1992.tb00083.x
9. Lawson DD, Moore DH, Schneider JS, Sagebiel RW. Nevus counting as a risk factor for melanoma: comparison of self-count with count by physician. J Am Acad Dermatol. 1994;31:438–444. https://doi.org/10.1016/S0190-9622(94)70207-1
10. Hamidi R, Peng D, Cockburn M. Efficacy of skin self-examination for the early detection of melanoma. Int J Dermatol. 2010;49:126–134. https://doi.org/10.1111/j.1365-4632.2009.04268.x
11. Elliott TM, Whiteman DC, Olsen CM, Gordon LG. Estimated healthcare costs of melanoma in Australia over 3 years post-diagnosis. Appl Health Econ Health Policy. 2017;15:805–816. https://doi.org/10.1007/s40258-017-0341-y
12. Serra-Arbeloa P, Rabines-Juárez Á, Álvarez-Ruiz M, Guillén-Grima F. Cost of cutaneous melanoma by tumor stage: a descriptive analysis. [Estudio descriptivo de costes en melanoma cutáneo de diferentes estadios]. Actas Dermosifiliogr. 2017;108:229–236. https://doi.org/10.1016/j.ad.2016.09.010
13. Alexandrescu D. Melanoma costs: a dynamic model comparing estimated overall costs of various clinical stages. Dermatol Online J. 2009;15:1. https://doi.org/10.5070/D353F8Q915
14. Girgis A, Clarke P, Burton RC, Sanson-Fisher RW. Screening for melanoma by primary health care physicians: a cost-effectiveness analysis. J Med Screen. 1996;3:47–53. https://doi.org/10.1177/096914139600300112
15. Freedberg KA, Geller AC, Miller DR, Lew RA, Koh HK. Screening for malignant melanoma: a cost-effectiveness analysis. J Am Acad Dermatol. 1999;41(Pt 1):738–745. https://doi.org/10.1016/S0190-9622(99)70010-1
16. Losina E, Walensky RP, Geller A, Geller A, Beddingfield 3rd FC, Wolf LL, et al. Visual screening for malignant melanoma: A cost-effectiveness analysis. Arch Derm. 2007;143:21–28. https://doi.org/10.1001/archderm.143.1.21
17. van der Leest R, de Vries E, Bulliard J-L, Paoli J, Peris K, Stratigos A, Trakatelli M, et al. The euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010. J Eur Acad Derm Venereol. 2011;25:1455–1465. https://doi.org/10.1111/j.1468-3083.2011.04228.x
18. Geller AC, Zhang Z, Sober AJ, Halpern AC, Weinstock MA, Daniels S, et al. The first 15 years of the American Academy of Dermatology skin cancer screening programs: 1985–1999. J Am Acad Dermatol. 2003;48:34–41. https://doi.org/10.1067/mjd.2003.9
19. Moreno-Ramirez D, Ferrandiz L, Nieto-García A, Carrasco R, Moreno-Alvarez P, Galdeano R, et al. Effect of dermoscopy on the management of patients with pigmented lesions at high risk for malignant melanoma. Arch Dermatol. 2007;143:467–474. https://doi.org/10.1001/archderm.143.4.479
20. National Cancer Institute. SEER cancer statistics factsheets: melanoma of the skin. Surveillance, epidemiology, and end results program. Available online: https://seer.cancer.gov/statfacts/html/melan.html
21. Cancer Research UK. Melanoma skin cancer incidence statistics. Available online: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/incidence#heading-Zero
22. Bellenghi M, Puglisi, R, Pontecorvi, G, De Feo, A, Carè, A, Mattia, G. Sex and gender disparities in melanoma. Cancers. 2020;12:1819. https://doi.org/10.3390/cancers12071819
23. Paddock LE, Lu SE, Bandera EV, Rhoads GG, Fine J, Paine S, et al. Skin self-examination and long-term melanoma survival. Melanoma Res. 2016;26:401–408. https://doi.org/10.1097/CMR.0000000000000255
24. David J. Men's Health and the Primary Care Physician. Boca Raton, FL, USA: CRC Press; 2021. pp. 424–427. https://doi.org/10.1201/9780429347238-55
25. Melanoma Research Alliance. Early warning signs of melanoma and other skin cancers. Available online: https://www.curemelanoma.org/about-melanoma/educate-yourself/know-what-to-look-for
26. AIM at Melanoma Foundation. How to do a skin self-examination. Available online: https://www.aimatmelanoma.org/melanoma-101/early-detection-of-melanoma/how-to-do-a-skin-self-examination
27. Melanoma Research Foundation. What melanoma looks like. Available online: https://melanoma.org/melanoma-education/what-melanoma-looks-like
28. The American Melanoma Foundation. Available online: https://melanomafoundation.org
29. Rigel DS, Friedman RJ, Kopf AW, Polsky D. ABCDE - An evolving concept in the early detection of melanoma. Arch Dermatol. 2005;141:1032–1034. https://doi.org/10.1001/archderm.141.8.1032
30. Rigel D, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. CA Cancer J Clin. 2010;60:301–316. https://doi.org/10.3322/caac.20074
31. Aldridge, R, Zanotto, M, Ballerini, L, Fisher, R, Rees, J. Novice identification of melanoma: not quite as straightforward as the ABCDs. Acta Derm Venereol. 2011;91:125–130. https://doi.org/10.2340/00015555-1070
32. Healsmith, M, Bourke, J, Osborne, J, Graham-Brown, R. An evaluation of the revised seven-point checklist for the early diagnosis of cutaneous malignant melanoma. Br J Dermatol. 1994;130:48–50. https://doi.org/10.1111/j.1365-2133.1994.tb06881.x
33. Thomas L, Tranchand P, Berard F, Secchi T, Colin C, Moulin G. Semiological value of ABCDE criteria in the diagnosis of cutaneous pigmented tumors. Dermatology. 1998;197:11–17. https://doi.org/10.1159/000017969
34. Titus L, Clough-Gorr K, Mackenzie T, Perry A, Spencer S, Weiss J, et al. Recent skin self-examination and doctor visits in relation to melanoma risk and tumor depth. Br J Dermatol. 2013;168:571–576. https://doi.org/10.1111/bjd.12003
35. Melanoma: Clinical Features and Diagnosis. Available online: https://www.medilib.ir/uptodate/show/15806
36. Manne SL, Heckman CJ, Kashy D, Lozada C, Gallo J, Ritterband L, et al. Prevalence and correlates of skin self-examination practices among cutaneous malignant melanoma survivors. Prev Med Rep. 2020;19:101110. https://doi.org/10.1016/j.pmedr.2020.101110
37. De Giorgi V, Grazzini M, Rossari S, Gori A, Papi F, Scarfi F, et al. Is skin self-examination for cutaneous melanoma detection still adequate? A retrospective study. Dermatology. 2012;225:31–36. https://doi.org/10.1159/000339774
38. Jones OT, Ranmuthu CKI, Hall PN, Funston G, Walter FM. Recognising skin cancer in primary care. Adv Ther. 2020;37:603–616. https://doi.org/10.1007/s12325-019-01130-1
39. Pannebakker MM, Mills K, Johnson M, Emery JD, Walter FM. Understanding implementation and usefulness of electronic clinical decision support (eCDS) for melanoma in English primary care: a qualitative investigation. BJGP Open 2019;3. https://doi.org/10.3399/bjgpopen18X101635

