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İstanbul Tıp Fakültesi Dergisi

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Journal of Istanbul Faculty of Medicine
İstanbul Tıp Fakültesi Dergisi

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İstanbul Tıp Fakültesi Dergisi

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Journal of Istanbul Faculty of Medicine (J Ist Faculty Med) an international, scientific, open access periodical published in accordance with independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of İstanbul University, İstanbul Faculty of Medicine and it is published quarterly on January, April, July and October. The publication language of the journal is English.

Journal of Istanbul Faculty of Medicine (J Ist Faculty Med) aims to contribute to the literature by publishing manuscripts at the highest scientific level on all fields of medicine. The journal publishes original experimental and clinical research articles, reports of rare cases, reviews articles by invited researchers who have a reputable place in the international literature in their field, and letters to the editors as well as brief reports on a recently established method or technique or preliminary results of original studies related to all disciplines of medicine from all countries.

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In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: An English and a Turkish abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Research articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript types

Research articles: This is the most important type of article since it provides new information based on original research. The main text of research articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for research articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and

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Methods section and the statistical software that was used during the process must be specified.
Units should be prepared in accordance with the International System of Units (SI).

Editorial comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Invited review articles: Invited reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. The invited reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Invited Review Articles.

Case reports: There is limited space for case reports in the journal and 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 publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables
Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Research Article	3500	250 (Structured)	50	6	7 or total of 15 images
Invited Review Article	5000	250	50	6	5 or total of 10 images
Case Report	1000	200	4	2	3 or total of 5 images
Letter to the Editor	500	No abstract	5	1	1

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Figures and figure legends
Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of research articles should be mentioned in the Discussion section before the conclusion paragraph.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

REFERENCES

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal article: Blasco V, Colavolpe JC, Antonini F, Zieleskiewicz L, Nafati C, Albanèse J, et al. Long-termoutcome in kidneyrecipientsfromdonorstreatedwithhydroxyethylstarch 130/0.4 andhydroxyethylstarch 200/0.6. Br J Anaesth 2015;115(5):797-8.

Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR,

editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts accepted for publication, not published yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub ahead of print articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. DiagnIntervRadiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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- Conflict of interest (if exists)
- Acknowledgement (if exists)
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Journal of Istanbul Faculty of Medicine
İstanbul Tıp Fakültesi Dergisi

EDITORIAL

Dear Colleagues,

Upon entering 2024, we as the editorial board of Journal of Istanbul Faculty of Medicine wish everyone a good, happy, and successful year.

While trying to overcome the effects of the pandemic, we unfortunately experienced an earthquake last year on February 06, 2023. A magnitude 7.7 Mw earthquake occurred in Kahramanmaraş at 4:17 a.m., with the epicenter in Pazarcık district. Nine hours later, a magnitude 7.6 Mw aftershock earthquake with its epicenter in the Ekinözü district occurred approximately 9 hours after this main shock at 1:24 p.m. After these earthquakes, 33,777 aftershocks occurred in the region, the largest of which was 6.7 Mw. Approximately 50,500 people died and 107,204 people were injured, with thousands of disabled people having died due to various organ failures as a result of the earthquake. Additionally, 301,000 buildings were damaged or destroyed, with people having lost their homes and workplaces. Life was stopped in many provinces, and its effects continue with other earthquakes in Türkiye.

Türkiye's women's volleyball team achieved consecutive successes and became the Fédération Internationale de Volleyball (FIVB) Volleyball Women's Nations League Champion, as well as European Women's Volleyball Championship winner for the first time in its history in 2023, becoming a hope in these difficult times throughout the country.

The 2023 Nobel Prizes have also been awarded. The Karolinska Institute announced that the most recent Nobel prize on October 02, 2023 had been awarded to Hungarian-American Katalin Karikó and American Drew Weissman. The duo were recognized for "their discoveries concerning nucleoside-base modifications that enabled the development of effective mRNA vaccines against COVID-19."

2023 was an important year for Türkiye, as it celebrated its 100th anniversary as the Republic of Türkiye upon its declaration on October 29, 1923. The people owe thanks and gratitude to all those who gave their lives, who fought in its wars, who made this country a homeland, and who sacrificed so much for this cause, especially Gazi Mustafa Kemal ATATÜRK. The 2nd century of the Republic of Türkiye has begun, in which the people of Türkiye's duty should be to advance the country further in the light of science and to work and produce more for this purpose. As the Journal of Istanbul Faculty of Medicine, we start 2024 with enthusiasm and love for this and aim to ensure that our journal becomes more recognized, followed, read, and shared internationally.

As 2023 drew to an end, some changes occurred in our editorial team. We bid farewell to Prof. Zeynep Solakoğlu, Prof. Alev Yılmaz, Assoc. Prof. Beldan Polat, Assoc. Prof. Zafer Cebeci, and Assoc. Prof. Şule Öztürk Sarı, who all made significant contributions to our journal, and we also welcome our two new associate editors, Assist. Prof. Serkan Bayram and Assoc. Prof. Gonca Keskindemirci, who've joined our editorial team in this new year.

The journal's first issue of 2024 publishes ten original articles and three case reports. At the top of the list is an intriguing article showing the potential genetic and demographic factors that are able to modify

heteroplasmy levels in mitochondrial variants across blood and muscle tissues. Another important study included in this issue is on management strategies regarding placenta accreta conducted nationwide by tertiary centers. The journal has an article that reports the results from a single-center experience regarding a liver re-transplant. In addition to these articles, this issue has other preclinical and clinical studies and case reports that may interest you.

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We wish you a happy and prosperous new year in 2024 and look forward to receiving your valuable submissions. Thank you in advance for your contributions.

Sincerely,

On behalf of the editorial board of the Journal of Istanbul Faculty of Medicine
Prof. Dr. Birsen Karaman
Prof. Dr. Ayşe Kubat Üzüm
Editors in Chief Journal of Istanbul Faculty of Medicine, JMED

RESEARCH / ARAŞTIRMA
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HETEROPLASMY-ASSOCIATED MITOCHONDRIAL DNA VARIANTS IN HUMAN BLOOD AND SKELETAL MUSCLE SAMPLES

İNSAN KAN VE İSKELET KASI ÖRNEKLERİNDE HETEROPLAZMİYLE İLİŞKİLİ MİTOKONDRİYAL DNA VARYANTLARI

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ABSTRACT

Objective: Mitochondrial heteroplasmy, a recognized trait in eukaryotic cells, plays a pivotal role in complex disorders like mitochondrial diseases. High-throughput sequencing has improved precision in detecting low-level heteroplasmy and can identify ultra-low-level variants (<1%) associated with heteroplasmy attributes. We aimed to investigate potential genetic and demographic factors associated with heteroplasmy levels in mitochondrial variants by analyzing both blood and muscle tissues in individuals, regardless of their phenotypes.

Material and Methods: High-throughput sequencing was conducted on the mitochondrial genomes of 10 individuals, with an equal gender distribution. Variants with heteroplasmy ratios both ranging from 5% to 95% and out of this range were used for statistical analysis.

Result: A total of 194 heteroplasmic variants were identified, of which 13 displayed lower heteroplasmy ratios in both blood and skeletal muscle samples from females, while the mitochondrial control region (D-Loop) exhibited higher ratios.

Conclusion: The study findings confirm the correlation between the m.10398A>G variant and mitochondrial heteroplasmy levels, consistent with prior research. Additionally, we identified the m.1811A>G variant in *MT-RNR2* and the m.12308A>G vari-

ÖZET

Amaç: Ökaryotik hücrelerin tanımlanmış bir özelliği olan mitokondriyel heteroplazmi, mitokondriyel hastalıkların fenotipik çeşitliliğinde önemli bir rol oynar. Düşük düzeydeki heteroplazminin tespitindeki hassasiyeti artıran yeni nesil dizileme (YND) teknolojisi, heteroplazmi özellikleri ile ilişkili ultra-düşük düzeydeki (%<1) varyantları saptayabilmektedir. Çalışmamız, fenotiplerine bakılmaksızın, bireylerdeki mitokondriyel varyantların heteroplazmi düzeyleri ile ilişkilendirilebilecek potansiyel genetik ve demografik faktörleri incelemeyi amaçlandı.

Gereç ve Yöntem: Cinsiyet dağılımı eşit olan 10 bireyin mitokondriyel genomları üzerinde, yüksek-çıktılı yeni nesil dizileme yöntemi uygulandı. Heteroplazmi oranları %5 ile %95 arasında değişen ve bu aralığın dışında kalan varyantlar, istatistiksel analizler için kullanıldı.

Bulgular: Toplamda 194 heteroplazmik varyant tanımlandı, bunlardan 13'ü dişi bireylerin hem kan hem de iskelet kası örneklerinde daha düşük heteroplazmi oranları sergilerken, mitokondrial kontrol bölgesi (D-ilmiği) daha yüksek oranlara sahipti.

Sonuç: Çalışma bulguları, önceki araştırmalarla uyumlu olarak m.10398A>G varyantı ile mitokondriyel heteroplazmi düzeyleri arasındaki korelasyonu doğruladı. Ayrıca, *MT-RNR2* genindeki m.1811A>G varyantının ve *MT-TL2* genindeki m.12308A>G

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ant in *MT-TL2*, both associated with higher heteroplasmy. Conversely, the m.582T>C variant in *MT-TF*, m.3260A>G in *MT-TL1*, m.3302A>G in *MT-TL1*, m.4409T>C in *MT-TM,* and m.4267A>G in MT-TI were linked to lower heteroplasmy, all involving transition-type alterations. Furthermore, our study hinted at a potential age-related threshold for variant accumulation in the control region. Future studies, involving larger cohorts and advanced expression analysis methods, will further contribute to the validation and enhancement of these findings.

Keywords: Mitochondrial heteroplasmy, *MT-TL1, MT-TL2, MT-RNR2, MT-TM, MT-TI, MT-TF*

varyantının da yüksek heteroplazmi ile ilişkili olduğu gösterildi. Bunun yanı sıra, hepsi tranzisyon tipinde olan, *MT-TF* genindeki m.582T>C, *MT-TL1* genindeki m.3260A>G, *MT-TL1* genindeki m.3302A>G, *MT-TM* genindeki m.4409T>C ve MT-TI genindeki m.4267A>G varyantlarının ise düşük heteroplazmi oranı ile ilişkili olduğu bulundu. Çalışmamız ayrıca, kontrol bölgesindeki varyant birikimi için potansiyel bir yaş sınır eşiği olabileceğini de işaret etmiştir. Gelecekte, daha büyük örnek sayısı ve gelişmiş analiz yöntemlerinin kullanılacağı çalışmalar, bu bulguların doğrulanması ve geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: Mitokondriyel heteroplazmi, *MT-TL1, MT-TL2, MT-RNR2, MT-TM, MT-TI, MT-TF*

INTRODUCTION

Mammalian mitochondrial DNA (mtDNA) is a double-stranded circular molecule of about 16.5 kb long in the mitochondrial matrix. It encodes two rRNAs (12S rRNA, 16S rRNA), 22 tRNAs, and 13 subunits of the electron transport chain (ETC) complexes I, III, IV, and V (1, 2). Regulation of their transcription relies on a specific region named the control region, also called the displacement loop (D-loop) region (3, 4).

A unique aspect of mtDNA and mitochondria is their presence in multiple copies within a cell, and the structure of multiplicity is influenced by factors like metabolism and exposure to stressors such as reactive oxygen species (ROS) (5). This multi-copy nature leads to a wide range of ratios (from 5% to 95%) of wild-type and variant alleles at specific mtDNA positions, a phenomenon called heteroplasmy (6). Heteroplasmy, combined with somatic mosaicism resulting from post-zygotic changes in mtDNA, contributes to the varying impact of pathogenic mtDNA variants. Notably, pathogenic mtDNA changes are anticipated to predominantly affect neural and skeletal muscle cells due to mitochondria's primary role in providing adenosine triphosphate (ATP) for cellular processes and metabolites for macromolecule synthesis (7). Heteroplasmy varies among tissues due to energy needs and changes over time due to relatively more primitive repair mechanisms (8). While the differences in tissue and age-related heteroplasmy have been recognized for a long time, the prevalence of these differences in mitochondrial diseases has now been confirmed through advanced sequencing techniques, also known as next-generation sequencing (NGS). This confirmation is supported by studies and relevant to the various clinical presentations observed in both rare and common genetic disorders (9, 10).

Acknowledging the pivotal contribution of NGS in elucidating the mutational landscape of mtDNA and its dynamic heteroplasmic profiles across diverse tissue types, our primary objective rests in the comparative assessment of heteroplasmic ratios. In this study, our primary objective was to investigate the potential genetic and demographic factors that may modify the level of heteroplasmy in mitochondrial variants across two distinct tissue types. To achieve this, we performed NGS analyses of mitochondrial genomes extracted from blood and skeletal muscle samples, without regard to individuals' disease status or clinical phenotypes.

MATERIAL and METHODS

Ethical approval was obtained from the Istanbul Faculty of Medicine Ethics Council at Istanbul University (Date: 23.11.2018, No: 1626 and 872). Written informed consent was obtained from the participants or their legal guardians. DNA was isolated from blood and residual biopsy samples were obtained from the leg region for S1-S3 and from the shoulder and arm area (*M. deltoideus*) for S4-S10. mtDNA (16,569 bp) was sequenced using Ion Torrent's Ion PGM by generating amplicon libraries of 400 bp-length of fragmented long-PCR products and aligned with the corrected Cambridge reference sequence (11). Variant alleles with a minimum of three reads from both forward and reverse strands were chosen for further analysis, and heteroplasmy levels were evaluated based on established cut-off values from prior studies, with lower and upper thresholds set at 0.05 and 0.95, respectively (12). Mann-Whitney U test or Student's t-test for mean comparisons and the Pearson test for numeric data correlations were performed for statistical investigation.

RESULTS

The study subjects were composed of five females and five males, with an average age of 36.6 years. All mtDNA was verified to be encompassed by the sequenced reads. The mean sequence depth was 1648±512 (range: 171 to 2000). There was no significant difference (p=0.94) in sequence depth between blood (1675±488) and skeletal muscle (1627±528). mtDNA was totally covered, unveiling 194 variants.

Initially, we compared the mtDNA variants present in the blood and skeletal muscle samples from our cohort of 10

subjects. This comparative analysis unveiled 48 variants exclusively detected in blood samples, 67 variants exclusively found in skeletal muscle, and 79 variants that were present in both blood and skeletal muscle samples.

Statistical analysis

The heteroplasmy ratio of the variants identified in both blood and skeletal muscle was lower in females.

Heteroplasmy ratios were examined in both blood and skeletal muscle to explore potential influencing factors. This involved comparing tissue origin, and subject characteristics such as gender and age. Analysis of gender distribution revealed a lower heteroplasmy ratio in females (p=0.022) compared to males (Figure 1A). Overall heteroplasmy ratio comparisons between tissue types did not yield any significant differences (p=0.44) (Data not shown). However, the heteroplasmy ratio in variants observed across both tissues was lower than those found exclusively in blood or skeletal muscle (Figure 1B). This difference showed statistical significance for blood (p=0.0063) and borderline significance for skeletal muscle (p=0.055). Given the observed gender-related variation in heteroplasmy ratio, we examined its interplay with tissue origin. This assessment revealed that the reduction in heteroplasmy ratio among females was specific to variants present in both tissues (p=0.011) (Figure 1C). Furthermore, when the heteroplasmy ratios of the 194 variants presented in our study were individually assessed in each sample (total of 472), it was observed that transitions (Ti) were notably lower than the transversion (Tv) (p=0.017) (Figure 1D).

Variants detected in both tissues (blood and skeletal muscle) are more likely to be shared among individuals, regardless of their heteroplasmy ratio

Since the notable difference in heteroplasmy ratio was specifically observed in variants read across both tissues, rather than solely in blood or skeletal muscle, we proceeded to assess the variants based on their sharing ratio across two tissues and among 10 subjects. Our findings indicated that over half of the variants (52.58%) were detected in a single subject and within only one tissue type. Conversely, the variants identified in more than half of the subjects were found in both tissue types. This positive correlation between variant sharing ratio across tissues and subjects appeared unrelated to the heteroplasmy ratio (Supplementary data).

The relative frequency of variants in the control region displayed an age-dependent increase

Due to the recognized distinct variant frequencies in the control region and coding region of mtDNA, with the control region being acknowledged as a polymorphic range that accumulates variants, we examined heteroplasmy distribution in both areas (13, 14).

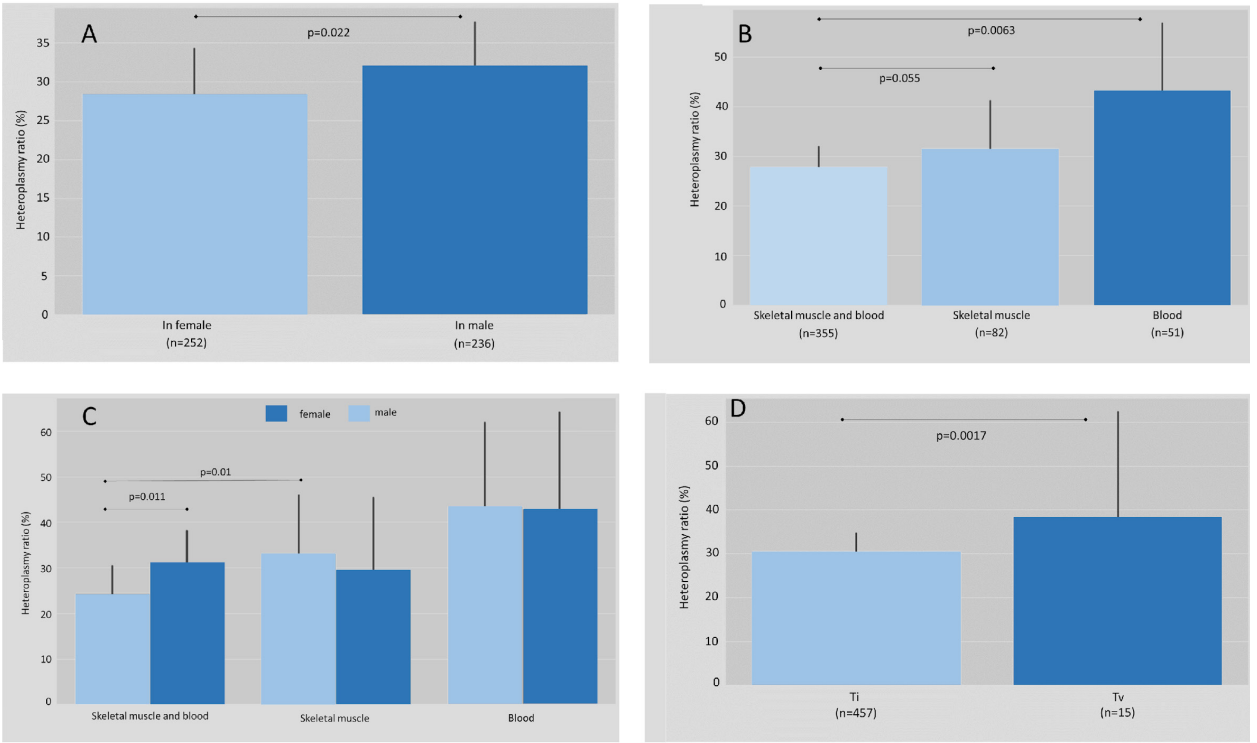

Figure 1: The correlations of the heteroplasmy ratio with gender (A), tissue origin (B), gender-dependent tissue origin (C), and substitution types (D)

The heteroplasmy distribution across mtDNA indicated an accumulation of heteroplasmy and a reduction of homoplasmy in the control region (Data not shown). To explore differences in heteroplasmy ratio or variant frequencies, our findings showed that the variant frequency within the control changed with age. This alteration appeared as an increase at earlier ages, followed by a slight decrease at later stages. The positive correlation between control region variant frequency and age became statistically significant by the age of 42 (r=0.92, p=0.0086). After age 49, there was a tendency of decreasing of the variant frequency, implying an increased frequency in the coding region (Figure 2). However, the status of the variant frequency between 42 and 49 could not be shown due to a lack of samples between these ages. Additionally, the Ti/Tv ratio significantly declined (p=0.033) after age 42 (Figure 3).

The mitochondrial variant m.10398A>G is linked to higher heteroplasmy

A recent study indicated an association between the m.10398A>G variant and overall heteroplasmy levels (14). To investigate further, we compared heteroplasmy levels between subjects with and without the m.10398A>G variant, considering the significant heteroplasmy ratio difference between the coding and control regions (Figure 4A). This comparison highlighted a significantly higher overall heteroplasmy level in the presence of this variant (Figure 4B). This trend was notably pronounced within the coding region (Figure 4C) and among individuals of the female gender (Figure 4D).

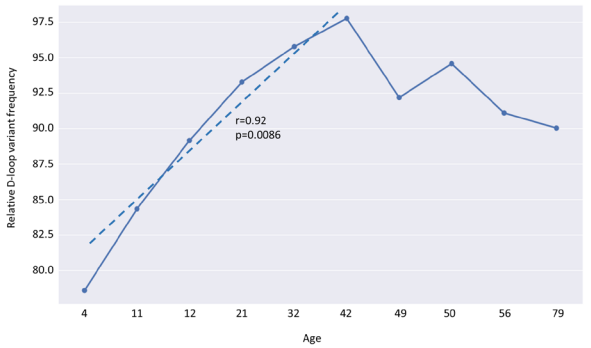

Figure 2: Positive correlation between control region variant frequency and age

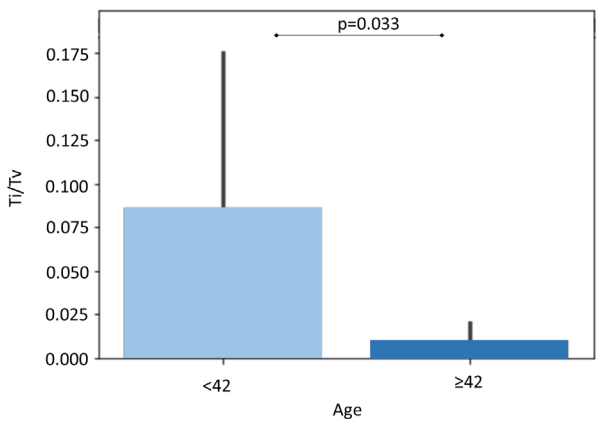

Figure 3: Decreased Ti/Tv ratio observed after age 42

Other heteroplasmy-related mtDNA variants

Supporting the correlation between the presence of the m.10398A>G variant and mitochondrial heteroplasmy ratio, we wondered if other variants could similarly impact heteroplasmy levels. To explore this, we compared heteroplasmy levels in cases carrying each of the 194 variants against non-carriers. Two variants (m.1811A>G and m.12308A>G) exhibited an association with higher heteroplasmy ratios akin to m.10398A>G, while five variants (m.582T>C, m.3260A>G, m.3302A>G, m.4267A>G, and m.4409T>C) appeared to correlate with lower heteroplasmy levels (Figure 5). All these variants were of the transition type and found in both tissues. The mean heteroplasmy ratio for higher-heteroplasmy-associated variants across three cases (97.5±1.68) was higher than that for lower-heteroplasmy-associated variants across eight cases (0.39±0.12). Positive associations of m.1811A>G and m.12308A>G with heteroplasmy ratio were particularly pronounced in the coding region (p=0.00031 for m.1811A>G, p=0.0005 for m.12308A>G). Notably, the higher-heteroplasmy-associated variants were situated in *MT-TL2* and *MT-RNR2* genes, while the lower-heteroplasmy-associated variants were in *MT-TM*, *MT-TI*, *MT-TL1*, and *MT-TF* genes.

DISCUSSION

Mitochondrial heteroplasmy, prevalent in multicellular organisms, is a recognized characteristic of eukaryotic cells. Yet, in a medical context, its significance is amplified due to its pivotal role in the pronounced clinical diversity observed in mitochondrial diseases (15-19).

The clinical severity of mitochondrial disorders is notably modulated by the magnitude and tissue-specific allocation of heteroplasmic mutations (20). In addition to mitochondrial disorders, a multitude of complex diseases including metabolic disorders, neurodegenerative conditions, and diverse forms of cancer have also been demonstrated to exhibit correlations with the heteroplasmy levels of mitochondrial variants (21-25).