40. Walter FM, Prevost AT, Vasconcelos J, Hall PN, Burrows NP, Morris HC, et al. Using the 7-point checklist as a diagnostic aid for pigmented skin lesions in general practice: a diagnostic validation study. Br J Gen Pract 2013;63:e345–e353. https://doi.org/10.3399/bjgp13X667213
41. Mittal, A, Pushpam, D, Bakhshi, S. Management of advanced melanoma in the current era: a medical oncology perspective for the Indian scenario. Natl Med J India. 2020;33:89–98. https://doi.org/10.4103/0970-258X.310984
42. Graham-Brown R, Osborne JE, London SP, Fletcher A, Shaw D, Williams B, et al. The initial effects on workload and outcome of a public education campaign on early diagnosis and treatment of malignant melanoma in Leicestershire. Br J Dermatol. 1990;122:53–59. https://doi.org/10.1111/j.1365-2133.1990.tb08239.x
43. Doherty V, MacKie R. Experience of a public education programme on early detection of cutaneous malignant melanoma. Br Med J. 1988;297:388–391. https://doi.org/10.1136/bmj.297.6645.388
44. Cantisani C, Ambrosio L, Cucchi C, Meznerics FA, Kiss N, Bánvölgyi A, et al. Melanoma detection by non-specialists: an untapped potential for triage? Diagnostics. 2022;12:2821. https://doi.org/10.3390/diagnostics12112821
45. Zhang Y, Ali K, George JA, Reichenberg JS, Fox MC, Adamson AS, et al. Toward automated assessment of mole similarity on dermoscopic images. J Med Imaging. 2021;8:014506. https://doi.org/10.1117/1.JMI.8.1.014506
46. Gaudy-Marqueste C, Wazaefi Y, Bruneu Y, Triller R, Thomas L, Pellacani G, et al. Ugly duckling sign as a major factor of efficiency in melanoma detection. JAMA Dermatol. 2017;153:279–284. https://doi.org/10.1001/jamadermatol.2016.5500
47. Jensen JD, Elewski BE. The ABCDEF Rule: combining the "ABCDE Rule" and the "Ugly Duckling Sign" in an effort to improve patient self-screening examinations. J Clin Aesthetic Dermatol. 2015;8:15.
48. Ersser S, Effah A, Dyson J, Kellar I, Thomas S, McNichol E, et al. Effectiveness of interventions to support the early detection of skin cancer through skin self-examination: a systematic review and meta-analysis. Br. J. Dermatol. 2019;180:1339–1347. https://doi.org/10.1111/bjd.17529
49. Czajkowska Z, Hall N, Sewitch M, Wang B, Körner A. The role of patient education and physician support in self-efficacy for skin self-examination among patients with melanoma. Patient Educ Couns. 2017;100:1505–1510. https://doi.org/10.1016/j.pec.2017.02.020
50. Duarte AF, Sousa-Pinto B, Azevedo LF, Barros AM, Puig S, Malvehy J, et al. Clinical ABCDE rule for early melanoma detection. Eur J Dermatol. 2021;31:771–778. https://doi.org/10.1684/ejd.2021.4171
51. Coroiu A, Moran C, Bergeron C, Drapeau M, Wang B, Kezouh A, et al. Short and long-term barriers and facilitators of skin self-examination among individuals diagnosed with melanoma. BMC Cancer. 2020;20:123. https://doi.org/10.1186/s12885-019-6476-5
52. De Giorgi V, Papi F, Giorgi L, Savarese I, Verdelli A, Scarfì F, et al. Skin self-examination and the ABCDE rule in the early diagnosis of melanoma: Is the game over? Br J Dermatol. 2013;168:1370–1371. https://doi.org/10.1111/bjd.12250
53. Kulkarni R, Wesley Y, Leachman S. To Improve Melanoma Outcomes Focus on Risk Stratification Not Overdiagnosis. JAMA Dermatol. 2022;158:485–487. https://doi.org/10.1001/jamadermatol.2022.0097
54. Robinson JK, Wahood S, Ly S, Kirk J, Yoon J, Sterritt J, et al. Melanoma detection by skin self-examination targeting at-risk women: a randomized controlled trial with telemedicine support for concerning moles. Prev Med Rep. 2021;24:101532. https://doi.org/10.1016/j.pmedr.2021.101532
55. Sarikaya Solak S, Yondem H, Cicin I. Evaluating sun protection behaviors and skin self-examination practices among the family members of melanoma patients in Turkey: a cross-sectional survey study. Dermatol Ther. 2020;33:e14268. https://doi.org/10.1111/dth.14268
56. Koh U, Horsham C, Soyer HP, Loescher LJ, Gillespie N, Vagenas D, et al. Consumer acceptance and expectations of a mobile health application to photograph skin lesions for early detection of melanoma. Dermatology. 2019;235:4–10. https://doi.org/10.1159/000493728
57. Manne SL, Marchetti MA, Kashy DA, Heckman CJ, Ritterband LM, Thorndike FP, et al. mySmartCheck a digital intervention to promote skin self-examination among individuals diagnosed with or at risk for melanoma: a randomized clinical trial. Ann Behav Med. 2022;56:791–803. https://doi.org/10.1093/abm/kaab090
58. Hubbard G, Kyle RG, Neal RD, Marmara V, Wang Z, Dombrowski SU. Promoting sunscreen use and skin self-examination to improve early detection and prevent skin cancer: quasi-experimental trial of an adolescent psycho-educational intervention. BMC Public Health. 2018;18:666. https://doi.org/10.1186/s12889-018-5570-y
59. Carcioppolo N, Kim S, Sanchez M, Mao B, Malova E, Ryan A, et al. Evaluating a game-based randomized experiment to increase melanoma identification among adults living in the US. Soc Sci Med. 2022;310:115281. https://doi.org/10.1016/j.socscimed.2022.115281
60. Swann R, McPhail S, Witt J, Shand B, Abel G, Hiom S, et al; The National Cancer Diagnosis Audit Steering Group. Diagnosing cancer in primary care: results from the national cancer diagnosis audit. Br J Gen Pract. 2018;68:e63–e72. https://doi.org/10.3399/bjgp17X694169
61. Katz B, Rabinovitz H. Introduction to dermoscopy. Dermatol Clin. 2001;19:221–258. https://doi.org/10.1016/S0733-8635(05)70263-1
62. Jones OT, Jurascheck LC, van Melle M, Hickman S, Burrows NP, Hall P. et al. Dermoscopy for melanoma detection and triage in primary care: a systematic review. BMJ Open. 2019;9:e027529. https://doi.org/10.1136/bmjopen-2018-027529
63. Dinnes J, Deeks JJ, Chuchu N, di Ruffano LF, Matin RN, Thomson DR, et al. Dermoscopy with and without visual inspection for diagnosing melanoma in adults. Cochrane Database Syst Rev. 2018;12: CD011902. https://doi.org/10.1002/14651858.CD011902.pub2
64. Vestergaard M, Macaskill P, Holt P, Menzies S. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br. J. Dermatol. 2008;159:669–676. https://doi.org/10.1111/j.1365-2133.2008.08713.x
65. Koelink C, Vermeulen K, Kollen B, de Bock G, Dekker J, Jonkman M, et al. Diagnostic accuracy and cost-effectiveness of dermoscopy in primary care: a cluster randomized clinical trial. J Eur Acad Dermatol Venereol. 2014;28:1442–1449. https://doi.org/10.1111/jdv.12306
66. Jones O, Jurascheck L, Utukuri M, Pannebakker M, Emery J, Walter F. Dermoscopy use in UK Primary care: a survey of GP's with a special interest in dermatology. J Eur Acad Dermatol Venerol. 2019;33:1706–1712. https://doi.org/10.1111/jdv.15614
67. Tromme I, Devleesschauwer B, Beutels P, Richez P, Praet N, Sacré L, et al. Selective use of sequential digital dermoscopy imaging allows a cost reduction in the melanoma detection process: a Belgian study of patients with a single or a small number of atypical nevi. PLoS One. 2014;9:e109339. https://doi.org/10.1371/journal.pone.0109339
68. Menzies S, Emery J, Staples M, Davies S, McAvoy B, Fletcher J, et al. Impact of dermoscopy and short-term sequential digital dermoscopy imaging for the management of pigmented lesions in primary care: a sequential intervention trial. Br J Dermatol. 2009;161:1270–1277. https://doi.org/10.1111/j.1365-2133.2009.09374.x
69. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscopy for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. BMC Dermatol. 2010;10:9. https://doi.org/10.1186/1471-5945-10-9
70. Sgouros D, Lallas A, Julian Y, Rigopoulos D, Zalaudek I, Longo C, et al. Assessment of SIAscopy in the triage of suspicious skin tumours. Ski Res Technol. 2014;20:440–444. https://doi.org/10.1111/srt.12138
71. Giavina-Bianchi M, Santos AP, Cordioli E. Teledermatology reduces dermatology referrals and improves access to specialists. EClinicalMedicine. 2020;29:100641. https://doi.org/10.1016/j.eclinm.2020.100641
72. Marwaha SS, Fevrier H, Alexeeff S, Crowley E, Haiman M, Pham N, et al. Comparative effectiveness study of face-to-face and teledermatology workflows for diagnosing skin cancer. J Am Acad. Dermatol. 2019;81:1099–1106. https://doi.org/10.1016/j.jaad.2019.01.067
73. Mohan G, Molina G, Stavert R. Store and forward teledermatology improves dermatology knowledge among referring primary care providers: a survey-based cohort study. J Am Acad Dermatol. 2018;79:960–961. https://doi.org/10.1016/j.jaad.2018.05.006
74. Romero G, De Argila D, Ferrandiz L, Sánchez M, Vañó S, Taberner R, et al. Practice models in teledermatology in Spain: longitudinal study 2009–2014. [Modelos de práctica de la teledermatología en España. Estudio longitudinal 2009-2014]. Actas Dermo-Sifiliográficas. 2018;109:624–630. https://doi.org/10.1016/j.ad.2018.03.015
75. CCHP. Telehealth policy trend maps. Available online: https://www.cchpca.org/policy-trends
76. Glazer AM, Winkelmann RR, Farberg AS, Rigel DS. Analysis of trends in US melanoma incidence and mortality. JAMA Dermatol. 2017;153:225–226. https://doi.org/10.1001/jamadermatol.2016.4512
77. Matsumoto M, Wack S, Weinstock MA, Geller A, Wang H, Solano FX, et al. Five-year outcomes of a melanoma screening initiative in a large health care system. JAMA Dermatol. 2022:158;504–512. https://doi.org/10.1001/jamadermatol.2022.0253
78. Welch H, Mazer B, Adamson A. The rapid rise in cutaneous melanoma diagnoses. N Engl J Med. 2021;384:72–79. https://doi.org/10.1056/NEJMsb2019760
79. Herbert A, Koo MM, Barclay ME, Greenberg DC, Abel GA, Levell NJ, et al. Stage-specific incidence trends of melanoma in an English region 1996-2015: Longitudinal analyses of population-based data. Melanoma Res. 2020;30:279–285. https://doi.org/10.1097/CMR.0000000000000489

80. Watts CG, McLoughlin K, Goumas C, van Kemenade CH, Aitken JF, Soyer HP, et al. Association between melanoma detected during routine skin checks and mortality. JAMA Dermatol. 2021;157:1425–1436. https://doi.org/10.1001/jamadermatol.2021.3884
81. Walter FM, Morris HC, Humphrys E, Hall PN, Prevost AT, Burrows N, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented suspicious pigmented lesions in primary care: randomised controlled trial. Br Med J. 2012;345:e4110. https://doi.org/10.1136/bmj.e4110
82. Murchie P, Adam R, Khor WL, Raja EA, Iversen L, Brewster D, et al. Impact of rurality on processes and outcomes in melanoma care: results from a whole-Scotland melanoma cohort in primary and secondary care. Br J Gen Pract. 2018;68:e566–e575. https://doi.org/10.3399/bjgp18X697901
83. Privalle A, Havighurst T, Kim K, Bennett DD, Xu YG. Number of skin biopsies needed per malignancy: comparing the use of skin biopsies among dermatologists and nondermatologist clinicians. J Am Acad Dermatol. 2020;82:110–116. https://doi.org/10.1016/j.jaad.2019.08.012
84. Haenssle HA, Fink C, Schneiderbauer R, Toberer F, Buhl T, Blum A, et al. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. Ann Oncol. 2018;29:1836–1842.
85. Phillips M, Marsden H, Jaffe W, Matin RN, Wali GN, Greenhalgh J, et al. Assessment of accuracy of an artificial intelligence algorithm to detect melanoma in images of skin lesions. JAMA Netw Open. 2019;2:e1913436. https://doi.org/10.1001/jamanetworkopen.2019.13436
86. Brinker TJ, Hekler A, Enk AH, Berking C, Haferkamp S, Hauschild A, et al. Deep neural networks are superior to dermatologists in melanoma image classification. Eur J Cancer. 2019;119:11–17. https://doi.org/10.1016/j.ejca.2019.05.023
87. Dick V, Sinz C, Mittlböck M, Kittler H, Tschandl P. Accuracy of computer-aided diagnosis of melanoma: a meta-analysis. JAMA Dermatol. 2019;155:1291–1299. https://doi.org/10.1001/jamadermatol.2019.1375
88. Phillips M, Greenhalgh J, Marsden H, Palamaras I. Detection of malignant melanoma using artificial intelligence: an observational study of diagnostic accuracy. Dermatol Pract Concept. 2020;10:e2020011. https://doi.org/10.5826/dpc.1001a11
89. Dascalu A, David EO. Skin cancer detection by deep learning and sound analysis algorithms: a prospective clinical study of an elementary dermoscope. Discov Sci. 2019;43:107–113. https://doi.org/10.1016/j.ebiom.2019.04.055
90. Giavina-Bianchi M, de Sousa RM, de Almedia Paciello VZ, Vitor WG, Okita AL, Prôa R, et al. Implementation of artificial intelligence algorithms for melanoma screening in a primary care setting. PLoS One. 2021;16:e0257006. https://doi.org/10.1371/journal.pone.0257006
91. Jain A, Way D, Gupta V, Gao Y, Marinho GDO, Hartford J, et al. Development and assessment of an artificial intelligence-based tool for skin condition diagnosis by primary care physicians and nurse practitioners in teledermatology practices. JAMA Netw Open. 2021;4:e217249. https://doi.org/10.1001/jamanetworkopen.2021.7249
92. Dildar M, Akram S, Irfan M, Khan HU, Ramzan M, Mahmood AR, et al. Skin cancer detection: a review using deep learning techniques. Int J Environ Res Public Health. 2021;18:5479. https://doi.org/10.3390/ijerph18105479
93. Kassianos A, Emery J, Murchie P, Walter F. Smartphone applications for melanoma detection by community patient and generalist clinician users: a review. Br J Dermatol. 2015;172:1507–1518. https://doi.org/10.1111/bjd.13665
94. Kong FW, Horsham C, Ngoo A, Soyer HP, Janda M. Review of smartphone mobile applications for skin cancer detection: what are the changes in availability functionality and costs to users over time? Int J Dermatol. 2020;60:289–308. https://doi.org/10.1111/ijd.15132
95. OHSU. War on melanoma. Available online: https://www.ohsu.edu/war-on-melanoma/sklipr-home-dermoscopy
96. Kaushal A, Altman R, Langlotz C. Geographic distribution of US cohorts used to train deep learning algorithms. JAMA. 2020;324:1212–1213. https://doi.org/10.1001/jama.2020.12067
97. Parikh RB, Teeple S, Navathe AS. Addressing bias in artificial intelligence in health care. JAMA. 2019;322:2377–2378. https://doi.org/10.1001/jama.2019.18058

Yüksek İhtisas Üniversitesi
Sağlık Bilimleri Dergisi
Yüksek İhtisas University Journal of
Health Sciences
ISSN 2717-8439
E-ISSN 2717-9257