While measuring mitochondrial heteroplasmy is of vital significance, it presents challenges due to technical and biological factors. Advances in sequencing technologies have largely overcome technical obstacles, allowing for more accurate measurement of even low-level heteroplasmy. Furthermore, various NGS-based methods, including modified approaches, exhibit varying sensitivity

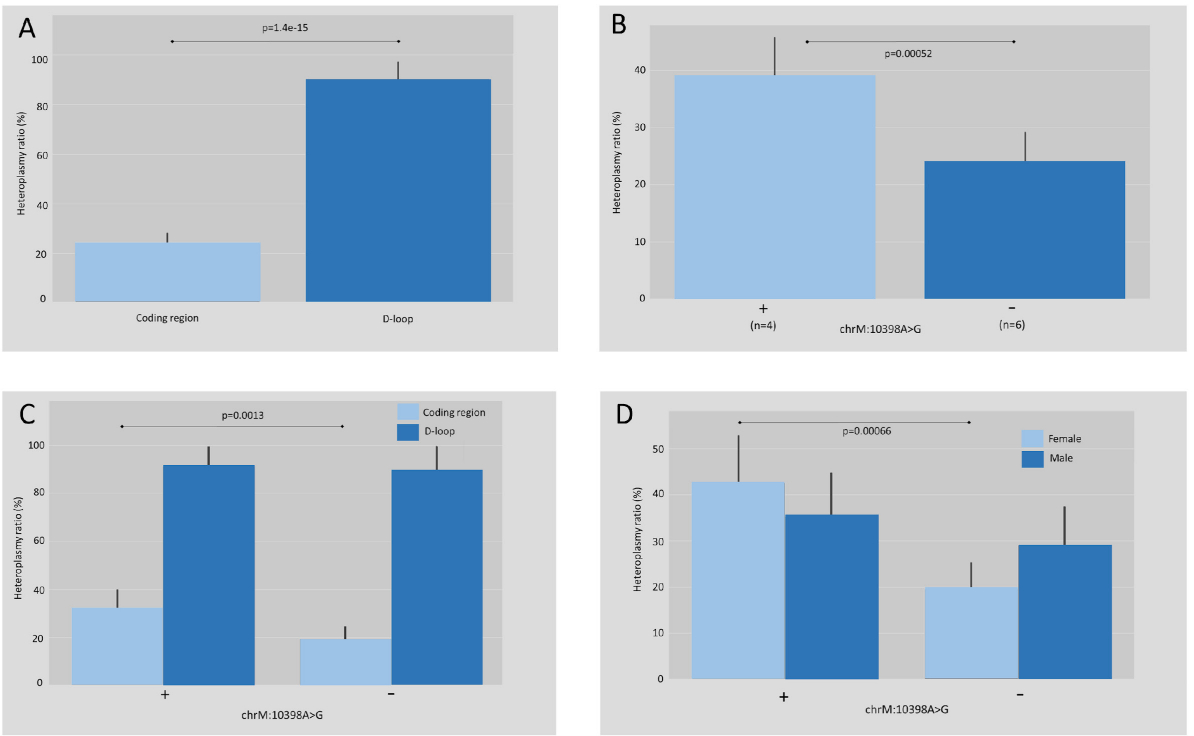

Figure 4: Heteroplasmy ratio alteration influenced by m.10398A>G variant. While both the control region (A) and m.10398A>G variant (B) are tied to increased heteroplasmy ratios, the elevated heteroplasmy linked to the m.10398A>G variant was limited to the coding region (C) and the female gender (D)

to heteroplasmy levels (26, 27). Nevertheless, biological mysteries about mitochondrial heteroplasmy, such as its nature, mechanism, and tissue distribution, remain elusive. In this study, we investigated correlations between mitochondrial heteroplasmy levels and associated features in 10 patients using deep sequencing.

While aligning with prior studies in some aspects, our findings introduced novel insights into the determinants of mitochondrial heteroplasmy ratios. Our investigation identified 13 heteroplasmic variants with heteroplasmy levels ranging from 5% to 95%. Since this count fell short of yielding statistically robust conclusions, we considered low-level heteroplasmies in our subsequent analyses, based on prior studies employing deep sequencing and single-cell analysis that have underscored the prevalence of heteroplasmic variants, often at extremely low levels (<1%), in the tissues of even healthy individuals (10, 15, 28, 29).

Nonetheless, our limited pool of heteroplasmic variants sufficed to reveal that skeletal muscle exhibited a higher heteroplasmic variant ratio compared to blood. This finding can be rationalized by disparities in mitotic activity between the two tissues, as demonstrated for the m.3243A>G variant in *MT-TL1* gene, which displayed a declining heteroplasmy over time in mitotically active blood cells but not in post-mitotic tissues such as skeletal muscle (30).

A significant finding in our study was the gender-related variation in heteroplasmy levels. Within our cohort, females exhibited lower heteroplasmy ratios compared to males. While a urine sample study involving 235 patients found higher heteroplasmy for the m.3243A>G variant in males, a leukocyte DNA investigation of 1035 individuals did not detect notable gender disparities (15, 31). The correlation between mitochondrial heteroplasmy and gender appears contentious in light of prior research. However, even when acknowledging such a correlation, the precise mechanism driving gender-related modulation in heteroplasmy remains enigmatic.

We also observed a more pronounced reduction in heteroplasmy among females, particularly in variants identified within both skeletal muscle and blood. These findings suggest that gender-related distinctions in mitochondrial heteroplasmy might be confined to specific tissue types. Notably, given the elevated heteroplasmy ratios of tissue-specific variants relative to common

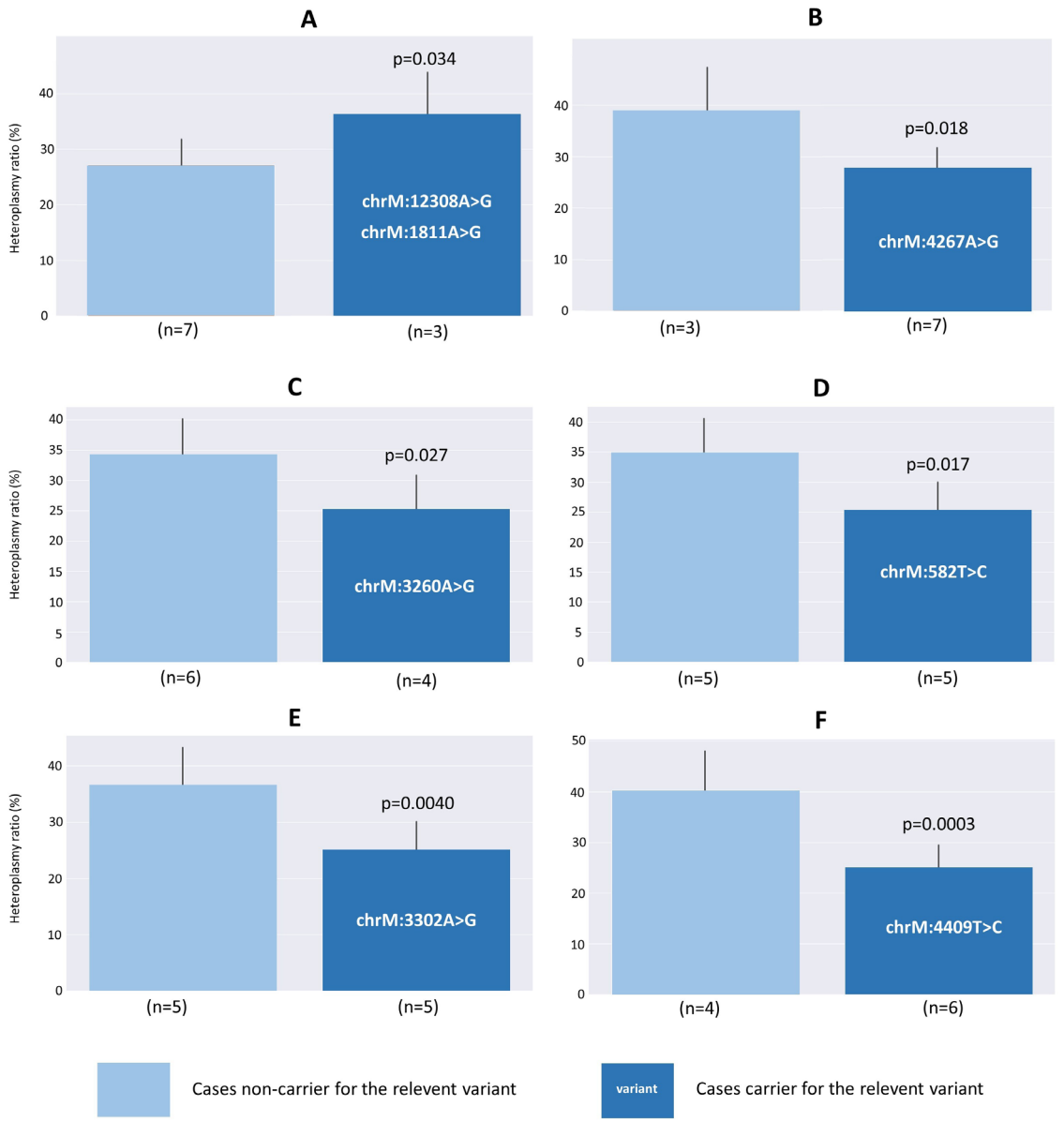

Figure 5: Variants increasing (**A** and **B**) or decreasing (**C** to **G**) the heteroplasmy ratio of total mtDNA variants

variants, we hypothesize that tissue-restricted variants may selectively amplify their heteroplasmy ratios during tissue development. It is established that, contingent on cell type, mitochondrial variations originating from a single molecule within a cell can either diminish or proliferate clonally over time. Given that this process hinges on cell division and fitness, gender-dependent disparities in heteroplasmy ratios can be attributed to gender-driven distinctions in the mitotic activity and fitness of mitochondrial variants within cells of the analyzed tissues across genders.

Our study made an original discovery by establishing a positive relationship between control region variant frequency and age. This finding aligns with prior research, which has emphasized the accumulation of sequence variants within the control region (13, 14). However, our data also suggests that there may be a threshold for such variant accumulation within the control region, possibly occurring between the ages of 42 and 49. It's important to acknowledge that a more precise cutoff age would require a wider age range in our cohort. While this correlation hasn't been reported before, numerous studies have investigated age- and tissue-dependent changes in mito-

chondrial variants. One of these studies measured length heteroplasmy in a polycytosine tract of the mitochondrial HV2 region in blood, brain, heart, liver, skeletal muscle, and hair shaft samples collected during autopsies of 25 individuals and revealed that the frequency of heteroplasmy did not differ significantly with age (32). However, a differentiated distribution pattern was observed across blood and organ tissues over the age of 28 for all heteroplasmic mtDNAs, while in hair shafts over the age of 44 for the homoplasmic individuals in that study. Although our subsequent finding implied a connection between age and mitochondrial variant frequency, the majority of our prior data unraveled the factors influencing the heteroplasmy ratio of mitochondrial variants.

It is noteworthy that mitochondrial heteroplasmy can also be influenced by the nuclear genome (33). A Genome-Wide Association Study (GWAS) identified 20 loci, including the mitochondrial transcription factor A (*TFAM*) gene, as being linked to heteroplasmy (34). However, genetic variants serving as modifier factors for mitochondrial variant heteroplasmy are not confined solely to nuclear genome variants. Recent investigations propose that mitochondrial genome variants may also assume a role as modifiers in mitochondrial variant heteroplasmy levels. Notably, one of these studies demonstrated an association between the m.10398A>G variant and elevated heteroplasmy levels in brain tissue (35). In consonance with this study, our findings also indicate an association of this variant with higher heteroplasmy ratios in both blood and skeletal muscle. However, in contrast to the prior study's observation in the control region, our results highlight this association within the coding region. This variance could potentially stem from variations in cohort size or the nature of the utilized tissue.

As our findings associated the m.10398A>G variant and mitochondrial heteroplasmy levels, we probed the possibility of additional variants exhibiting similar associations. Subsequent analyses unveiled seven additional mtDNA variants that appear to be correlated with elevated or balanced heteroplasmy levels. Among these, two exhibited higher heteroplasmy levels in mtDNA variants, with a notable concentration within the coding region. Intriguingly, all these variants were characterized as transitions and were present in both tissue types.

The heteroplasmy association of these variants may be attributed to the function of the genes in which they are situated. Nevertheless, a conspicuous common feature between *MT-TL2* and *MT-RNR2* genes for higher-heteroplasmy-associated variants, or between *MT-TM*, *MT-TI*, *MT-TL1*, and *MT-TF* genes for lower-heteroplasmy-associated variants could not be discerned. Notably, the m.1811A>G variant, a higher-heteroplasmy-associated variant, has been reported to induce significant changes in mitochondrial 16S rRNA secondary structure (36). However, whether alterations in the secondary structure of mitochondrial 16S rRNA could influence heteroplasmy remains an area requiring further investigation. Another plausible scenario is that these variants might act as expression quantitative trait loci (eQTL) for specific mitochondrial genes, akin to the demonstrated role of the m.10398A>G variant in a prior study. In that context, the m.10398A>G variant was identified as an eQTL for the *MT-ND3* gene in the brain and the *MT-ND4* gene in lymphoblastoid cell lines (35). Evaluating the potential eQTL role of these variants necessitates expression analysis conducted within the pertinent tissues.

The primary limitation of this study lies in its small sample size. Furthermore, the study population's inherent heterogeneity challenged discerning potential phenotype-genotype correlations pertaining to mitochondrial variants.

CONCLUSION

Our recent study has highlighted that mitochondrial heteroplasmy levels are influenced by both tissue type and gender, aligning with prior research. Additionally, our study suggests a potential age-related threshold for variant accumulation within the control region, alongside identifying additional seven novel association of mtDNA variants that could potentially serve as modifiers for mitochondrial heteroplasmy. Subsequent investigations employing larger cohorts and expression analysis methodologies are anticipated to validate and expand upon our findings.

Ethics Committee Approval: The study has ethical approval from the Istanbul Faculty of Medicine Ethics Council at Istanbul University (Date: 23.11.2018, No: 1626 and 872).

Informed Consent: Written informed consent was obtained from the participants or their legal guardians.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Z.O.U.; Data Acquisition- A.G., A.D., G.Ş.; Data Analysis/Interpretation- Ç.G., A.G., G.Ş., G.T., Z.O.U.; Drafting Manuscript- Ç.G., Z.O.U.; Critical Revision of Manuscript- Ç.G., A.G., G.Ş., G.T., Z.O.U.; Final Approval and Accountability- Ç.G., Z.O.U.

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Conflict of Interest: The authors have no conflict of interest to declare.

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Data Availability Statement: Data available within the article or its supplementary materials.

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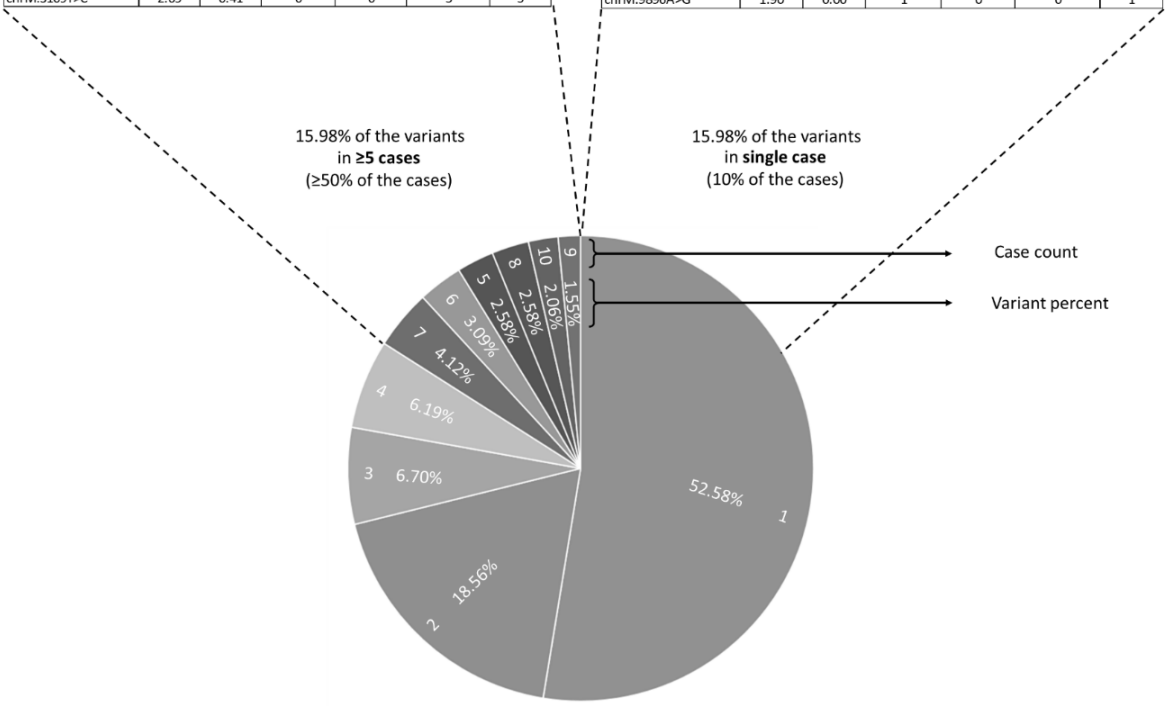
Variant	Heteroplasmy		Tissue origin			Total number
	Mean	Std	only SM	only B	SM and B	
chrM:1630A>G	0.35	0.10	0	0	10	10
chrM:522CAC>C	2.75	0.44	0	0	10	10
chrM:4267A>G	0.45	0.15	0	0	10	10
chrM:3264T>C	1.31	0.64	0	0	10	10
chrM:608A>G	0.43	0.10	0	0	9	9
chrM:4274T>C	0.43	0.10	0	0	9	9
chrM:3291T>C	0.46	0.12	0	0	9	9
chrM:4289T>C	0.37	0.06	0	0	8	8
chrM:3271T>C	0.43	0.11	0	0	8	8
chrM:593T>C	0.39	0.08	0	0	8	8
chrM:4263A>G	0.33	0.07	0	0	8	8
chrM:1616A>G	0.34	0.06	0	0	8	8
chrM:10398A>G	98.80	0.18	0	0	7	7
chrM:4279A>G	0.33	0.09	0	0	7	7
chrM:7028C>T	99.38	0.10	0	0	7	7
chrM:11719G>A	98.17	0.40	0	0	7	7
chrM:5613T>C	0.33	0.06	0	0	7	7
chrM:4409T>C	0.30	0.05	0	0	7	7
chrM:9909T>C	5.09	0.88	0	0	7	7
chrM:15326A>G	99.66	0.10	0	0	7	7
chrM:10415T>C	0.36	0.11	0	0	6	6
chrM:4302A>G	0.33	0.09	0	0	6	6
chrM:1659T>C	0.26	0.05	0	0	6	6
chrM:3302A>G	0.43	0.11	0	0	6	6
chrM:3260A>G	0.38	0.06	0	0	6	6
chrM:12261T>C	0.74	0.36	0	0	6	6
chrM:1438A>G	99.78	0.04	0	0	5	5
chrM:3288A>G	0.43	0.07	0	0	5	5
chrM:582T>C	0.40	0.09	0	0	5	5
chrM:4300A>G	0.26	0.05	0	0	5	5
chrM:3109T>C	2.69	0.41	0	0	5	5

Variant	Heteroplasmy		Tissue origin			Total number
	Mean	Std	only SM	only B	SM and B	
chrM:5728T>C	0.50	0.00	1	0	0	1
chrM:14709T>C	0.25	0.00	0	1	0	1
chrM:642T>C	0.25	0.00	0	1	0	1
chrM:982A>AT	99.45	0.00	1	0	0	1
chrM:7510T>C	0.40	0.00	1	0	0	1
chrM:9698T>C	97.98	0.00	0	1	0	1
chrM:13676A>G	2.50	0.00	1	0	0	1
chrM:14128A>G	19.93	0.00	1	0	0	1
chrM:14723T>C	0.40	0.00	1	0	0	1
chrM:636A>G	0.30	0.00	1	0	0	1
chrM:3480A>G	98.60	0.00	0	1	0	1
chrM:7505T>C	0.45	0.00	1	0	0	1
chrM:14167C>T	99.28	0.00	0	1	0	1
chrM:5692T>C	0.21	0.00	1	0	0	1
chrM:3283G>A	0.40	0.00	0	1	0	1
chrM:9055G>A	98.54	0.00	0	1	0	1
chrM:983C>T	99.45	0.00	1	0	0	1
chrM:199T>C	99.65	0.00	1	0	0	1
chrM:6956T>C	99.75	0.00	1	0	0	1
chrM:16224T>C	98.05	0.00	0	1	0	1
chrM:16002T>C	0.43	0.00	0	1	0	1
chrM:263A>G	99.60	0.00	0	1	0	1
chrM:8276C>T	99.42	0.00	1	0	0	1
chrM:3277G>A	0.20	0.00	0	1	0	1
chrM:14370A>C	4.45	0.00	1	0	0	1
chrM:15812G>A	99.69	0.00	1	0	0	1
chrM:5327C>A	2.36	0.00	1	0	0	1
chrM:625G>A	0.30	0.00	0	1	0	1
chrM:15908T>C	0.22	0.00	0	1	0	1
chrM:9896A>G	1.90	0.00	1	0	0	1



Supplementary Data: Variants' Percentage Distribution and Counts of Cases Sharing the Same Variants. The pie chart shows the total number of samples sharing the same variant (Case count), and the percentage of the shared variant (Variant percent). The tables above the pie chart display the mean and standard derivation of the heteroplasmy ratio of individual variants and the count of the cases sharing this variant, with (Tissue origin) and without (Total number) considering tissue type. While all variants shared by more than half of the cases (SM + B > 5 and Total number > 5) were read in both tissues (left table), all variants unique to a single case, not shared by more than one case (SM + B = 0 and Total number = 1), were read just in one of two tissues (right table).

RESEARCH / ARAŞTIRMA
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NRF2 ACTIVATOR DIMETHYL FUMARATE DIMINISHED STEATOSIS, INFLAMMATION AND LIPID PEROXIDATION IN THE LIVER OF BINGE ETHANOL-TREATED RATS

NRF2 AKTİVATÖRÜ DİMETİL FUMARAT, AŞIRI ETANOL UYGULANAN SIÇANLARIN KARACİĞERİNDE YAĞLANMA, ENFLAMASYON VE LİPİD OKSİDASYONUNU AZALTTI

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ABSTRACT

Objective: This study was conducted to explore the impact of dimethyl fumarate (DMF), which has antioxidant and anti-inflammatory effects, on binge ethanol (EtOH)-induced hepatic steatosis, inflammation, and lipid peroxidation in rats.

Material and Method: To examine the potential protective effect of DMF against EtOH-induced hepatic damage, rats were divided into four groups control, DMF, EtOH, and DMF+EtOH. Rats were administered EtOH (4.5 g/kg orally, 3 doses with 12-h intervals). DMF (30 mg/kg; gavage) was applied to rats one hour before each application of EtOH in the DMF+EtOH group. Serum markers of liver damage, triglyceride (TG), tumor necrosis factor-alpha (TNF-α), lipid and protein oxidation products, myeloperoxidase (MPO), and antioxidant enzymes together with histopathological examinations were performed in liver tissue. Protein expressions associated with antioxidant mechanism (nuclear factor erythroid 2-related factor; Nrf2 and heme oxygenase-1; HO-1), lipid metabolism (sterol regulatory element-binding protein-1c; SREBP-1c and peroxisome proliferator-activated receptor-alpha; PPAR-α), oxidative stress (cytochrome P4502E1; CYP2E1), and inflammation (nuclear factor-kappa B; NF-κB) were also investigated in the rats' livers.

Result: DMF reduced elevated levels of serum markers of liver damage and hepatic TG, TNF-α and reactive oxygen species levels, lipid and protein oxidation products, and MPO activity together with the alleviation of histopathological lesions in

ÖZET

Amaç: Bu çalışma, antioksidan ve anti-inflamatuar etkilere sahip dimetil fumaratın (DMF) sıçanlarda binge etanol (EtOH) ile indüklenen karaciğer steatozu, inflamasyon ve lipit peroksidasyonu üzerindeki etkisini araştırmak amacıyla yapıldı.

Gereç ve Yöntem: EtOH ile indüklenen karaciğer hasarına karşı DMF'nin potansiyel koruyucu etkisini incelemek için sıçanlar kontrol, DMF, EtOH ve DMF+EtOH olmak üzere dört gruba ayrıldı. Sıçanlara EtOH (4,5 g/kg oral, 12 saat arayla 3 doz) verildi. DMF+EtOH grubundaki sıçanlara her EtOH uygulamasından bir saat önce DMF (30 mg/kg; gavaj) uygulandı. Karaciğer hasarı serum belirteçleri, trigliserid (TG), tümör nekroz faktörü-alfa (TNF-α), lipid ve protein oksidasyon ürünleri, miyeloperoksidaz (MPO) ve antioksidan enzimler ile birlikte karaciğer dokusunda histopatolojik incelemeler gerçekleştirildi. Karaciğerde antioksidan mekanizma (nükleer faktör eritroid 2 ile ilişkili faktör; Nrf2 ve hem oksijenaz-1; HO-1), lipid metabolizması (sterol düzenleyici element bağlayıcı protein-1c; SREBP-1c ve peroksizom proliferatör ile aktive olan reseptör-alfa; PPAR-α) oksidatif stres (sitokrom P4502E1; CYP2E1) ve inflamasyon (nükleer faktör-kappa B; NF-κB) ile ilişkili protein ekspresyonları da araştırıldı.