YIU Saglik Bil Derg 2024;5:31–41
https://doi.org/10.51261/yiu.2024.1453277

DERLEME / REVIEW

Otizm Spektrum Bozukluğunun Enterik Sinir Sistemi ile İlişkisi

The Relationship Between Autism Spectrum Disorder and the Enteric Nervous System

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ÖZ

Bu derlemenin amacı, otizm spektrum bozukluğunda enterik sinir sisteminde olan değişikliklerle ilgili çalışmaları değerlendirerek günümüz gelişmelerini ortaya koymaktır. Otizm spektrum bozukluğu, sosyal iletişimi negatif etkileyen, bozulmuş tekrarlayan davranışlar sergileyen genetik ve çevresel olarak değişkenlik gösteren kısıtlı sosyal iletişimle karakterize olan nörodejeneratif bozuklukların kombinasyonudur. Mental Bozuklukların Tanısal ve İstatistiksel El Kitabında (DSM-V); otizm spektrum bozukluğu, otistik bozukluk, Asperger bozukluğu, çocukluk çağı dezintegratif bozukluğu ve başka türlü tanımlanmayan yaygın gelişimsel bozukluk olarak alt gruplara ayrılarak tanımlanmıştır. Otizm spektrum bozukluğunun nöropatolojisinde serebellum, limbik sistem ve korteksteki belirli beyin alanlarının etkilendiği bildirilmiştir. Enterik sinir sistemi, bağırsak beyin eksenini oluşturan çok önemli bir yapıdır. Enterik sinir sistemi gastrointestinal fonksiyonun birçok yönünü koordine etmekten sorumlu olan nöron ve glial hücre ağından oluşmaktadır. Enterik sinir sistemi; gastrointestinal kanalda lokal hareketliliğin kontrolü ve koordinasyonundan, sıvıların mukoza epiteli boyunca hareketinden, kan akışındaki değişikliklerden ve bağışıklık sistemi ile etkileşimlerde görev almaktadır. Otizm spektrum bozukluğu olan bireylerde bağırsak beyin arasındaki iletişimin bozulması bağırsak beyin ekseninin uyumsuzluğu ile sonuçlanmaktadır. Bunlara bağlı olarak sindirim sorunları ve gastrointestinal disfonksiyon ortaya çıkmaktadır. Bağırsak– beyin ekseninde çift yönlü iletişim sayesinde her iki sistemde oluşan sorunlar karşılıklı olarak sistemler üzerinde olumsuz etkiler oluşturabilmektedir. Otizm spektrum bozukluğu olan bireylerde de enterik sinir sisteminde oluşan değişiklikler nedeniyle gastrointestinal sorunlar görülmektedir. Bu sorunların çözümü için otizm spektrum bozukluğu ve enterik sinir sistemi ilişkisi konusunda daha fazla araştırmaya gereksinim vardır. Bu araştırmalar sonucunda otizm spektrum bozukluğunda gastrointestinal sorunların iyileştirilmesi otizm spektrum bozukluğu olan bireylerde genel yaşam kalitesini artıracaktır.

Anahtar Sözcükler: Otizm spektrum bozukluğu, enterik sinir sistemi, gastrointestinal semptom

ABSTRACT

The aim of this review is to evaluate the studies on changes in the enteric nervous system in autism spectrum disorder and to present current developments. Autism spectrum disorder is a combination of neurodegenerative disorders characterised by genetically and environmentally variable restricted social communication with impaired repetitive behaviours that negatively affect social communication. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), autism spectrum disorder is subdivided into autistic disorder, Asperger's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified. It has been reported that certain brain areas in the cerebellum, limbic system and cortex are affected in neuropathology of autism spectrum disorder. The enteric nervous system is a major component of the gut-brain axis. The enteric nervous system is composed of a network of neurons and glial cells responsible for coordinating many aspects of gastrointestinal function. The enteric nervous system is responsible for the control and coordination of local motility in the gastrointestinal tract, the movement of fluids through the mucosal epithelium, changes in blood flow and immune system interactions. Impaired communication between the gut and brain resulting in incompatibility of the gut-brain axis in people with autism spectrum disorder. Digestive problems and gastrointestinal dysfunction occur depending on these. By means of bidirectional communication on the intestine-brain axis, problems occurred in both systems may have negative effects on the systems in mutual way. People with autism spectrum disorder also have gastrointestinal problems because of changes in the enteric nervous system. More studies on the relationship between autism spectrum disorder and enteric nervous system are needed to solve these problems. As a result of these studies, improvement of gastrointestinal problems in autism spectrum disorder will improve the overall quality of life in people with autism spectrum disorder.

Keywords: Autism spectrum disorder, enteric nervous system, gastrointestinal symptom

Cite this article as: Gözil R, Barç ED, Bahçelioğlu M. Otizm Spektrum Bozukluğunun Enterik Sinir Sistemi ile İlişkisi. YIU Saglik Bil Derg 2024;5:31–41

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Geliş Tarihi/Received: 15.03.2024, **Kabul Tarihi/Accepted:** 08.05.2024, **Çevrimiçi Yayın Tarihi/Available Online Date:** 31.05.2024

Giriş

Otizm spektrum bozukluğu, sosyal iletişimi negatif etkileyen, bozulmuş tekrarlayan davranışlar sergileyen genetik ve çevresel olarak değişkenlik gösteren kısıtlı sosyal iletişimle karakterize olan nörodejeneratif bozuklukların kombinasyonudur (1). Asya, Avrupa ve Kuzey Amerika'da otizm prevalansı %1 iken dünya da her 59 çocuktan birinde, yetişkinlerde ise her 100 yetişkinden birinde görülmektedir (1). Otizmin sıklığı cinsiyete göre farklılık göstermektedir (2,3). Mental Bozuklukların Tanısal ve İstatistiksel El Kitabına (DSM-V) göre erkeklerde görülme sıklığı kadınlara göre dört kat fazla iken, Türkiye epidemiyolojik verilerine göre ise bu oran 4,6:1 olarak bildirilmiştir (2,3). Mental Bozuklukların Tanısal ve İstatistiksel El Kitabında (DSM-V); otizm spektrum bozukluğu; otistik bozukluk, Asperger bozukluğu, çocukluk çağı dezintegratif bozukluğu ve başka türlü tanımlanmayan yaygın gelişimsel bozukluk olarak alt gruplara ayrılarak tanımlanmıştır (4). Otizm spektrum bozukluğu birçok sistemi etkileyerek fonksiyon kayıplarına neden olmaktadır. Otizm spektrum bozukluğunda, bilişsel, davranışsal semptomlar dışında gastrointestinal bozuklukların meydana geldiği bildirilmektedir (1,5–18). Otizm spektrum bozukluğu olan bireylerin genel popülasyona göre sıklıkla ishal/kabızlık, karın ağrısı yaşadıkları belirtilmiştir (1,5–18). Bu bağlamda; ortaya çıkan gastrointestinal disfonksiyonun bağırsaklarda yer alan enterik sinir sisteminin yapısındaki değişikliklere bağlı olarak ortaya çıktığı düşünülmektedir (19).

Çalışmamızda, otizm spektrum bozukluğunda enterik sinir sisteminde olan değişikliklerle ilgili çalışmaları değerlendirerek günümüz gelişmelerini ortaya koymayı amaçlamaktayız.

Otizm Spektrum Bozukluğunun Nöroanatomisi

Otizm spektrum bozukluğunun nöropatolojisinde beyincik, limbik sistem ve korteksteki belirli beyin alanlarının etkilendiği bildirilmiştir (20). Bu oluşumların tamamı değil belirli bölgelerinin etkilenebildiği belirtilmiştir (20). Bu oluşumlar amigdalanın belirli çekirdekleri, fusiform yüz bölgesi gibi yapılardır (20). Beynin ön kısmının erken ve aşırı büyümesi ile karakterize olan ve buna bağlı olarak değişen kortikal organizasyonun bütün bağlantılarının etkilendiği saptanmıştır (20). Anomaliler arasında sitoarkitektonik laminer farklılıklar, fazla beyaz cevher nöronları, GABAerjik serebellar Purkinje hücrelerinin sayısında azalma ve gelişimsel olarak izlenebilen anomalilere neden olan diğer olayların da yer aldığı tespit edilmiştir (20).

Donovan ve Basson (21) yaptıkları çalışmada otizm spektrum bozukluğu olan bireylerin beyninde çok sayıda nöroanatomik farklılıklar bildirmişlerdir (21). Bunlar manyetik rezonans görüntüleme ile ölçülen bölgeye özgü hacimsel değişiklikler, gri veya beyaz maddede spesifik bozukluklar ve postmortem beyin dokusunda tespit edilen hücresel farklılıklar olarak tanımlanmıştır (21). Ayrıca kortikal alanlarda aşırı büyüme de dâhil olmak üzere neokortikal yapısal farklılıkların ortaya çıkabileceği belirtilmiştir (20). Hipokampus, limbik sistem, entorinal korteks ve amigdalada daha küçük hücre boyutu ve artmış hücre yoğunluğu her yaştan otizm spektrum bozukluğu olan bireylerde gözlendiği bildirilmiştir (22). Genç otizm spektrum bozukluğu olan bireylerde, prefrontal kortekste nöron sayısında artış ve Broka'nın Diagonal Bandının dikey kolunda anormal derecede genişlemiş hücreler olduğu gösterilmiştir (21).

Otizm Spektrum Bozukluğunda Serebellumda Görülen Değişiklikler

Serebellum, motor, öğrenme ve kasların koordinasyonu sağlayan önemli bir organdır (20). Son yıllarda, anatomik, deneysel ve nörogörüntüleme çalışmaları, serebellumun konuşma ve motor işlevlerinin yanı sıra duygusal düzenleme de bilişsel işlevleri desteklediği gösterilmiştir (23). Ayrıca, serebellumun otizm spektrum bozukluğunda beynin etkilenen kilit bölgelerinden biri olduğu vurgulanmıştır (23). Otizm spektrum bozukluğundaki serebellar bulgular, nöral yapı ve fonksiyonun çeşitli seviyelerinde gelişimsel farklılıklar olduğu gösterilmiştir (23). Bu nedenle serebellumun, davranışsal değişiklikleri olan otizm spektrum bozukluğunda önemli bir işlevi olduğu bildirilmiştir (23). Sentral serebellar vermis lobüllerinin (VI+VII) hipoplazisi, otizm spektrum bozukluğu olan bireylerde beyinlerinde tespit edilen ilk nöroanatomik değişikliklerdir (21).

Ayrıca, serebellumda, serebellar çekirdeklerde artış, Purkinje hücre sayısının serebellar hemisferinin arşiserebellar ve neoserebellar kortekslerinde azalma, akson yoğunluk değişikliği, beyaz maddede bozulmuş miyelin varlığı, gri madde hacminin azaldığı bildirilmiştir (21,23). Fareler ile yapılan deneysel bir çalışmada, tüberoz skleroz geni Tsc1'in özellikle gelişmekte olan serebellumun Purkinje hücrelerinde inaktivasyonu nedeniyle farelerde otizm benzeri davranış gösterdiği saptanmıştır (24).

Serebellar disfonksiyonun otizm spektrum bozukluğuna yol açabileceği tartışmaları yoğun bir şekilde devam etmektedir (21). Primatlardan elde edilen veriler, serebellumun serebro-serebellar bağlantılar aracılığıyla otizm spektrum bozukluğunda bozulan motor ve diğer kortikal alanların aktivitesini de etkilediğini ortaya koymuşlardır (21,25).

Otizm Spektrum Bozukluğunda Korpus Amigdalada Görülen Değişiklikler

Amigdalanın görevi korku, haz ve agresyon gibi duygusal durumları yönetmektir (21).

Otizm spektrum bozukluğunda korpus amigdalada anormal büyüme görüldüğü bildirilmiştir (24). Bu nedenle otizm spektrum bozukluğunda sosyal etkileşim, ödül tahmini, duygusal hafıza, yüz, duygu tanımadaki bozukluklar, amigdala ve ilişkili yapıların işlev bozukluğunun göstergesi olabileceği

tanımlanmıştır (21). Özellikle otizm spektrum bozukluğu olan çocuklarda amigdalanın boyutunda meydana gelen değişiklikler nedeniyle yapılan bir çalışmada toplam 89 çocuktan (1–5 yaş) elde edilen veriler sonucunda sağ ve sol amigdala boyutlarının, toplam beyin hacmine göre arttığı ortaya koyulmuştur (21).