Bulgular: DMF, EtOH uygulanan sıçanlarda histopatolojik lezyonların iyileşmesinin yanında artmış serum karaciğer hasarı belirteçlerini, hepatik TG, TNF-α ve reaktif oksijen türleri düzeylerini, lipid ve protein oksidasyon ürünlerini ve MPO aktivitesini de azalttı. DMF+EtOH grubunda Nrf2 ve HO-1ekspresyonlarının

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EtOH-treated rats. Increased Nrf2 and HO-1 and decreased SREBP-1c and CYP2E1 expressions were also detected in the DMF+EtOH group compared with the EtOH group.

Conclusion: Our results demonstrate that DMF may provide a protective effect against EtOH-induced hepatic lesions. These outcomes may be linked to the anti-oxidative, anti-inflammatory, and anti-lipogenic potential of DMF-induced Nrf2 activation.

Keywords: Dimethyl fumarate, nuclear factor erythroid 2-related factor, ethanol, liver damage, oxidative stress

EtOH grubuna göre arttığı ve SREBP-1c ve CYP2E1 ekspresyonlarının ise EtOH grubuna göre azaldığı saptandı.

Sonuç: Sonuçlarımız, DMF'nin EtOH tarafından indüklenen karaciğer lezyonlarının oluşumuna karşı koruyucu bir etki sağlayabileceğini göstermektedir. Bu etkiler, DMF ile indüklenen Nrf2 aktivasyonunun antioksidan, anti-inflamatuar ve anti-lipojenik potansiyeli ile ilişkili olabilir.

Anahtar Kelimeler: Dimetil fumarat, nükleer faktör eritroid2 ilişkili faktör, etanol, karaciğer hasarı, oksidatif stres

INTRODUCTION

Alcoholic liver disease (ALD) develops due to excessive alcohol consumption and has various stages, including steatosis (fatty liver), steatohepatitis (ASH), fibrosis, and cirrhosis. The liver functions as the primary site for alcohol metabolism. The hepatotoxicity of ethanol (EtOH) is attributed to the oxidation byproducts of EtOH rather than EtOH itself. EtOH is converted to acetaldehyde (AA) through reactions catalyzed by alcohol dehydrogenase (ADH), cytochrome P450 (CYP2E1), and catalase enzymes in the liver (1,2). Hepatic lipid accumulation, oxidative stress, inflammation, and toxic AA accumulation are significant factors in the pathogenesis of ALD (1,2).

Steatosis is the first stage of ALD, which is reversible with abstinence and involves fat accumulation along with minimal liver injury. However, according to the 'two hit' hypothesis, steatosis makes the liver sensitive to some insults (as second hit) such as oxidative stress, endotoxins, and cytokines. Thus, the formation of more severe forms of ALD such as ASH is triggered (3).

Nuclear factor-erythroid-2-related factor 2 (Nrf2) acts as a transcription factor. It stimulates the transcription of various antioxidant and cytoprotective genes, including heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) by binding to the antioxidant response element (ARE) by translocating into the nucleus (4). Nrf2 not only controls oxidative stress, but also negatively regulates lipogenesis through sterol regulatory element-binding protein-1c (SREBP-1c) and its target genes, including fatty acid synthase, and ATP-citrate lyase, and positively regulates fatty acid oxidation through PPAR-α and its target genes related to β-oxidation (5). Furthermore, there is an inverse relationship between Nrf2 and "nuclear factor-kappa B" (NF-κB), the primary transcription factor responsible for pro-inflammatory gene expression (6).

Due to the multifunctional efficiency of Nrf2, several antioxidant phytochemicals and some synthetic Nrf2 activators were detected to be useful in several chronic diseases including liver diseases (4,6-8). Moreover, it has been suggested that Nrf2 activation can protect EtOH-treated rodents (9,10). However, contradictory results have also been obtained showing that activation of Nrf2 increases alcoholic liver damage (9,11,12).

Dimethyl fumarate (DMF) is the only Nrf2 activator approved for clinical use. It is used to treat psoriasis and multiple sclerosis and exhibits minimal side effects. DMF exerts immunomodulatory, antioxidative, and anti-inflammatory effects (13). It is metabolized to monomethyl fumarate (MMF) in the small intestine. MMF emerges as an active metabolite of DMF and binds to cysteine 151 of Keap-1. Consequently, Nrf2 dissociates from Keap-1 and migrates to the nucleus to initiate the transcription of antioxidant genes (13). Previous reports have shown that DMF-induced Nrf2 activation has protective potential against tissue/organ damage including the liver (13,14-16). It has also been found to be effective in preventing liver damage induced by ischemia-reperfusion, thioacetamide, and carbon tetrachloride in rodents. Nevertheless, limited studies have investigated the effect of DMF in EtOH-treated rodents (14-19).

This research aimed to examine the influence of DMF treatment on liver injury, steatosis, inflammation, and the balance between oxidant and antioxidant factors induced by binge ETOH consumption. Furthermore, the effect of DMF treatment on protein expressions of proteins/enzymes related to lipid metabolism (SREBP-1c and PPAR-α), oxidative stress (CYP2E1), inflammation (NF-κB), and antioxidant system (Nrf2, HO-1) was investigated in the liver of binge EtOH-treated rats.

MATERIALS and METHODS

Animals

Female Sprague-Dawley rats (180-200 g) were obtained from the Bezmialem Vakif University Experimental Application and Research Center. The rats were housed in a stainless-steel cage (three to four per cage) at 24-26°C temperature 12-hour light/dark cycle and provided with regular feed. All procedures were handled as per the guidelines approved by Bezmialem Vakif University Animal Experiments Local Ethics Committee (Date: 24.01.2019, No: 2019/14).

Experimental procedures

Twenty-four rats were divided into four groups:

a) Control (n=6): Rats were treated with saline in accordance with the experimental protocol.

b) DMF (n=4): DMF was dissolved in dimethyl sulfoxide (DMSO; 0.08%) and applied orally to rats at a dosage of 30 mg/kg three times at 12-hour intervals.

c) EtOH group (n=7): EtOH was diluted with saline (56% v/v; approximately 10 ml/kg) and administered to rats by oral gavage at a concentration of 4.5 g/kg three times at 12-hour intervals (binge model).

d) DMF+EtOH group (n=7); DMF was administered orally to rats at a dosage of 30 mg/kg 1 hour before each EtOH application three times at 12-hour intervals doses.

In this study, the protocol used for ALD induction and DMF doses was based on previous studies (15,17,20,21). DMF and other chemicals were acquired from Sigma Aldrich (Merck KGaA, Darmstadt, Germany).

Blood and tissue samples

At the 12th h after the last EtOH treatments, all animals were injected with xylazine (15 mg/kg) and ketamine (35 mg/kg) intraperitoneally and blood samples were taken from their hearts under anesthesia and collected into dry tubes. Subsequently, they were centrifuged at 2390xg for 15 minutes, and sera were separated. Following excision, the livers were removed and preserved at -20°C till further assessment. The liver index was calculated by dividing the liver weight by the body weight and multiplying the result by 100.

Liver samples were homogenized in ice-cold 0.01 M phosphate-buffered saline (PBS) with a pH of 7.4. Subsequently, the homogenates were subjected to centrifugation at 600xg for 10 minutes to yield supernatant, which was then utilized for biochemical analyses. A portion of this supernatant underwent further centrifugation at 10000xg for 20 minutes at +4°C to yield the postmitochondrial phase, intended for the assessment of antioxidant enzyme activities. The specimens were preserved at -80°C until analyses.

Biochemical analyses in serum

Biochemical evaluations in serum were conducted using a Cobas Integra 800 autoanalyzer manufactured by Roche Diagnostics (Mannheim, Germany), to measure liver function biomarkers including aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) activities.

Biochemical analyses in the liver

TG and tumor necrosis factor- α (TNF-α) levels and myeloperoxidase (MPO) activity

Hepatic lipids were extracted using chloroform and methanol in a ratio of 2:1, and following the evaporation step, the extracts were reconstituted using a mixture of alcohol:ether (3:1). TG levels were quantified using a kit supplied by Biolabo Biochemistry and Coagulation (Maizy, France). TNF-α levels were assessed using the sandwich ELISA technique (Abbkine, Wuhan, China). Liver homogenates (10%; w/v in 0.01M PBS; pH 7.4) were subjected to sonication for 30 seconds, followed by centrifugation at 5000xg for 5 minutes at +4°C. The supernatants were utilized for the quantification of TNF-α levels. For the determination of MPO activity, pieces of the livers were extensively homogenized in ice-cold 50 mM PBS with a pH: of 6.0, consisting of hexadecyltrimethylammonium bromide (HTAB). Following three cycles of freeze-thawing and subsequent centrifugation at 15000xg, the supernatants were utilized to measure MPO activity (22).

Lipid and protein oxidation products

Lipid peroxidation was carried out by determination of thiobarbituric acid reactive substances (TBARS) and diene conjugate (DC) levels. The Buege-Aust reagent was combined with the homogenates, and the mixture was subjected to incubation in a boiling water bath for 15 minutes, followed by cooling and subsequent centrifugation at 1000xg. The absorbance of supernatants was then recorded at 532 nm for the determination of TBARS levels (23). DC levels were determined following the method described by Buege and Aust. Initially, hepatic lipids were isolated using a mixture of chloroform and methanol in a ratio of 2:1, and subsequently reconstituted in cyclohexane. Absorbance was registered at 233 nm, and DC levels were computed utilizing a molar extinction coefficient of $2.52x10^4M^{-1}cm^{-1}$ (23). To assess protein oxidation, advanced oxidation protein products (AOPP) were measured spectrophotometrically at 340 nm (24).

Antioxidant parameters

Glutathione (GSH) levels were determined at 412 nm using the Ellman reagent [5,5-dithiobis-(2-nitrobenzoate)] (25). SOD activity was evaluated using a method based on the capability of riboflavin-sensitized o-dianisidine to enhance the rate of photooxidation (26). Spectrophotometric determination of GSH-Px activity was carried out using cumene hydroperoxide as the substrate (27). The enzymatic reaction was monitored at 340 nm and 37°C. The calculation of GSH-Px activity was performed using the NADPH extinction coefficient ($6.22x10^3M^{-1}cm^{-1}$). Protein levels of supernatants were determined by bicinchoninic acid (28).

Nrf2, HO-1, SREBP-1c, PPAR-α, NF-κB, CYP2E1 protein expressions (Western Blot)

Liver tissues were homogenized using a hand homogenizer in a buffer consisting of 50 mM Tris HCl, 140 µM NaCl, 1% sodium deoxycholate, 1% triton-X100, 2 µM EDTA 8.7% glycerol, 0.1% sodium dodecyl sulfate (SDS) and protease inhibitor cocktail (P8340, Sigma-Aldrich). The homogenates underwent two cycles of freezing and thawing at -80°C, followed by sonication. After that, they were sub-

jected to centrifugation at 13000 xg for 20 minutes at +4°C to collect supernatants. Equal amounts of protein (60 µg protein/well) were loaded onto 10% SDS-polyacrylamide gels within a mini electrophoresis system (Mini-Protean 3 cell) and then transferred to the polyvinylidene fluoride (PVDF) membrane (Millipore Corporation, USA). To prevent non-specific binding, the PVDF membranes were blocked with a PBS-T solution consisting of 0.1% Tween 20 and 5% non-fat dry milk. The membranes were left to incubate overnight at +4°C with primary antibodies: Nrf2 (1:400, #ABP53068, Abbkine, Wuhan, China), HO-1 (1:400, # orb5455, Biorbyt, United Kingdom), SREBP-1c (1:400, #ABP53239, Abbkine, Wuhan, China), PPAR-α (1:400, #ABP55667, Abbkine, Wuhan, China), NF-kB p65 (1:400, #ABP53069, Abbkine, Wuhan, China), CYP2E1 (1:400, #ABP53942, Abbkine, Wuhan, China). Following primary antibody incubation, the membranes were washed with PBS-T and then incubated with a secondary antibody (1:1500, horseradish peroxidase; IgG conjugated with HRP; A21020; goat anti-rabbit secondary antibody, Abbkine, Wuhan, China) for 1 hour and 15 minutes at room temperature. At the end of the incubation, membranes were washed 3x10 min with PBS-T. Immunoreactivity of the protein bands was detected with a chemiluminescence kit (ECL; Abbkine Superluminescence ECL plus) and displayed on the Fusion Fx (Vilber, France). Quantification of protein bands was carried out using ImageJ software (National Institutes of Health, Bethesda, USA). An internal standard (actin; 1:1000, #ABP57457, Abbkine, Wuhan, China) was used to normalize the values of the samples.