Otizm Spektrum Bozukluğunda Frontal Korteksde Görülen Değişiklikler

Otizmde görülen sosyal etkileşim ve emosyonel bozukluklar nedeniyle, frontal kortekste meydana gelen anomaliler de önem kazanmaktadır (21,22). Anormal kortikal büyüme, kortikal kalınlıkta değişiklikler, bu bölgede meydana gelen nöronların düzensizliği ve diğer bölgelerle bağlantı bozukluklarının meydana geldiği bildirilmiştir (21). Frontal korteks, karar verme, planlama, bellek, emosyonel, sosyal davranış, öğrenme ve iletişim gibi kognitif işlevleri kontrol etmektedir (21,22). Yüksek işlevli otizm olarak da adlandırılan gecikmiş dil gelişimine sahip otizm spektrum bozukluğu olan yetişkinler üzerinde yapılan bir manyetik rezonans görüntüleme çalışmasında, frontal, oksipital, temporal, parietal, singulat ve fusiform giruslarda kortikal kalınlığın arttığı, supramarginal ve postsentral girus ile presentral giruslarda da kortikal kalınlığın azaldığı gözlenmiştir (22).

Otizm Spektrum Bozukluğunun Nörofizyolojisi

Otizm spektrum bozukluğunda beynin nörofizyolojik yapılanmasının değiştiği bildirilmiştir (20). Son yıllarda yapılan çalışmalar; moleküler olayların transkripsiyon, translasyon, sinaptik iletim, epigenetik ve immünoenflamatuvar yanıtlar gibi patolojik süreçlere dâhil olduğu bildirilmiştir (26). Otizm spektrum bozukluğu olan bireylerin beyinlerinde astrositler, mikroglial aktivasyon, bağırsak mikrobiyotasının neden olduğu nöroenflamasyon ve immün disregülasyon arasındaki korelasyonlarda patolojik mekanizmaların yer aldığı saptanmıştır (26). Özellikle, hamilelik sırasında enfeksiyonun, bebeğin sinir sistemini etkileyerek maternal immün aktivasyonu indüklediği tespit edilmiştir (27). Bu bağışıklık tepkilerinin, sosyal etkileşim ve iletişimde bozulmalara neden olarak, otizmin patofizyolojisinde kilit bir rol oynadığı bildirilmiştir (27).

Otizm spektrum bozukluğunda gözlenen işlevsiz bağışıklık aktivitesi, bağışıklık sisteminin hem doğal hem de adaptif kollarını kapsar ve her iki alandaki pertürbasyonların nörogelişim üzerinde etkili olduğu saptanmıştır (27,28). Beyin dokusu, beyin-omurilik sıvısı, dolaşımdaki kan ve gastrointestinal dokular dâhil olmak üzere otizm spektrum bozukluğunda normalin dışındaki seviyelerde gözlenen sitokinler, nöronal yaşamı ve proliferasyonu değiştirebilir (27,28). Benzer şekilde, otizm spektrum bozukluğunda gözlenen hücresel işlev bozukluğu, sitokin üretimi, anormal hücre lizisi ve beyin-reaktif antikorların üretimi dâhil olmak üzere çeşitli şekillerde atipik merkezi sinir sistemi işlevine katkıda bulunabilir (28). Otizm spektrum bozukluğunda; dinlenme durumu elektroensefalografisindeki izlemlerin otizm spektrum bozukluğu biyobelirteci olarak kullanıldığı bildirilmektedir (29).

Enterik Sinir Sistemi

Enterik sinir sistemi, gastrointestinal fonksiyonun birçok yönünü koordine etmekten sorumlu olan nöron ve glial hücre ağından oluşmaktadır (30). Enterik sinir sisteminin; gastrointestinal kanalda lokal hareketliliğin kontrolü ve koordinasyonundan, sıvıların mukoza epiteli boyunca hareketinden, kan akışındaki değişikliklerden ve bağışıklık sistemi ile etkileşiminden sorumlu olduğu bildirilmektedir (30). Omurgalılardan izole edilen bağırsak segmentlerinin, bağırsağın beyin ve omurilikle bağlantısının kesilmiş olmasına rağmen, belirli uyaranlara yanıt verebildiği 1700'lü yılların ortalarından beri enterik sinir sisteminin varlığını ortaya koymaktadır (31). Bağırsağın lokal uyarımının bağırsağın izole segmentlerinde polarize tepkiler uyandırabileceği bildirildikten hemen sonra lokal uyarımı takiben köpek bağırsağının dışa dönük segmentlerinde polarize sinirsel tepkilerin varlığı doğrulanmış ve bağırsağın lokal olarak uyarılmasının, uyarılan noktanın üstünde eksitasyon ve altında inhibisyon ürettiğini saptamışlardır (31). Bununla birlikte, günümüzde yaygın olan *'peristaltik refleks'* teriminin, izole bağırsak segmentleri boyunca içeriğin gerçek itişini tanımlamak için Tredelenburg tarafından kullanıldığı bildirilmiştir (31).

Enterik Sinir Sisteminin Embriyolojisi

Embriyonik gelişim sırasında, multipotent ve yüksek oranda göç edebilen mezenkimal benzeri hücre tipi olan nöral krest hücresi, epitelyal-mezenkimal geçiş yoluyla kapanan kraniyal nöral kıvrımlardan ve gövde nöral tüpünün kapalı kıvrımlarından ayrılmaktadır (32). Bu yeni oluşan hücreler, nöral tüpün belirli aksiyal seviyelerinden (kraniyal, kardiyak, vagal, gövde ve sakral) ortaya çıkar (32). Çoklu organ primordiumlarını kolonize etmek için embriyo boyunca yoğun bir şekilde göç ederek başın bağ dokusu, endokrin hücreler, melanositler ve enterik sinir sistemi ile periferik sinir sisteminin glia ve nöronları dâhil olmak üzere çeşitli hücre tiplerine farklılaşır (32).

Enterik sinir sistemi prekürsörleri, nöral tüpün vagal ve sakral segmentlerinden köken almaktadır (33). Vagal nöral krest, enterik sinir sistemi prekürsörlerinin ana kaynağıyken, sakral nöral krest distal bağırsağa ve ön gövde nöral krest ön bağırsak enterik sinir sistemine küçük bir katkı sağlamaktadır (33). Vagal nöral krest hücreleri enterik sinir sisteminin büyük çoğunluğunu oluşturmaktadır (33). Farede embriyonik 9,5. günde ve insan embriyolarında 4. haftadan önce preenterik nöral krest türevi hücreler (pre-ENCDC'ler) ön bağırsağı istila ederek, bağırsak boyunca rostrokaudal yolculuklarına başlamaktadır (33). Farelerde embriyonik 14. günde ve insanlarda 7. haftada, bu göç tamamlanmaktadır (33). Farelerde ve insanlarda, nöral krest türevi hücreler bağırsağı ilk kez kolonize ettikten sonra

içe doğru radyal olarak göç ederek miyenterik ve submukozal pleksusları oluşturan iki ganglion katmanını meydana getirir (33). Nöral krest türevi hücreler göç ettikçe, çoğalarak nöronlara ve glia'lara farklılaşmaktadır (33). Yapısal ve işlevsel bir enterik sinir sistemi oluşturmak için enterik nöral krest hücreleri; hücre çoğalması, hücre sağkalımı, yönlendirilmiş göç, konsantrik pleksuslar halinde örüntüleme, nöronal, glial hücreler ve bunların alt tiplerine farklılaşma, ganglion oluşumu, akson uzaması ve sinaptogenez gibi temel işlevleri yerine getirmektedir (32).

Enterik Pleksuslar

Enterik sinir sisteminde iki ana ganglionlu pleksus (miyenterik, submukozal) ve birkaç küçük pleksus yer almaktadır (30–37).

Miyenterik Pleksus (Auerbach Pleksusu)

Miyenterik pleksus adıyla da bilinen Auerbach pleksusu, tüm gastrointestinal sistem boyunca uzanan ve çoklu düz kas katmanlarını innerve eden bir grup gangliondan oluşmaktadır (36). Bu sinir topluluğu, muskularis externa'nın, sirküler iç ve longitudinal dış kas tabakaları arasında uzanan bir sinir şeridi, küçük ganglion ağıdır ve çoğunlukla gastrointestinal motilitenin kontrolünden sorumludur (30–36). Ağ, daire çevresinde gastrointestinal yol boyunca süreklidir (35). Tek sinir hücresi gövdeleri, genellikle bir sinir teline bitişik olan, pleksusun ana ağ örgüsü dışında görülür (35). Ganglionlar bazen pleksusun düğümleri olarak anılırlar, çünkü bunlar sinir zincirlerinin birleşme yerlerinde uzanırlar, bunlar da internodal veya interganglionik iplikler veya sıklıkla interganglionik bağlar olarak adlandırılırlar (35).

Miyenterik pleksus, primer pleksus, sekonder pleksus ve tersiyer pleksuslardan oluşur (36,37). Ganglion ve internodal iplikçikler birlikte, miyenterik pleksusun birinci ağını meydana getirir (36,37). Pleksusun sekonder ağını oluşturan, daha büyük sinir demetleri, birincil internodal iplikçiklerden dallar alır veya gangliondan ortaya çıkarlar, ancak genellikle bitişik ganglionları birbirine bağlamazlar (34,35,37). Sekonder pleksuslar, sirküler kas demetleri ile paralel olarak uzanırlar ve çoğu zaman iç içe geçmiş şeritleri çaprazlarlar (36,37). Tersiyer pleksus ise primer pleksus tarafından oluşturulan ağ örgüsü arasındaki boşluklarda dolaşan ince sinir demetlerinden ortaya çıkar (35–37). Tersiyer pleksusun sinir demetleri, primer internodal iplikçiklerden, ganglionlardan ve sekonder iplikçiklerden oluşurlar (35–37). Merkezi sinir sisteminden bağımsız olarak hareket etmektedir (35,36). Merkezi sinir sistemi ve enterik sinir sistemini birbirine bağlayan otonom sinir sisteminden innervasyon almaktadır (36).

Auerbach pleksusu enterik sinir sisteminin iki önemli bileşeninden biridir (33,35,36). Özofagustan rektuma kadar uzanan, birbirine bağlı nöronlardan oluşmaktadır (36). Eksitatör ve inhibitör motor nöronlar bağırsaklardaki düz kas hücrelerinin elektriksel bir sinsityum (Birden fazla hücrenin aralarındaki hücre zarını yok ederek çok çekirdekli tek bir hücre olmaları durumu) içinde var olmasını sağlamaktadır (36). Bu sinyallerin kontrolü, bu düz kasların gevşemesine veya kasılmasına neden olabilen çeşitli nörotransmitterler tarafından başlatılmaktadır (36). Bu sürecin sonucu olan belirli hareket kalıpları, gıdaları gastrointestinal sistem boyunca taşıyan peristaltizmi oluşturmaktadır (36). Bu sürece dâhil olan çok sayıda nörotransmitter bulunmaktadır (31–37). Bağırsak gevşemesinden sorumlu olanların en önemlileri vazoaktif intestinal peptid (VIP), nitrik oksit, hipofiz adenilat siklaz aktive edici peptid ve pürindir (32–37). Alternatif olarak, bağırsak kasılmasının uyarılması çoğunlukla taşikininler ve asetilkolinden kaynaklanmaktadır (31–33,36). Gastrointestinal sistem boyunca Cajal'ın interstisyel hücreleriyle birlikte hareket ederek, distal gevşeme ve proksimal kasılma arasında gidip gelen sistem, atıkların vücut içinde ve dışında hareketini kolaylaştırmaktadır (31,35,36). İnnervasyon öncelikle dorsal motor çekirdekten kaynaklanan vagal efferentler tarafından olmaktadır (34–36). Miyenterik pleksus ayrıca pelvik splanknik sinirlerden de bir miktar innervasyon alır (35–37). Bu sinirler miyenterik pleksusta boncuk zinciri benzeri terminaller oluşturur (36,37).