Histopathological examination

Tissues were kept in 10% formalin, dehydrated using the rising concentration of EtOH, and subsequently fixed in paraffin wax. Each sample was cut into 4-5 µm slices by using a microtome, and subsequently, the sections were stained using hematoxylin and eosin (H&E) for microscopic analysis.

Statistical analyses

Statistical analysis was conducted using the SPSS software (version 21.0; SPSS Corp., Armonk, NY, USA) program. The data for all variables were presented as mean ± standard deviation (SD). The distribution of data and assessment of normality were conducted using the Shapiro-Wilk test. For variables showing a normal distribution, the one-way ANOVA test was applied, followed by post-hoc Tukey's test. The homogeneity of variances was examined using the Levene test. In cases where the data did not exhibit a normal distribution, the Kruskal-Wallis test was carried out, followed by the post-hoc Mann-Whitney U test. In all cases, levels of $p<0.05$ were considered to be significant.

RESULTS

Final body weight, liver weight, and liver index

No significant alterations were observed in these parameters among the groups when compared to controls (data not shown).

Hepatic damage markers in serum and liver histology

Serum ALT ($p<0.01$), AST ($p<0.05$), and LDH ($p<0.01$) activities exhibited increases in the EtOH group, with no change in ALP activity. Administration of DMF significantly reduced serum ALT, LDH, and ALP levels ($p<0.05$), although AST activity in EtOH-treated rats remained unchanged (Table 1).

Histological examination of the liver revealed macro-microvesicular steatosis and mild inflammation in the EtOH group. Two of the seven rats had decreased steatosis and inflammation and five rats showed normal histology in the DMF+EtOH group (Figure 1).

TG and TNF-α levels and MPO activities in liver

A notable increase (2.2-fold; $p<0.01$) in TG levels was observed in the EtOH group. DMF administration led to a notable reduction (40.4%; $p<0.01$) in TG levels that were elevated due to EtOH. TNF-α levels and MPO activity also exhibited significant (105.0%; $p<0.01$) and (80.2%; $p<0.05$) in the EtOH group, respectively. In the DMF+EtOH group, statistically significant reductions were found in TNF-α levels (53.8%; $p<0.01$) and MPO activity (33.4%; $p<0.05$) compared to the EtOH group (Figure 2).

Hepatic prooxidant and antioxidant parameters

Significant increases were detected in TBARS (42.0%; $p<0.01$), DC (22.2%; $p<0.001$), and AOPP (26.4%; $p<0.05$) levels in the EtOH group. Notably, in rats

Table 1: The effect of dimethyl fumarate (DMF) serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) activities in binge ethanol (EtOH)-treated rats (Means±SD)

	Control (n=6)	DMF (n=4)	EtOH (n=7)	DMF+EtOH (n=7)
ALT (U/L)	53.0±7.63	46.5±10.5	71.8±8.49[a]	56.0±11.7[b]
AST (U/L)	77.7±8.91	77.0±5.95	94.6±8.40[a]	87.0±13.4
LDH (U/L)	370.2±57.3	391.5±60.5	519.4±64.9[a]	401.0±88.8[b]
ALP (U/L)	96.5±11.7	115.0±38.6	107.0±20.5	69.7±22.9[b]

a: $p<0.05$ as compared to the control, b: $p<0.05$ as compared to EtOH

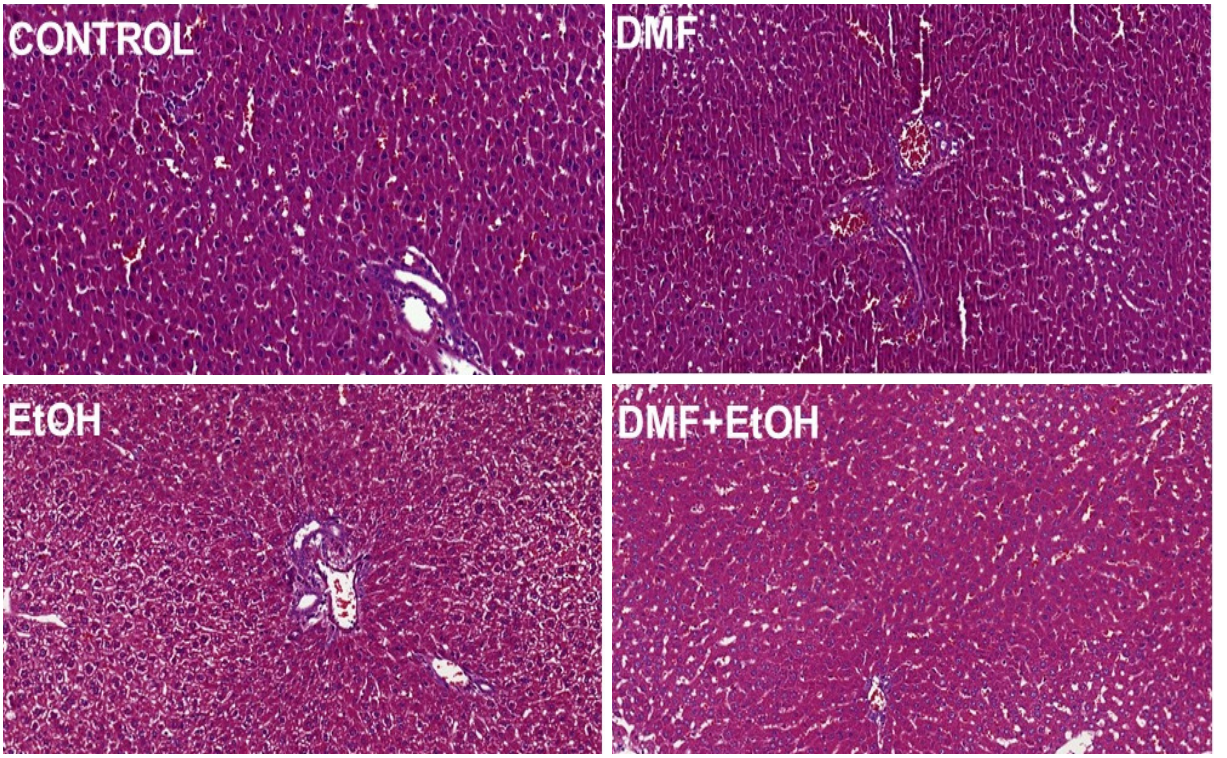

Figure 1: The effect of dimethyl fumarate (DMF) on hepatic histopathology in rats treated with binge ethanol (EtOH) [Hematoxylin and eosin (H&E) staining; x200].

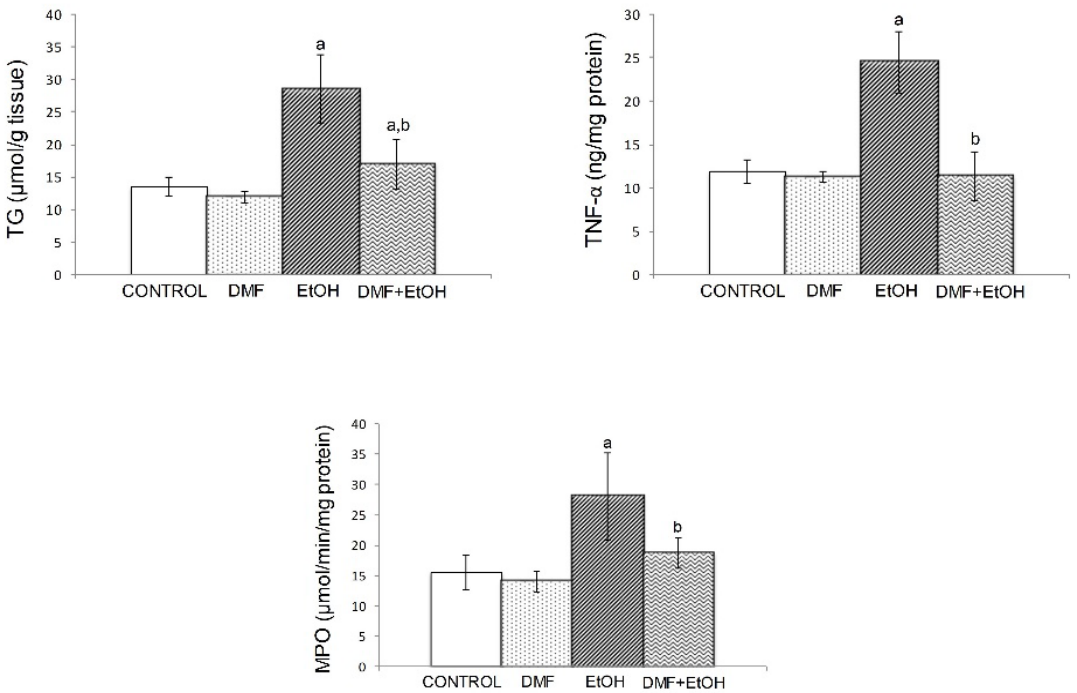

Figure 2: The effect of dimethyl fumarate (DMF) on triglyceride (TG) and tumor necrosis factor-alfa (TNF-α) levels and myeloperoxidase (MPO) activity of the liver in binge ethanol (EtOH)-treated rats (Means ±SD).
a: $p<0.05$ as compared to the control, b: $p<0.05$ as compared to EtOH

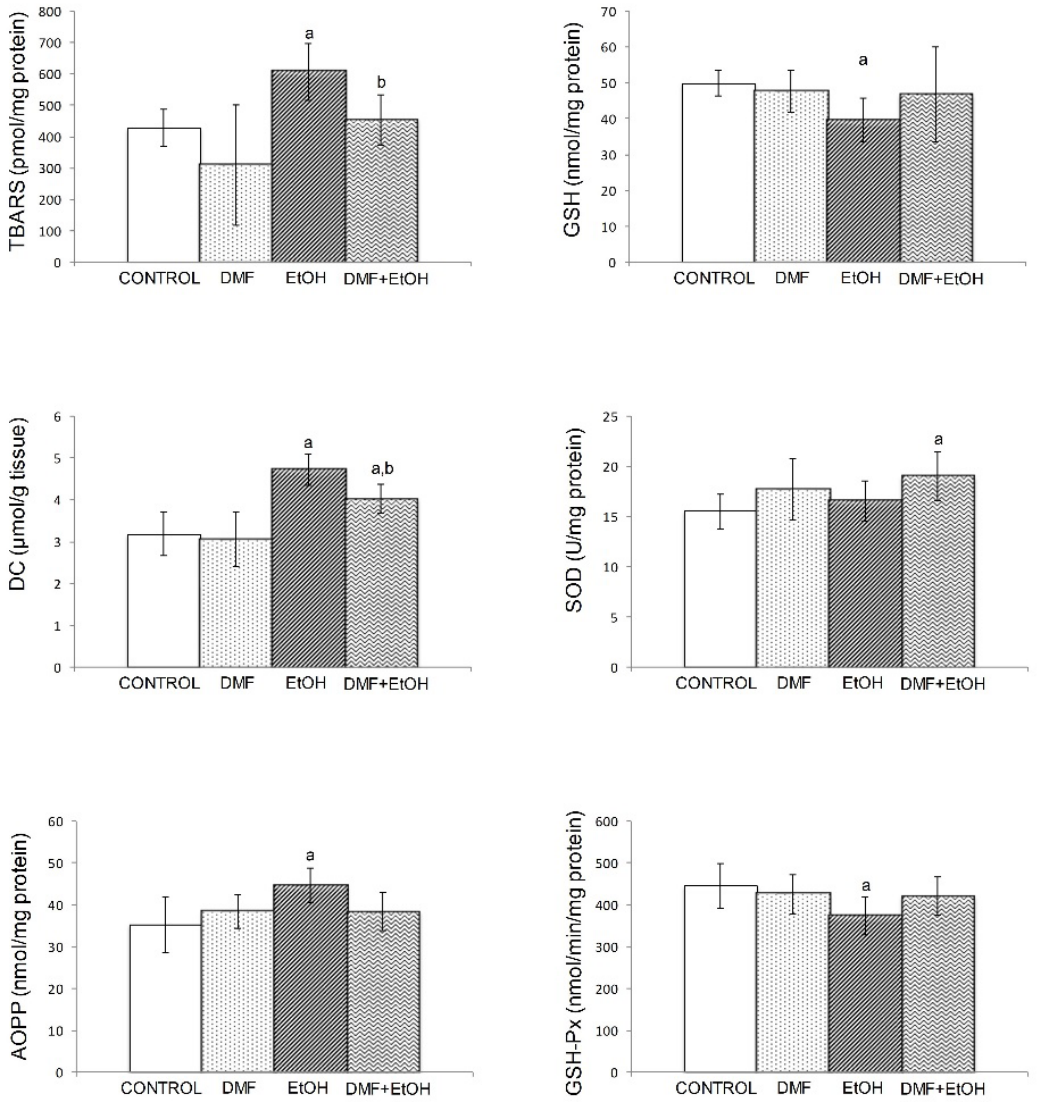

Figure 3: The effect of dimethyl fumarate (DMF) on thiobarbituric acid reactive substances (TBARS), diene conjugates (DC), and advanced oxidized protein products (AOPP) as well as glutathione (GSH) level and superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities in binge ethanol (EtOH)-treated rats (Means±SD).
[a]p<0.05 as compared to the control, [b]p<0.05 as compared to EtOH.

with steatosis-administered DMF, significant decreases were observed in liver TBARS (25.1%; p<0.05), DC (17.0%; p<0.05), and AOPP levels (14.1%; p<0.05) (Figure 3).