Submukozal Pleksus (Meissner Pleksusu)

Meissner pleksusu olarak da bilinen submukozal pleksus, submukozal bölgede sirküler kas ve mukoza arasında yer alır (32–35). Submukozal pleksus en çok ince ve kalın bağırsakta ganglionlu bir ağ olarak belirgindir (35). Özofagusta ganglionlu bir pleksus olarak bulunmaz ve midenin submukozal alanında seyrektir (35). İnsanlarda bağırsak submukozal pleksusu, muskularis mukozanın serozal tarafında bulunan bir iç submukozal ağdan ve dairesel kas tabakasının luminal tarafına bitişik bir dış pleksustan oluşur (34). İnsan ince ve kalın bağırsağında, iç ve dış pleksuslar arasında üçüncü bir ara pleksus bulunur (34). Submukozal pleksus lümen ortamının algılanması, gastrointestinal kan akışının düzenlenmesi, epitel hücre fonksiyonları ve sekresyonu kontrol etmektedir (37).

Bu pleksuslar, lokal olarak bağırsak epitelinin entero-endokrin hücreleri ve glial hücrelerinden, distal olarak merkezi sinir sisteminin otonom nöronlarından, sistemik olarak hormonal sinyallerle, mikrobiyota ve lümen içeriği gibi farklı yönden sürekli uyarı almaktadır (1,31,32,34).

Mukozal Pleksus

Mukozal pleksusun ince sinir lifleri sırasıyla interglandüler, periglandüler ve subglandüler ağları oluşturmak üzere, tübüler bezler arasında glandüler epitele yakın ve fundusların bir yuva gibi çevreleyen lamina propria bağ dokusunda belirgindir (34,37). Sinir demetleri çoğunlukla düz kas hücrelerinin uzun eksenlerine paralel uzanmaktadır (34,37).

Subserozal Pleksus

Subserozal pleksus, longitudinal kas tabakası ile mezotelyum arasındaki subserozal tabakada bulunmaktadır (38). Vagus siniri aracılığıyla ekstrinsik lifleri ve splanknik sinirler tarafından

Tablo 1. Dogiel tarafından sınıflandırılan nöron çeşitleri ve özellikleri (30,31,34,35,37)

Nöron Çeşitleri	Nöron özellikleri
Tip I nöronlar	Bir aksonu ve en fazla 20 tane dendriti bulunmaktadır.
Tip II nöronlar	Bir aksonu ve aksonlara benzeyen en fazla 16 tane uzun dendriti bulunmaktadır. Enterik refleksleri uyandıran fizyolojik uyaranlara doğrudan tepki vermeleri nedeniyle enterik refleks yollarının ilk nöronları oldukları sonucuna varılmıştır
Tip III nöronlar	Bir aksonu ve en fazla 10 tane dendriti bulunmaktadır. En yaygın "multipolar" enterik nöronlardır.
Tip IV nöronlar	Bir aksonu kısa dendritleri bulunmaktadır. Miyenterik pleksustan mukozaya projekte olurlar. Sekretomotor nöronları temsil edebilirler.
Tip V nöronlar	Uzun dallanmış dendritleri bulunmaktadır. Dikkat çekici kümeler olarak görülürler.
Tip VI nöronlar	Bir aksonu ve ince dendritleri (aksonal dendritler) bulunmaktadır.
Tip VII nöronlar	Nadir olarak bulunmaktadır. İnsan, köpek ve domuzda tanımlanmıştır

taşınan sempatik postganglionik aksonları içeren sinir liflerinden oluşmaktadır (37). Özofagus, mide ve rektumun ön kısmında bulunmaktadır (37).

Destek Hücreleri

Enterik glia hücresi

Enterik sinir sisteminin glia hücreleri, merkezi ve periferik glialardan farklı olarak gastrointestinal duvarın tüm katmanlarına yayılan geniş bir ağ oluşturmaktadır (33,35,39). Tipik bir enterik glia hücresi, enterik ganglionlardaki nöron hücre gövdeleri ve interganglionik bağlantılardaki sinir lifi demetleri ile ilişkili, düzensiz, yıldız şeklinde, küçük hücreler olarak tanımlanmaktadır (39). Enterik glia ve nöronlar arasındaki yıldız görünümü ve yakın fiziksel ilişki, merkezi sinir sistemindeki astrositler ve nöronlar arasındaki ilişkiyle benzerlik göstermektedir (35,39). Aslında, enterik glia ve astrositler elektrofizyolojik özellikleri ve benzer proteinleri içerdikleri için moleküler düzeyde de benzemektedirler (39). Enterik glia hücresinin, enterik nöronlar ve diğer komşu hücre tipleriyle multipl çift yönlü iletişimi sayesinde majör gastrointestinal fonksiyonları düzenlediği bildirilmektedir (39). Son yıllarda ki çalışmalar, enterik glia hücresinin bağırsak duvarında farklı lokalizasyon, fenotip ve aktivite ile ilişkili heterojen bir popülasyonu temsil ettiği öne sürülmektedir (39).

Enterik glia hücreleri arasındaki morfolojik farklılıklara dayanarak enterik glial hücre popülasyonları sınıflandırılmıştır (39). Enterik glia tipleri ile astrositler arasındaki benzerlik nedeniyle merkezi sinir sisteminin protoplazmik astrositlerine benzeyen kısa ve düzensiz dallanmaya sahip yıldız şeklindeki intraganglionik gliaları "*protoplazmik*" veya *"tip I"* enterik gliositler olarak tanımlamışlardır (39). Merkezi sinir sisteminin beyaz cevher yollarının fibröz astrositlerine benzeyen interganglionik lif yolları içindeki uzun gliaları "*fibröz*" veya *"tip II*" enterik gliositler, birkaç uzantıya sahip subepitelyal gliaya "*mukozal*" veya *"tip III*" enterik gliositler olarak isimlendirilmişlerdir (39). Kas sisteminde sinir lifleriyle birlikte çalışan uzun glialara *"kas içi"* veya *"tip IV"* enterik gliositler olarak bildirmişlerdir (39). Bu temel morfolojik farklılıkların, enterik glia popülasyonları arasında daha spesifik moleküler ve fonksiyonel farklılıkların ortaya çıkabileceğini, reseptör ekspresyonu, kanal ekspresyonu ve fonksiyon farklılıkların, farklı bağırsak bölgelerindeki myenterik ve submukozal pleksusların intraganglionik glial hücreleri arasında heterojenlik gösterebileceğini bildirmişlerdir (39).

Cajal'ın İnterstisyel Hücreleri

Mezenkimal kökenli interstisyel hücreler birçok organda düz kas hücreleri ile etkileşime girerek elektriksel bağlantı oluşturup, önemli düzenleyici işlevleri yerine getirmektedir (37,38). Cajal'ın interstisyel hücreleri, döngüsel spontan depolarizasyon ve yavaş dalgalar üretme yetenekleri nedeniyle gastrointestinal kanalın pacemaker'ları olarak adlandırılmaktadır (37). Cajal'ın interstisyel hücreleri düz kas hücreleri ve nöronlarla yakın temas halindedir (37). Aksonal varikoziteler (nörotransmitterlerin depolandığı bölgeler) düz kas hücrelerine kıyasla Cajal'ın interstisyel hücreleriyle daha yakın temas halindedir (37). Ayrıca, Cajal'ın interstisyel hücreleri düz kaslarla ara bağlantıları yapar (37). Son yıllarda yapılan çalışmalar, Cajal'ın interstisyel hücrelerinin nöromusküler iletimde (nöronlar ve düz kaslar arasında) aracı bir rol oynadığını göstermektedir (37).

Enterik Nöronlar

Enterik sinir sistemi iki konsantrik ganglionlu pleksus halinde organize olmuş enterik nöronlar ve glial hücrelerden oluşmaktadır (32). Enterik nöronlar geleneksel olarak morfolojileri, elektrofizyolojik özellikleri ve nörotransmitter ekspresyonlarına göre sınıflandırılmaktadır (35).

Morfolojilerine göre Enterik Nöronlar

Enterik nöron morfolojisi ilk olarak Dogiel tarafından nöronal hücre gövdeleri, akson ve dendritlerin şekil ve sayılarına göre tanımlanmıştır (30,31,34,35,37) (Tablo 1).

Elektrofizyolojik Özelliklerine göre Enterik Nöronlar

Enterik nöronların elektrofizyolojik özelliklerine göre sınıflandırılması, türler arasında karşılaşılan farklılıklar ve nöronların özellikleri; nörotransmitterlerin, hormonların ve diğer ajanların, örneğin histamin ve prostaglandinler gibi enflamatuvar aracıların etkileri ile değiştirilebilmektedir (31,34,35,37). AH nöronlarının primer duyusal nöronlar olduğu, S nöronlarının ise internöronlar ve motor nöronlar olduğu düşünülmektedir (31,34,35,37).

b. 1. S nöronları

S nöronları, 20–100 ms süren kısa süreli hiperpolarizasyon sonrası potansiyel tarafından takip edilen kısa aksiyon potansiyelleri sergilemektedir (31,34,35,37). S nöronları, Dogiel tip I ve ipliksi morfolojileri içeren çeşitli şekillere sahiptirler (30,31,34,35,37). Hızlı uyarıcı postsinaptik potansiyeller göstermektedirler (31,34).

b. 2. AH nöronları

AH nöronları, düşme fazında bir bükülme ve bunu takip eden uzun hiperpolarizasyon sonrası potansiyel ile daha büyük aksiyon potansiyelleri göstermektedir (31,34,35,37).

Fonksiyonlarına göre Enterik Nöronlar

Enterik nöronlar; motor nöronlar, intrinsik primer afferent nöronlar, intestinofugal nöronlar ve internöronlar olmak üzere dört gruptan oluşmaktadır (30,34,35,37).

c. 1. Motor Nöronlar

Enterik sinir sisteminin motor nöronları sirküler ve longitudinal kas tabakalarını, intrinsik arteriyolleri ve enteroendokrin hücreleri içeren epitelyumu innerve etmektedir (30,34,35,37). Eksitatör, inhibitör, sekretomotor, vazomotor ve enteroendokrin hücreleri innerve eden nöronlar olmak üzere beş tip tanımlanmıştır (37). Eksitatör motor nöronlar ağırlıklı olarak asetilkolin adı verilen nörotransmitter kullanmaktadırlar (30,31,34,35,37). Submukozanın sınırına yakın uzanan sirküler kası innerve ederler (40). İnhibitör motor nöronlar ise primer olarak nitrik oksit nörotransmitteri, sekonder olarak da vazoaktif intestinal peptid (VIP), adenozin trifosfat (ATP) ve karbon monoksit (CO) nörotransmitterleri içermektedir (30,31,34,35,37). Anal yönde hücre gövdelerine yakın (2 mm içinde) olan kaslara projekte olmaktadır (37). Eksitatör motor nöronlar düz kas kasılmasını uyarırken, inhibitör motor nöronların deşarj olmasıyla meydana gelen hareketsizlik nedeniyle anüse doğru itici kasılmaya neden olmaktadır (30,31,34,37). Otonom sinir sisteminin (Ach salınımının sempatik inhibisyonu), nörotransmitterlerin (VIP, NO, P maddesi ve CGRP), kortikotropin salgılatıcı faktör (CRF) gibi hormonların, endojen opioidlerin ve bağırsak manipülasyonunun etkisine bağlı anormal eksitatör ve inhibitör girdinin hayvan deneylerinde çeşitli gastrointestinal dismotilite formlarına neden olduğu bildirilmiştir (40).

Submukozal ganglionlarda hücre gövdeleri bulunan sekretomotor nöronlar ince ve kalın bağırsak mukozasını innerve etmektedir (40). Kan damarlarının kollateral innervasyonu, nöroepitelyal ve nörovasküler bağlantı noktalarında eş zamanlı olarak salınan asetilkolinle kan akışını sekresyonla birleştirir (40). Asetilkolin kan damarlarına etki ederek endotelden nitrik oksit salgılanmasıyla kan damarları genişler ve uyarılmış salgıyı desteklemek için kan akışını artırır (41). Sekretomotor nöronlar, ikiye ayrılarak kolinerjik ve nonkolinerjik olarak adlandırılmaktadır (34). Sekretomotor nöronlara benzer şekilde, vazomotor nöron hücre gövdeleri de submukozal pleksus ganglionlarında bulunmaktadır, epitelyal salgıyı ve kan akışını düzenlemek için birlikte çalışmaları ve bu reflekslerin sempatik sistem aracılığıyla ekstrinsik modülasyon altında olduğuna dikkat etmek gerekmektedir (40).

Enteroendokrin hücreler, bağırsak mukozasında bulunan ve bağırsak lümenindeki çeşitli kimyasal ve mekanik uyaranlarla etkileşime giren özelleşmiş hücrelerdir (40).

c. 2. İnternöronlar

İnternöron olarak da işlev görebilen intrinsik duyusal nöronlar miyenterik pleksusta bulunmaktadır (31,35,37,40). İnternöronlar oral veya anal olarak projekte olan tek eksenli çıkan ve inen internöronlar olarak ikiye ayrılmaktadır (35,37,40). Bu farklı alt sınıfların her birindeki nöronlar, bağırsak uzunluğu boyunca uzanan zincirler oluşturmak için benzer nöronlarla birbirine bağlanmaktadır (35,37). Çıkan internöronlar lokal duyusal nöronlardan girdiler alır ve eksitatör motor nöronlara projeksiyon yaparken, inen internöronlar lokal duyusal nöronlardan girdiler alır ve inhibitör motor nöronlara projeksiyon yapar (40). Tıpkı motor nöronlar gibi internöronların da primer nörotransmitteri asetilkolindir (31,34,35,37,40). Ayrıca, ATP özellikle inen tipte ikincil bir nörotransmitter olarak tanımlanmıştır (30,31,34,40).

c. 3. İntrinsik Primer Afferent Nöronlar

İntrinsik primer afferent nöronların, kemosensoriyel ve mekanosensoriyel özellikleri bulunmaktadır (30,32,34,35,37,40). Dogiel Tip II morfolojisine sahiptir (30,32,34,35,37,40). Bağırsağın fiziksel durumunu tespit edebilmektedir (40). Hem submukozal pleksus hem de miyenterik pleksusda yer almaktadır (35,37,40). Primer nörotransmitterleri arasında asetilkolin, kalsitonin geniyle ilişkili peptid ve taşikinin bulunmaktadır (40).

c. 4. İntestinofugal Nöronlar

Hücre gövdeleri myenterik pleksusta bulunan intestinofugal nöronlar, bağırsağın distansiyonuna ilişkin bilgileri alıp, bu bilgileri merkezi olarak prevertebral ganglionlara iletmektedir (42). Distal kolonda bağırsağın diğer bölgelerine göre daha fazla sayıda bulunan bu nöronlar, gastrointestinal sistemin tüm seviyelerine projeksiyon yapan postganglionik sempatik nöronları innerve etmektedir (42). Sempatik prevertebral ganglion nöronları ile intestinofugal nöronlar, intestino-intestinal inhibitör nöral reflekslerin temelini oluşturmaktadır (42).

Metod

Bu çalışma, ulusal ve uluslararası literatürde enterik sinir sisteminin otizm spektrum bozukluğu olan çocuklardaki etkisi ve önemini araştıran çalışmaları gözden geçirmek amacıyla sistematik inceleme türünde gerçekleştirilmiştir. İnceleme PRISMA (43) kriterlerine uyumlu olarak yapılmıştır.

Tablo 2. Makale tarama verileri (n=49)

	Değişken	Toplam sayı (n)	%
Yazar Sayısı	Üç ve daha az yazar	27	55,10
	Dört ve beş yazar	9	18,36
	Altı ve daha fazla yazar	13	26,53
Yayın Yılı	1994–2004	2	4,08
	2005–2015	18	36,73
	2016–2023	29	59,18
Yazım türü	Derleme (review)	24	48,97
	Kısa rapor (brief report)	1	2,04
	Araştırma makalesi	20	40,81
	Kitap bölümü (chapter)	2	4,08
	Tez	1	2,04
	DSM-V (Mental bozuklukların tanısal ve istatistiksel el kitabı)	1	2,04
Sık kullanılan anahtar kelimeler (n=92)	Otizm spektrum bozukluğu Otizm	17	18,47
	Otonom sinir sistemi Enterik sinir sistemi Enterik nöron ve glia	7	7,60
	Vagus siniri Vagal sinir aktivitesi Efferent ve afferent vagal sinir aktivitesi Vagus sinir stimülasyonu	5	5,43
	Gastrointestinal (Gis) sistem Gis sorunları Gis bozuklukları Kabızlık, ishal, gastroözofageal reflü, karın ağrısı	11	11,95
	Diyet Ketojenik Glutensiz Kazeinsiz Vitamin, Mineral, Prebiyotik, Probiyotik	12	13,04
	Bağışıklık Bağışıklık sistemi Enfeksiyon Maternal bağışıklık aktivasyonu İnflamatuvar yanıt	4	4,34
	Bağırsak-beyin ekseni Beyin-bağırsak-mikrobiyom sistemi Mikrobiyota-bağırsak-beyin ekseni Mikrobiyom Mikrobiyota Disbiyoz Bağırsak mikrobiyotası Bağırsak disbiyozu Sızdıran bağırsak	20	21,73

Çalışma; 10 Kasım 1994 ile 31 Aralık 2023 tarihleri arasında yayınların retrospektif taranmasıyla gerçekleştirilmiştir. "Enterik Sinir Sistemi ve Otizm Spektrum Bozukluğu, Gastrointestinal Semptom" anahtar kelimeleri kullanılarak Ulusal Tez Merkezi (https://tez.yok.gov.tr/UlusalTezMerkezi/), Google Scholar (https://scholar.google.com/) ve PubMed (https://pubmed.ncbi.nlm.nih.gov/) arama motoru kullanılarak veri tabanlarında tarama yapılmıştır.

Bulgular

Derleme kapsamına alınan makaleler tam metinlerine ulaşılarak, sistematik inceleme yapılarak, çalışmamız amacına uygun olarak değerlendirilmiş ve analiz edilip sunulmuştur.

Bulgular;

- Otizm spektrum bozukluğunun etiyolojisi
- Mental Bozuklukların Tanısal ve İstatistiksel El Kitabında (DSM-V); otizm spektrum bozukluğu alt gruplarının tanımlanması
- Otizm spektrum bozukluğundaki gastrointestinal semptomlar
- Enterik sinir sistemi önemi
- Enterik sinir sistemi yapısı
- Enterik sinir sistemi ve otizm spektrum bozukluğundaki bağlantılar olarak saptanmıştır.

Kategorize edilen bulgular sentezlenmiş ve sonuçlar derleme makalemizde sunulmuştur. Bu kapsamda toplam 49 makalenin tarama verileri Tablo 2'de yer almaktadır (Tablo 2).

Enterik Sinir Sistemindeki İşlev Bozukluklarının Otizm Spektrum Bozukluğu Üzerindeki Etkileri

Otizm Spektrum Bozukluğu olan çocuklarda gastrointestinal semptomların görülme sıklığının %30–37,4 olduğu belirtilmiştir (10). Otizm spektrum bozukluğu olan çocuklarda gastrointestinal semptomların görülme sıklığı %9–70 arasında iken, sağlıklı çocuklarda bu oran %15–18 arasında değişmektedir (15). Epidemiyolojik olarak yapılan bir çalışmada ise; 2–5 yaş arası otizm spektrum bozukluğu olan çocuklarda gastrointestinal semptomların görülme sıklığı %43,1 olarak rapor edilmiştir (10). Retrospektif bir çalışmada da 18–36 aylık otizm spektrum bozukluğu olan bebeklerde kabızlık, ishal ve gıda alerjisi/intoleransının görüldüğünü bildirmişlerdir (10).

Otizm spektrum bozukluğunda gastrointestinal semptomların yüksek oranda görülmesinin multifaktöryel (genetik, çevresel ve davranışsal faktörlerin bir arada olması) nedenlerden dolayı olduğu düşünülmektedir (12). Son yıllarda yapılan çalışmalar sayesinde pediatrik ve yetişkin otizm spektrum bozukluğu olan popülasyonlarda yüksek oranda bozulmuş motilite, bağırsak gazlarının aşırı üretimi, şişkinlik, karın ağrısı, ishal, geğirme, öğürme, gastroözofageal reflü ve kabızlık gibi gastrointestinal semptomların olduğu saptanmıştır (1,5–19,44)

Bağırsaklar, sempatik sinir sistemi, parasempatik sinir sistemi ve enterik sinir sistemindeki nörotransmitterler tarafından kontrol edilmektedir (15). Sempatik sinir sistem enterik sinirlerin uyarılmasına neden olarak gastrointestinal aktivite üzerinde inhibitör etkiye neden olmaktadır (15). Parasempatik sinir stimülasyonu ise enterik sinir sistemi aktivitesinin artmasına yol açmaktadır (15). Parasempatik sinir lifleri sigmoid kolon, rektum ve anüse zengin bir nöral girdi sağlayarak defekasyonun kontrolünde önemli rol oynamaktadır (15). Yu ve ark. (2020), büyük ölçekli nöral haritalama tekniklerini kullanarak, çok sayıda beyin bölgesinin vagus siniri stimülasyonundan etkilendiğini göstermiş ve bu bağlantıyı "*vagus afferent ağı*" olarak adlandırmıştır (45). Vagal afferentler öncelikle beyin sapındaki nükleus traktus solitariusta sonlanmakta ve burada visseral bilgi, çoklu sinaptik bağlantılar yoluyla lokus soruleus, medulla oblongata'nın rostral ventrolateral parçası, dorsal rafe çekirdeği ve hipotalamusa bilgileri iletmektedir (45).

Vagus siniri, bağırsak ile beyin arasında sindirim, bağışıklık , ödül, hafıza ve kognitif gibi çeşitli işlevleri düzenleyen önemli bir bağlantıyı oluşturmaktadır (45). Aynı zamanda beyin ve bağırsak arasında hem afferent hem de efferent yönde bilgi iletmektedir (13). Vagal efferentler gastrointestinal salgıyı, motor fonksiyonları ve enterik endokrin sistemdeki aktiviteyi de düzenlemektedir (46). Hipotalamik-hipofiz-adrenal korteks ekseninde vagal afferentler ya da kolinerjik antienflamatuvar lifler vagal efferentleri de kullandığı için vagus sinirinin ikili bir antienflamatuvar etkisi olduğu düşünülmektedir (47). Ayrıca; vagus siniri bağırsaklardan, besinlerin ve suyun emiliminde de görev yaptığı için sıvı homeostazının hızlı bir şekilde düzenlenmesini de sağlamaktadır (45). Bunlarla birlikte vagal duyu nöronları aktive edildiğinde sindirimi de kolaylaştırmaktadır (45). Bütün bu çalışmalar, vagal duyu nöronlarının önemli bağırsak sinyallerini beyne ileterek sindirim, immünolojik ve psikolojik hastalıkların tedavisi için terapötik bir hedef olarak kullanılabileceğini de bildirilmişlerdir (45). Ayrıca, vagus sinir stimülasyonu bağırsaktaki afferent sinyalleri taklit ettiğinden depresyon tedavisinde kullanılabileceği ve öğrenme ile hafızayı da geliştirdiği bildirilmiştir (19).