Significant changes were also found in GSH (20.7%; p<0.01) levels and GSH-Px (16.0%; p<0.05) activities in the group. However, the activity of SOD remained unchanged when compared to the control group. In the DMF+EtOH group, GSH levels and GSH-Px activities returned to normal control values.

Protein expressions of Nrf2, HO-1, SREBP-1, PPAR-α, NF-κB and CYP2E1

Significant increases were found in Nrf2 (25.7%; p<0.05) and HO-1 (23%; p<0.01) protein expressions in the DMF-treated control group, whereas other protein expressions remained unchanged. However, an increase in protein expression of Nrf2 (22.7%; p<0.05) was found in the EtOH group as compared to the control. DMF treatment resulted in further increases (24.3%; p<0.05) in Nrf2 protein expression in EtOH-treated rats. Elevations in HO-1 protein expressions (35.7%; p<0.01 and 18.7%;

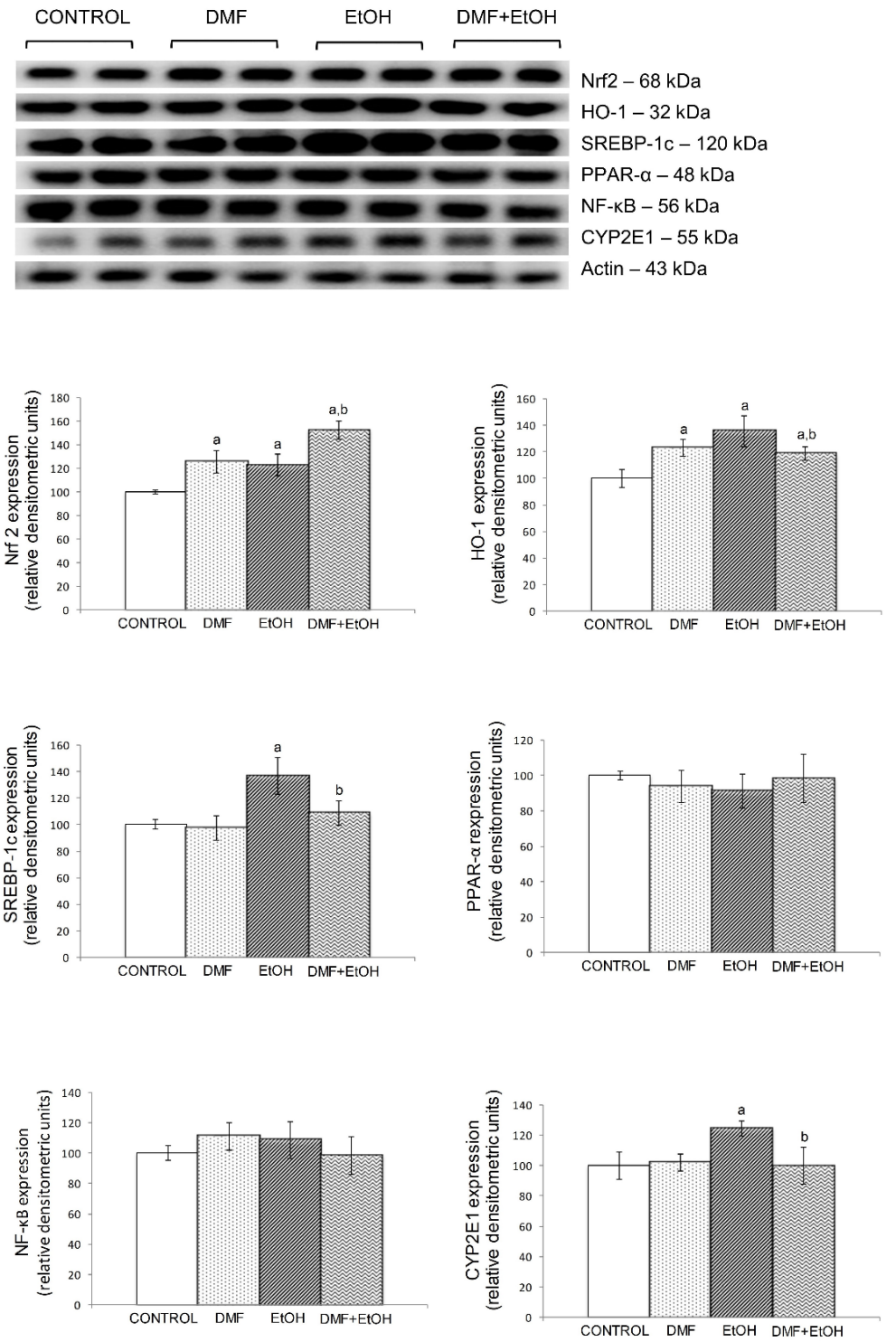

Figure 4: The effect of dimethyl fumarate (DMF) on hepatic nuclear factor erythroid 2-related factor (Nrf2), heme oxygenase-1 (HO-1), sterol regulatory element-binding protein-1c (SREBP-1c), peroxisome proliferator-activated receptor-alpha (PPAR-α), nuclear factor kappa B (NF-κB) and cytochrome P4502E1 (CYP2E1) protein expressions in binge ethanol EtOH-treated rats (Means±SD).
a: $p<0.05$ as compared to the control, b: $p<0.05$ as compared to EtOH.

p<0.05) were also detected in the EtOH and DMF+EtOH groups, respectively as compared to controls (Figure 4).

SREBP-1c protein expression (36.9%; p<0.001) increased significantly in the EtOH group, whereas PPAR-α expression remained unchanged. DMF administration caused a notable reduction (20.4%; p<0.01) in SREBP-1c, but PPAR-α expression remained unaffected. Although there were no significant changes in hepatic NF-κB expression in EtOH and DMF+ EtOH groups, CYP2E1 increased significantly (24.2%; p<0.01) in the EtOH group. A substantial decrease (19.7%; p<0.01) in CYP2E1 expression was found following DMF administration (Figure 4).

DISCUSSION

EtOH was administered orally according to the binge model in our study. This model causes a significant increase in blood EtOH levels. Thus, portal circulation contains high levels of EtOH and the liver is exposed to high EtOH concentrations. Binge EtOH application was reported to induce hepatic steatosis along with a slight elevation of serum transaminase levels. Therefore, this model is useful to investigate steatosis which is an early stage of ALD. Moreover, since female rats were reported to be more sensitive to alcohol than males, female rats were used in this study (29).

Lipogenesis, inflammation, and oxidative stress were reported as significant factors contributing to the development of ALD (1,2). Due to the effectiveness of Nrf2 activation in these events, which are mentioned to be effective in the pathogenesis of ALD, this study explored whether DMF, known as a Nrf2 activator, has a protective impact against EtOH-induced liver injury and uncover the underlying mechanisms. Although some investigators have researched the effect of DMF on cell damage in some tissues including the liver, there is limited information on its efficacy in EtOH-induced hepatotoxicity (17-19). DMF pre-treatment was detected to alleviate lethality induced by acute high doses of EtOH (17). In addition, DMF application was found to protect against hepatic lesions by decreasing increased intestinal permeability and serum LPS levels and oxidative stress in rodents fed on a Lieber De-Carli EtOH liquid diet (18,19).

In this study, statistically substantial increases in serum ALT, AST, LDH, and ALP activities were found in rats treated with EtOH. Histopathological examination of the liver revealed a microvesicular steatosis and mild inflammation. These findings are in accordance with previous studies (21,30,31). DMF treatment resulted in significant decreases in hepatic damage markers in serum and improvement in pathological findings such as steatosis and inflammation in binge EtOH-treated rats.

EtOH stimulates lipogenesis by affecting NADH/NAD^+ redox potential in the liver, thus increasing lipid accumulation (1,2). Binge EtOH treatment increased the expression of hepatic SREBP1c and lipogenesis-related genes but it decreased the expression of PPAR-α and β-oxidation-related genes (21,30,32,33). In this study, hepatic TG level and SREBP-1c protein expression increased in ETOH-treated rats and DMF treatment caused significant decreases in these parameters.

Binge EtOH treatment resulted in elevations in inflammatory cytokines such as TNF-α and IL-6 as well as increased NF-κB expression in the liver (30,31,34). NFκB regulates the expression of multiple genes that are effective in inflammatory response by inducing cytokines (6). TNF-α is a major cytokine associated with the inflammatory response and MPO activity is an indicator of neutrophil infiltration in the liver. In this study, the elevated hepatic TNF-α levels and MPO activities induced by EtOH were attenuated following DMF treatment.

Several investigators have reported that there are significant increases in ROS generation, lipid, and protein oxidation products together with changes in antioxidant system parameters in binge-EtOH-treated rodents (20,30,31,33,34). CYP2E1 and NADPH oxidase (NOX) in hepatocytes and Kupffer cells, respectively, are responsible for the formation of ROS due to ethanol (1,2). Hepatic CYP2E1 activity and expression were detected to increase in binge EtOH-treated rats (31,34,35). EtOH-induced oxidative stress augments the translocation of intestinal lipopolysaccharide (LPS) to the liver by increasing intestinal permeability, leading to the activation of NOXs and the formation of proinflammatory cytokines (3). In this study, ROS formation, MDA, DC and AOPP levels along with CYP2E1 protein expression increased, but antioxidant parameters (GSH levels and GSHPx activity) showed statistically insignificant decreases in binge EtOH-treated rats. However, CYP2E1 protein expression, ROS, TBARS, and DC levels were observed to decrease in DMF-treated rats who received binge EtOH drinking. Also, a trend of increasing SOD and GSH-Px activities and GSH levels due to DMF.

Furthermore, increases in protein expressions of Nrf2 and HO-1, a downstream target of Nrf2, were also found in EtOH-treated rats in the current study. Some investigators have also reported that Nrf2 protein and mRNA expressions were detected to increase together with CYP2E1 protein expression in EtOH-treated rats (36). Moreover, EtOH exposure augmented Nrf2-mediated HO-1 transcription in the liver of rats (37). HO-1 is a cytoprotective antioxidant enzyme and is induced by several factors such as Nrf2 translocation, oxidative stress, and inflammatory cytokines (38). Therefore, the Nrf2/HO-1 pathway may protect against further increases in

CYP2E1-induced oxidative stress due to EtOH treatment. However, in this study, this protection appears to be insufficient in binge EtOH-treated rats. It was also observed that CYP2E1 expression was decreased, Nrf2 was further expressed, while HO-1 protein expression remained above normal levels due to DMF application in EtOH-treated rats. These results obtained with DMF against binge EtOH-induced liver damage are in accordance with those previously reported in experimental models of NAFLD induced by a high-fat diet (HFD) (39) and HFD+streptozotocin (40).

CONCLUSION

In conclusion, these findings reveal that DMF exerts a protective impact against binge EtOH-induced liver damage. The multifunctional efficiency of DMF-induced Nrf2 activation such as anti-lipogenic, antioxidant, and anti-inflammatory potential may be effective in the amelioration of EtOH-induced hepatotoxicity. According to this, DMF may be a new therapeutic agent for ALD.

Ethics Committee Approval: This study was approved by Bezmialem Vakif University Animal Experiments Local Ethics Committee (Date: 24.01.2019, No: 2019/14).

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Author Contributions: Conception/Design of Study- İ.B., M.U.; Data Acquisition- İ.B., C.K., I.D.E.; Data Analysis/Interpretation- İ.B., S.D.A., M.U.; Drafting Manuscript- İ.B., M.U; Critical Revision of Manuscript- İ.B., S.D.A.; Final Approval and Accountability- İ.B., M.U.; Technical or Material Support- İ.B., C.K.; Supervision- M.U.