Enterik sinir sistemi otonom sinir sisteminin en büyük bölümünü oluşturduğundan gastrointestinal fonksiyonların düzenlenmesini sağlayan mikro devrelerden oluşmaktadır (19). Enterik ve merkezi sinir sisteminin nörotransmitterleri, sinyal yolakları ve anatomik özellikleri ortak olduğundan merkezi sinir sisteminin hastalığının altında yatan nedenlerde genellikle enterik sinir sisteminde de belirtiler görülmektedir (19). Beyinle bağırsak arasındaki vagal liflerin %90'ı afferenttir (19). Afferent lifler merkezi sinir sistemindeki nöronları uyararak enterik uyarılara yanıt vermelerini sağlayarak yemek borusu veya midedeki hareketliliği düzenlemek için vagovagal refleksleri başlatmaktadır (19). Bu refleksler, midenin genişlemesi ve besinlerin ince bağırsağa taşınana kadar depolanmasını ve öğütülmesini sağlamaktadır (19). İnce ve kalın bağırsak hareketleri enterik sinir sistemi tarafından kontrol edilmektedir (19). Bağırsaktan beyne giden sinyaller bulantı, şişkinlik, tokluk hislerini iletirken, aynı zamanda bilince ulaşmayan duygu durum belirleyiciliği de yapmaktadırlar (19).

Enterik sinir sistemi, besinlerin hareketi, sindirim enzimlerinin sekresyonu ve besinleri emilimi gibi sindirim fonksiyonların düzenlenmesinde çok önemli rol oynamaktadır (12). Bağırsaklar, zonulin proteini ve bütirat gibi kısa zincirli yağ asitleri, sekretuvar immünoglobulin A ve mukoza zarı bariyer bütünlüğü sinyalizasyonu, vagus siniri aktivasyonu, nöropeptitler, leptin ve serotonin gibi nörotransmitterler yoluyla beyni etkilemektedir (12). Bağırsak ve beyin arasındaki iletişim, bağırsak-beyin ekseni aracılığıyla merkezi sinir sistemi ile gastrointestinal sistem arasında çift yönlü olarak meydana gelmektedir (12). Bağırsak ve beyin arasındaki iletişim, nörokrin ve endokrin yollar gibi çeşitli mekanizmalar sayesinde oluşmaktadır (12). Bu eksenin, kognitif fonksiyon, davranış ve diğer beyin fonksiyonlarını etkilemesi, sindirim ve metabolizma gibi fizyolojik süreçleri düzenlemesi gibi önemli görevleri bulunmaktadır (12). Otizm spektrum bozukluğu olan bireylerde bağırsak beyin arasındaki iletişimin bozulması bağırsak beyin ekseninin uyumsuzluğu ile sonuçlanmaktadır (12). Bu durum sindirim sorunlarına neden olarak gastrointestinal fonksiyonu etkileyebilmektedir (12).

Otizm spektrum bozukluğundaki nöroanatomik değişiklikler, parasempatik sistemin aktivasyonunun azalması ve sempatik sistemin aşırı aktivasyonuyla bağırsak-beyin ekseninde düzensizliğe, bağırsak immün sisteminin humoral ve hücresel bileşenlerinin zayıflamasına, bağırsak osmotik dengesinin ve mukus üretiminin düzensizleşmesine ve kalıcı disbiyoza neden

olmaktadır (15). Bununla birlikte, otizm spektrum bozukluğu olan bireylerde sempatik aktivasyonu içeren stres reaksiyonunun bir parçası olarak ishal de görülebilmektedir (13).

Otizm spektrum bozukluğu olan bireylerde bağırsak mikrobiyotasının değişmesi veya disbiyoz nedeniyle bağırsak geçirgenliğinde (sızdıran bağırsak) artış meydana gelerek güçlü bir proenflamatuvar endotoksin olan lipopolisakkaritin üretildiği ve yayıldığı tespit edilmiştir (11). Bu molekül, duyguları ve davranışları kontrol eden amigdala gibi bölgelerin aktivitesini artırarak merkezi sinir sistemini modüle edebilmektedir (11). Aslında bağırsak geçirgenliği, bağırsak içeriğinin tamamının kan dolaşımına girmesini önleyerek immünolojik enflamatuvar yanıtların ve gastrointestinal hastalıkların baskılanmasını sağlamaktadır (48). Otizm spektrum bozukluğu olan çocukların propiyonik asit içeren gıda koruyucularına maruz kaldıklarında semptomlarının ağırlaşmasının nedeninin artmış bağırsak geçirgenliği ile ilişkili olabileceği belirtilmiştir (16). Gastrointestinal semptomları olan otizm spektrum bozukluğu olan çocukların %43'ünde bağırsak geçirgenliğinin bozulduğu bildirilmiştir (16).

Madra ve ark. (2020), otizm spektrum bozukluğu olan çocukların, kontrollere göre daha fazla stres reaktivitesi gösterdiği ve stres sonrası kortizol seviyeleri ile ilişkili daha fazla gastrointestinal semptomlara sahip olduğunu bildirmişlerdir (7). Otizm spektrum bozukluğu olan çocuklarda kronik gastrointestinal semptomlarla ilişkili en yaygın psikiyatrik bozukluğun anksiyete olduğu tespit edilmiştir (7). Bu çocuklarda anksiyetenin yaygın belirtileri arasında basit fobiler, yaygın anksiyete, ayrılma anksiyetesi, obsesif-kompulsif bozukluk ve sosyal fobiler yer almaktadır (7). Otizm spektrum bozukluğu olan bireylerde yüksek oranlarda görülen anksiyete ve sosyal geri çekilme gibi içselleştirme semptomlarının kabızlık, ishal, mide bulantısı ve mide ağrısı gibi gastrointestinal semptomlarla çift yönlü etkileşiminin olduğu saptanmıştır (5). Prosperi ve ark. (2019) yaptıkları çalışmada özellikle sözel becerileri sınırlı olan otizm spektrum bozukluğu olan çocuklarda uyumsuz davranışlarla gastrointestinal semptomları ilişkilendirerek bu davranışların bireyin kendisini ifade etme şekli olabileceğini öne sürmektedirler (14). Sözlü becerisi kısıtlı olan otizm spektrum bozukluğu olan çocukların; gastrointestinal ağrıyı uyumsuzluk, kendini yaralama, asabiyet, farklı sesler çıkarma (örn. sık sık yutkunma, inleme), mimikler (örn. Asık suratlılık), hiperaktivite, düzensiz uyku, anksiyete şeklinde gösterebildiklerini bildirmişlerdir (14). Özefajiti olan otizm spektrum bozukluğu tanısı almış çocukların %43'ünde asabiyet ve fonksiyonel kabızlığa ek olarak rijid-kompulsif davranışlar görüldüğü belirtilmiştir (7). Peeters ve ark. (2013), fonksiyonel dışkılama bozukluğu ile başvuran 4–12 yaş arası çocukların %29'unda otizm spektrum bozukluğu semptomlarının eşlik ettiğini belirtmişlerdir (18). Adams ve ark. (2011), gastrointestinal semptomların otizm şiddeti ile korelasyonu araştırmışlardır (17). Şiddetli otizm spektrum bozukluğu olan çocukların daha fazla gastrointestinal semptomlara sahip olma olasılığının yüksek olduğunu bildirmişlerdir (17).

Otizm spektrum bozukluğu olan bireylerde bağırsak enterokromaffin hücrelerinde serotonin üretiminin artması nedeniyle yüksek tam kan serotonin seviyesi veya hiperserotonemi görülmektedir (6). Preklinik çalışmalarda hiperserotoneminin duygu durum bozuklukları ile ilişkilendirildiği bildirilmiştir (6).

Otizm spektrum bozukluğu olan bireylerde yetersiz besin alımının vitamin ve mineral eksikliğine neden olduğu tespit edilmiştir (49). Otizm spektrum bozukluğu olan çocuklarda özellikle D vitamini eksikliğinin bağırsak florası bozukluğu, bağırsak iltihabı ve artmış bağırsak geçirgenliğine neden olduğu bildirilmiştir (49). Çok faktörlü bir bozukluk olması nedeniyle otizm spektrum bozukluğu tedavisi her bireyin ihtiyacına göre farklılık gösterdiğinden semptomların iyileştirilmesinde vitamin takviyeleri alternatif tedavi olarak düşünülmektedir (49). Wang ve ark. (2023), önemli minerallerden biri olan çinkonun kognitif gelişim ve beyin fonksiyonları için gerekli olan nörogenez, nöronal göç ve farklılaşmayı düzenleyerek yenidoğanların gelişiminde önemli rol oynadığını bildirmişlerdir (1). Çinko eksikliği otizm spektrum bozukluğu olan bireylerde daha fazla görülürken daha az oranda demir, krom, manganez, kobalt ve bakır eksikliği de görülebilmektedir (49,50). Vitamin ve mineral takviyelerinin, otizm spektrum bozukluğu olan çocuklar ve yetişkinler tarafından kullanılarak beslenme eksikliklerini giderme, çeşitli metabolik sorunları tedavi etme, semptomları ve genel yaşam kalitesini iyileştirmede faydalı olabileceği bildirilmiştir (49).

Bağırsaklar, bağırsak-beyin iletişiminde rol oynayan önemli bir biyoaktif peptit kaynağıdır (15). Periferik ve beyin dokuları üzerindeki doğrudan etkileri ile birlikte, bağırsak peptidleri enterik nöronları da etkilemektedir (15). Konsantrasyonları, mikrobiyotadan yayılan sinyallerle modüle edildiğinden, bağırsak peptitlerinin (GLP1/2, CCK, ghrelin, PYY, NPY, galanin, vb.) sinyali anksiyete, depresyon ve otizm spektrum bozukluğu gibi nörodejeneratif bozukluklarıyla ilgili patofizyolojik süreçlerin önemli bir modülatörüdür (15).

Mikroorganizmaların sentezlediği çok sayıda metabolit, bağırsak hareketliliği, bağırsak-beyin ekseninin kontrolü, bağırsak mikrobiyotası ve enterik sinir sistemi arasındaki etkileşime aracılık etmektedir (15). Bağırsak mikrobiyotası, enterik nöronlar üzerinde etkili olan biyoaktif molekülleri üreterek gastrointestinal hareketliliği düzenlemektedir (15). Böylece intrinsik primer afferent nöronları etkileyerek "bağırsak-beyin ekseni" sinyallerini oluşturmaktadır (15). Böylece bağırsak mikrobiyotasının beyin gelişimi ve fonksiyonu, sindirim, besin emilimi, bağışıklık ve bağırsak sağlığı üzerinde etkili olduğu bildirilmektedir (12). Mikrobiyotadaki bozulmalar bağırsak disbiyozisini geliştirmekte bu durum da otizm spektrum bozukluğu olan bireylerde gastrointestinal semptomların oluşmasına yol açabilmektedir (15).

Ayrıca, kronik bağırsak iltihabı olan yaşları 3–12 arası değişen otizm spektrum bozukluğu olan çocuklarda bağışıklık fonksiyon

bozukluğu, mikrobiyota çeşitliliğinde farklılıklar ve mukoza ile ilgili sitokin seviyelerinde artış olduğu bildirilmiştir (10).

Sonuç

Bağırsak-beyin ekseninde çift yönlü iletişim sayesinde her iki sistemde oluşan sorunlar karşılıklı olarak sistemler üzerinde olumsuz etkiler oluşturabilmektedir. Enterik sinir sistemi üzerinde gelişen olumsuz etkiler sistemin disfonksiyonuna neden olmaktadır. Otizm spektrum bozukluğu olan bireylerde de enterik sinir sisteminde oluşan değişiklikler nedeniyle gastrointestinal sorunlar görülmektedir. Bu sorunların çözümü için otizm spektrum bozukluğu ve enterik sinir sistemi ilişkisi konusunda daha fazla araştırmaya gereksinim vardır. Bu araştırmalar sonucunda otizm spektrum bozukluğunda gastrointestinal sorunların iyileştirilmesi otizm spektrum bozukluğu olan bireylerde genel yaşam kalitesini artıracaktır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - RG, MB, EDB; Tasarım - RG; Denetleme - RG, EDB; Analiz ve Yorum - RG; Literatür Taraması - RG, EDB; Yazıyı Yazan - EG, EDB; Eleştirel İnceleme - RG, MB.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - RG, MB, EDB; Design - RG, ED; Analysis and/or Interpretation - RG; Literature Search - RG, EDB; Writing - EG, EDB; Critical Reviews - RG, MB.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Kaynaklar

1. Wang X, Tang R, Wei Z, Zhan Y, Lu J, Li Z. The enteric nervous system deficits in autism spectrum disorder. Front Neurosci. 2023;17:1101071. https://doi.org/10.3389/fnins.2023.1101071
2. Doenyas C, Ekici B, Unay Ö S, Gönen İ, Tatlı B. Autism in Turkey: demographics, behavior problems, and accompanying medical conditions in a sample of Turkish youth with autism spectrum disorder. Int J Dev Disabil. 2023;69(2):179–189. https://doi.org/10.1080/20473869.2021.1937001
3. American Psychiatric Association D, Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association. 2013. https://doi.org/10.1176/appi.books.9780890425596
4. Carbone A, Dell'Aquila A. The Diagnosis of "pervasive developmental disorder not otherwise specified": a systematic literature review. Children (Basel). 2023;10(5). https://doi.org/10.3390/children10050844
5. Dovgan K, Gynegrowski K, Ferguson BJ. Bidirectional relationship between internalizing symptoms and gastrointestinal problems in youth with Autism Spectrum Disorder. J Autism Dev Disord. 2023;53(11):4488–4494. https://doi.org/10.1007/s10803-022-05539-6
6. Chernikova MA, Flores GD, Kilroy E, Labus JS, Mayer EA, Aziz-Zadeh L. The brain-gut-microbiome system: pathways and implications for autism spectrum disorder. Nutrients. 2021;13(12). https://doi.org/10.3390/nu13124497
7. Madra M, Ringel R, Margolis KG. Gastrointestinal issues and autism spectrum disorder. Child Adolesc Psychiatr Clin N Am. 2020;29(3):501–513. https://doi.org/10.1016/j.chc.2020.02.005
8. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord. 2014;44(5):1117–1127. https://doi.org/10.1007/s10803-013-1973-x
9. Wasilewska J, Klukowski M. Gastrointestinal symptoms and autism spectrum disorder: links and risks –a possible new overlap syndrome. Pediatric Health Med Ther. 2015;6:153–166. https://doi.org/10.2147/PHMT.S85717
10. Leader G, Abberton C, Cunningham S, Gilmartin K, Grudzien M, Higgins E, et al. Gastrointestinal symptoms in autism spectrum disorder: a systematic review. Nutrients. 2022;14(7):1471. https://doi.org/10.3390/nu14071471
11. Mehra A, Arora G, Sahni G, Kaur M, Singh H, Singh B, et al. Gut microbiota and autism spectrum disorder: from pathogenesis to potential therapeutic perspectives. J Tradit Complement Med. 2023;13(2):135–149. https://doi.org/10.1016/j.jtcme.2022.03.001
12. Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R, Alhawamdeh R. Role of gastrointestinal health in managing children with autism spectrum disorder. World J Clin Pediatr. 2023;12(4):171–196. https://doi.org/10.5409/wjcp.v12.i4.171
13. Ferguson BJ, Marler S, Altstein LL, Lee EB, Akers J, Sohl K, et al. Psychophysiological associations with gastrointestinal symptomatology in autism spectrum disorder. Autism Res. 2017;10(2):276–288. https://doi.org/10.1002/aur.1646
14. Prosperi M, Santocchi E, Muratori F, Narducci C, Calderoni S, Tancredi R, et al. Vocal and motor behaviors as a possible expression of gastrointestinal problems in preschoolers with autism spectrum disorder. BMC Pediatr. 2019;19(1):1–10. https://doi.org/10.1186/s12887-019-1841-8
15. Beopoulos A, Gea M, Fasano A, Iris F. Autonomic nervous system neuroanatomical alterations could provoke and maintain gastrointestinal dysbiosis in autism spectrum disorder (ASD): a novel microbiome-host interaction mechanistic hypothesis. Nutrients. 2021;14(1). https://doi.org/10.3390/nu14010065
16. Dargenio VN, Dargenio C, Castellaneta S, De Giacomo A, Laguardia M, Schettini F, et al. Intestinal barrier dysfunction and Microbiota–Gut–Brain axis: possible implications in the pathogenesis and treatment of autism spectrum disorder. Nutrients. 2023;15(7):1620. https://doi.org/10.3390/nu15071620
17. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism –comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 2011;11(1):22. https://doi.org/10.1186/1471-230X-11-22
18. Peeters B, Noens I, Philips EM, Kuppens S, Benninga MA. Autism spectrum disorders in children with functional defecation disorders. J Pediatr. 2013;163(3):873–8. https://doi.org/10.1016/j.jpeds.2013.02.028
19. Rao M, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. Nat Rev Gastroenterol Hepatol. 2016;13(9):517–528. https://doi.org/10.1038/nrgastro.2016.107
20. Blatt GJ. The neuropathology of autism. Scientifica (Cairo). 2012;2012:703675. https://doi.org/10.6064/2012/703675
21. Donovan AP, Basson MA. The neuroanatomy of autism –a developmental perspective. J Anat. 2017;230(1):4–15. https://doi.org/10.1111/joa.12542
22. Hashem S, Nisar S, Bhat AA, Yadav SK, Azeem MW, Bagga P, et al. Genetics of structural and functional brain changes in autism spectrum disorder. Transl Psychiatry. 2020;10(1):229. https://doi.org/10.1038/s41398-020-00921-3
23. Becker EB, Stoodley CJ. Autism spectrum disorder and the cerebellum. Int Rev Neurobiol. 2013;113:1–34. https://doi.org/10.1016/B978-0-12-418700-9.00001-0
24. Gadad BS, Hewitson L, Young KA, German DC. Neuropathology and animal models of autism: genetic and environmental factors. Autism Res Treat. 2013;2013:731935. https://doi.org/10.1155/2013/731935
25. Wang SS, Kloth AD, Badura A. The cerebellum, sensitive periods, and autism. Neuron. 2014;83(3):518–32. https://doi.org/10.1016/j.neuron.2014.07.016
26. Jiang CC, Lin LS, Long S, Ke XY, Fukunaga K, Lu YM, et al. Signalling pathways in autism spectrum disorder: mechanisms and therapeutic implications. Signal Transduct Target Ther. 2022;7(1):229. https://doi.org/10.1038/s41392-022-01081-0
27. Kaminski VL, Michita RT, Ellwanger JH, Veit TD, Schuch JB, Riesgo RDS, et al. Exploring potential impacts of pregnancy-related maternal immune activation and extracellular vesicles on immune alterations observed in autism spectrum disorder. Heliyon. 2023;9(5):e15593. https://doi.org/10.1016/j.heliyon.2023.e15593
28. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun. 2012;26(3):383–392. https://doi.org/10.1016/j.bbi.2011.08.007
29. Heunis T-M, Aldrich C, de Vries PJ. Recent advances in resting-state electroencephalography biomarkers for autism spectrum disorder -a review of methodological and clinical challenges. Pediatric Neurology. 2016;61:28–37. https://doi.org/10.1016/j.pediatrneurol.2016.03.010
30. Magalhães HIR, Castelucci P. Enteric nervous system and inflammatory bowel diseases: Correlated impacts and therapeutic approaches through the P2X7 receptor. World J Gastroenterol. 2021;27(46):7909–7924. https://doi.org/10.3748/wjg.v27.i46.7909

31. Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. Nat Rev Gastroenterol Hepatol. 2020;17(6):338–351. https://doi.org/10.1038/s41575-020-0271-2
32. Nagy N, Goldstein AM. Enteric nervous system development: A crest cell's journey from neural tube to colon. Semin Cell Dev Biol. 2017;66:94–106. https://doi.org/10.1016/j.semcdb.2017.01.006
33. Lake JI, Heuckeroth RO. Enteric nervous system development: migration, differentiation, and disease. Am J Physiol Gastrointest Liver Physiol. 2013;305(1):G1–24. https://doi.org/10.1152/ajpgi.00452.2012
34. Hansen MB. The enteric nervous system I. Organisation and classification. Pharmacology & Toxicology. 2003;92(3):105–113. https://doi.org/10.1034/j.1600-0773.2003.t01-1-920301.x
35. Alim E. Ratlarda perinatal stresin enterik sinir sistemi üzerine olan etkilerinin incelenmesi. Gazi Üniversitesi Sağlık Bilimleri Enstitüsü: Gazi Üniversitesi; 2020.
36. Shahrestani J MDJ. Neuroanatomy, Auerbach Plexus. Treasure Island (FL): StatPearls Publishing. 2023.
37. Fatu AM, Ciubotariu D, Antohe M-E, Iordache C, Ancuta C, Vâscu MB. Neuronal and synaptic organization of enteric nervous system-the premises of the multidisciplinary therapeutic approach. Romanian J Oral Rehabil. 2023;15(4):544–558.
38. Tamada H, Hashitani H. Calcium responses in subserosal interstitial cells of the guinea-pig proximal colon. Neurogastroenterol Motil. 2014;26(1):115–123. https://doi.org/10.1111/nmo.12240
39. Gulbransen BD, Sharkey KA. Novel functional roles for enteric glia in the gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2012;9(11):625–632. https://doi.org/10.1038/nrgastro.2012.138
40. Fleming 2nd MA, Ehsan L, Moore SR, Levin DE. The enteric nervous system and its emerging role as a therapeutic target. Gastroenterol Res Pract. 2020;2020:8024171. https://doi.org/10.1155/2020/8024171
41. Wang GD, Wang XY, Hu HZ, Fang XC, Liu S, Gao N, et al. Angiotensin receptors and actions in guinea pig enteric nervous system. Am J Physiol Gastrointest Liver Physiol. 2005;289(3):G614–26. https://doi.org/10.1152/ajpgi.00119.2005
42. Linden DR. Colitis is associated with a loss of intestinofugal neurons. Am J Physiol Gastrointest Liver Physiol. 2012;303(10):G1096–1104. https://doi.org/10.1152/ajpgi.00176.2012
43. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–269, w64. https://doi.org/10.7326/0003-4819-151-4-200908180-00135
44. Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. Compr Physiol. 2014;4(4):1339–1368. https://doi.org/10.1002/cphy.c130055
45. Yu CD, Xu QJ, Chang RB. Vagal sensory neurons and gut-brain signaling. Curr Opin Neurobiol. 2020;62:133–140. https://doi.org/10.1016/j.conb.2020.03.006
46. Uvnäs-Moberg K. Role of efferent and afferent vagal nerve activity during reproduction: integrating function of oxytocin on metabolism and behaviour. Psychoneuroendocrinology. 1994;19(5-7):687–695. https://doi.org/10.1016/0306-4530(94)90050-7
47. Bonaz B, Sinniger V, Pellissier S. The Vagus Nerve in the Neuro-Immune Axis: Implications in the Pathology of the Gastrointestinal Tract. Front Immunol. 2017;8:1452. https://doi.org/10.3389/fimmu.2017.01452
48. Ulluwishewa D, Anderson RC, McNabb WC, Moughan PJ, Wells JM, Roy NC. Regulation of tight junction permeability by intestinal bacteria and dietary components. J Nutr. 2011;141(5):769–776. https://doi.org/10.3945/jn.110.135657
49. Adams JB, Kirby J, Audhya T, Whiteley P, Bain J. Vitamin/mineral/micronutrient supplement for autism spectrum disorders: a research survey. BMC Pediatr. 2022;22(1):590. https://doi.org/10.1186/s12887-022-03628-0
50. Yasuda H, Tsutsui T. Assessment of infantile mineral imbalances in autism spectrum disorders (ASDs). Int J Environ Res Public Health. 2013;10(11):6027–6043. https://doi.org/10.3390/ijerph10116027

https://dergipark.org.tr/tr/pub/yuksekihtisas