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EFFECTS OF OBESITY DEGREES AND THE PRESENCE OF METABOLIC SYNDROME ON THE SEXUAL LIFE OF WOMEN AND MEN

OBEZİTENİN DERECESİ VE METABOLİK SENDROM VARLIĞININ KADIN VE ERKEK CİNSEL YAŞAMINA ETKİLERİ

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ABSTRACT

Objective: This study evaluated the sexual functions of women and men with different degrees of obesity and/or metabolic syndrome (MetSynd).

Material and Methods: Participants were divided into subgroups according to their degree of obesity and presence of MetSend, and their sexual functions were evaluated using the Female Sexual Function Index (FSFI) for women and the International Index of Erectile Function (IIEF) for men. The results were compared with a healthy control group.

Result: Two hundred and thirteen (213) patients (females/males:119/94) were included. The mean age was 39.72±6.64 and 37.84±6.83 years, and the BMI was 38.34±9.77 and 38.48±10.58 kg/m2, respectively, for females and males. Metabolic syndrome was diagnosed in 61.7% of females and 67.9% of males. In women, the BMI of those with severe sexual dysfunction (SD) was higher than those with moderate SD (p>0.05), and their age was found to be older (p=0.033). Sexual satisfaction was found to be higher in those with high BMI (p<0.001). The probability of having erectile dysfunction (ED) in men with obesity and MetSend is higher than in those without (p>0.05). While SD was detected

ÖZET

Amaç: Bu çalışmada farklı derecelerde obeziteli ve/veya metabolik sendrom (MetSend) tanılı kadın ve erkeklerin cinsel işlevlerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Katılımcılar obezite derecelerine ve MetSend varlığına göre alt gruplara ayrılmış, cinsel fonsiyonları Kadın Cinsel Fonksiyonu İndeksi (FSFI) ve Uluslararası Erektil Fonksiyon Endeksi (IIEF) kullanılarak değerlendirilmiştir. Sonuçlar sağlıklı kontrol grubuyla karşılaştırılmıştır.

Bulgular: Çalışmaya 213 hasta (kadın/erkek:119/94) dahil edilmiştir. Kadın ve erkekler için sırasıyla yaş 39,72±6,64/37,84±6,83 yıl; beden kitle indeksi (BKİ) 38,34±9,77/38,48±10,58 kg/m^2 saptanmıştır. Kadınların %61'ine, erkeklerin ise %67,9'una MetSend tanısı konmuştur. Kadınlarda seksüel disfonksiyonu (SD) ciddi olanların ortalama BKİ (p>0,05) ve yaşları (p=0,033) orta derecede SD bulunanlardan daha yüksek bulunmuştur. Cinsel tatmin ise yüksek BKİ'li bireylerde daha yüksek bulunmuştur (p<0,001). Obeziteli ve MetSend bulunan erkeklerde erektil disfonksiyon (ED) varlığı, bulunmayanlara göre daha yüksektir (p>0,05). Tüm kadınlarda SD tespit edilirken (%83,2'sinde kötü-SD, %16,8'inde orta-SD), erkeklerde ED %15 oranında

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in all women (severe-SD in 83.2%, moderate-SD in 16.8%), erectile dysfuntion was found in only 15% of men. In women, SD (moderate/severe) was associated with age (OR: 1.087, 95% CI: 1.008-1.172; p=0.030) and the presence of MetSend (OR: 4.257, 95% CI: 1.291-14.038; p=0.017), however no statistically significant relation was found in men.

Conclusion: Metabolic syndrome and obesity are closely associated with sexual dysfunction in both men and women, and it worsens as the severity of obesity increases. Contrary to expectations, sexual satisfaction in women is inversely proportional to the severity of obesity. Expectations regarding sexual satisfaction in obese individuals can be expected to be lower than in individuals of normal weight because social stigma may cause obese individuals to impose restrictions on enjoying sexual interaction. The fact that all women have SD and only 15% of men have ED calls into question the reliability of participant statements. This can be explained by the fact that sexuality is a male-dominated taboo in our country and similar Eastern cultures. Therefore, new studies with similar designs and more participants are needed to eliminate uncertainties.

Keywords: Obesity, metabolic syndrome, impotence, erectile dysfunction, female sexual dysfunction, sexual satisfaction

bulunmuştur. Kadınlarda orta/kötü SD'nun yaş (OR: 1,087, 95% CI: 1,008–1,172; p=0,030) ve MetSend varlığı (OR: 4,257; %95 CI: 1,291–14,038; p=0,017) ile ilişkili olduğu gözlenirken, erkeklerde bu parametreler arasında anlamlı ilişki bulunamamıştır.

Sonuç: Metabolik sendrom ve obezite varlığı hem kadın hem de erkeklerde SD ile ilişkili olup, obezite şiddeti arttıkça SD daha da kötüleşmektedir. Kadınlarda cinsel doyum beklenenin aksine obezite şiddetiyle ters orantılıdır. Obeziteli bireylerde cinsel doyum için beklentilerin, normal kilolulardan daha düşük olması beklenebilir. Çünkü toplumsal stigmatizasyon obeziteli bireylerin cinsel ilişkiden keyif almak konusunda bazı kısıtlamalar uygulamasına neden olabilir. Kadınların tamamında SD olup erkeklerin sadece %15'inde ED saptanması katılımcı beyanlarının güvenilirliğini sorgulatmaktadır. Bu durum bizde ve benzer doğu kültürlerinde cinselliğin erkek egemen bir tabu olması ile açıklanabilir. Bu nedenle belirsizlikleri ortadan kaldırmak için benzer tasarımda ve daha fazla katılımcıyla yapılacak yeni çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Obezite, metabolik sendrom, impotans, erektil disfonksiyon, kadın cinsel disfonksiyonu, cinsel tatmin

INTRODUCTION

Obesity negatively affects both physical and emotional well-being and psychosocial functions. According to Satman et al.'s 2010 prevalence study, obesity in the population aged ≥20 years in Türkiye was 32% (1). When compared to TURDEP-I study conducted in 1997-98, the proportion of normal-weight individuals decreased from 41% to 26%, and the ratio of overweight individuals increased from 35% to 37%; class-I obesity (BMI: 30-34.9 kg/m^2) from 16% to 24%, class-II obesity (BMI:35-39.9 kg/m^2) from 5% to 8.8%, class-III obesity (BMI:35-39.9 kg/m^2) (BMI≥ 40 kg/m^2) rate increased from 1% to 3.1% (1, 2). Between the two studies, obesity increased by 34% in women and 107% in men. According to the World Obesity Atlas published in 2023, the estimated increase rate of obesity in adults in our country is 2.3%/year, and it is predicted that the prevalence of obesity will reach 55% in 2035 (3).

Metabolic syndrome (MetSynd) is a condition in which several comorbidities coexist, including central obesity, insulin resistance or impaired glucose metabolism, dyslipidemia, and arterial hypertension (4). In Türkiye, one (1) in every four men and one (1) in every three women have MetSynd (5). High body fat mass (FM) in men with obesity is responsible for increased aromatase activity and changes in the testosterone/estradiol ratio (6). In these men, sexual dysfunction (SD), especially erectile dysfunction (ED), increased 1.3 times (7).

Some drugs used in the treatment of hypertension and endothelial dysfunction resulting from defects in smooth muscle contraction may explain the development of ED (6, 8). Although it has been suggested that female sexual dysfunction (FSD) is more complex and more closely related to psychosocial factors, successful control of hypertension also reduces FSD (8). Other problems include age, partner-related problems, low socio-economic status, low education level, and chronic diseases (9). It has been found that women with MetSynd have less satisfactory sexual lives and experience SD more frequently (9).

Research results on the relationship between obesity and female sexuality are conflicting. In a study evaluating the prevalence of FSD in our country, FSD was detected in 86% of women with obesity and 83% of women with normal weight (10). In another study, FSD was detected in 50% of obese women and 41% of normal-weight women; no significant difference was found (11). The general prevalence of FSD in Türkiye is 29.3%-86%, and it is reported that 3/4 of women with Class-I obesity and approximately half of those with Class II, -III, and above obesity have FSD and suggested that body image affects sexual health in women rather than BMI (12, 13).

It has been reported that ED is related to BMI, and the prevalence is 53.1% (14). Another study stated that the frequency of ED increased 1.5 times in overweight men and three times in obese men (15). In Türkiye, the age-adjusted prevalence of ED was found to be 69.2% (mild: 33.2%, moderate: 27.5%, severe: 8.5%), and the severity of ED increased with age (16). Erectile dysfunction is up to three times more common in men with MetSynd. It is reported that a total of 79-96% of people with MetSynd apply due to ED, and 29-66% of people with ED have

MetSynd (17). The presence of MetSynd is associated with an increased risk of ED, even in men with BMI <25 kg/m^2 (18).

In light of all these studies, it appears that obesity negatively affects sexual function in men, but shows contradictory results in women. We did not find any study in the literature in which men and women were evaluated together in a single center. This study assessed the factors affecting the sexual function (SF) of men and women diagnosed with MetSynd and different degrees of obesity who are followed up by the same team at the same center.

MATERIALS and METHODS

Patients who were followed up due to MetSynd and/or obesity at Istanbul University, Istanbul Faculty of Medicine, Department of Endocrinology and Metabolism, Outpatient Clinic between January 2016 and January 2019, were included in the study. The study was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 14.08.2015, No: 13) and was conducted by the Declaration of Helsinki Principles. Written informed consent was obtained from each participant.

Study population

One hundred and sixty-three subjects with MetSynd and obesity between 18-50 years old were included in the patient group and 50 healthy subjects with non-obese consisted of the control group. All participants were married or had sexual partners, and had sexual intercourse at least once a month. Postmenopausal women and sexually inactive women were excluded from the study.

The patient's demographic characteristics and bioimpedance analyses (Tanita, TBF-300, Japan) were collected through interviews with a research doctor or nurse. The participants were given 15 minutes for the surveys. By calculating BMI (kg/m^2) values, patients were divided into subgroups as normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), class-I (moderate) obesity (30.0-34.9 kg/m^2), class-II (severe) obesity (35.00-39.9 kg/m^2), class-III (morbid) obesity (40.0-49.9 kg/m^2), and super obesity (≥50.0 kg/m^2) (19). The criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)-2001 were used as Metabolic Syndrome Diagnostic Criteria (20).

Questionnaires

Beck Depression Inventory

The 'Beck Depression Inventory (BDI)', a self-report scale, was used to examine the depression status of the participants. This scale consists of 21 questions; each item is scored 0-3. The total score for the scale is between 0-63. According to the Turkish validity and reliability study conducted by Hisli et al., the higher the test score, the higher the severity of depression (21,22). In our study, those who scored ≥17 (moderate and severe) were considered to have depression.

SF-36 Item Short Form Survey

The Short Form Survey (SF-36) consists of eight multi-item scales (36 items in total) that assess patients' health status and impact on their lives (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health). Scores on each scale range from 0 (worst) to 100 (best). Higher scores indicate higher quality of life (23). A Turkish validity and reliability study was conducted (24).

Female Sexual Function Index

Sexual function was assessed by completing the FSFI, a validated 19-item self-report measure of female SF (25). Nineteen items analyze six distinct domains of female SF: desire disorder, arousal disorder, orgasmic disorder, sexual pain disorder, lubrication, and sexual satisfaction. Each domain is scored on a scale of zero or 1-6; A higher score indicates better function. The total score range is 2-36, and a score of ≤26.55 is defined as SD (26). Turkish validity-reliability study of the scale was conducted (27).

International Index of Erectile Function questionnaire

This study used the International Index of Erectile Function (IIEF) to question various sexual function (28). In this study, participants were asked 15 questions to determine erectile function, orgasm function, sexual desire, sexual intercourse satisfaction, and general satisfaction. Accordingly, ED is divided into five categories according to severity: no ED (between 26-30 points), mild (between 22-25 points), mild-moderate (between 17-21 points), moderate (between 11-16 points) and severe (between 6 and 10 points). The IIEF was adapted into Turkish by the Andrology Association (16).

Statistical analysis

Statistical analyses were performed using the SPSS-21 package program (SPSS Corp., Armonk, NY, USA). Normality control was performed by Shapiro Wilk or a single-sample Kolmogorov-Smirnov test where appropriate. Data was presented as mean and SD or frequency and percentage. In comparing the two groups, the variables showing normal distribution were compared with the student t-test and the Mann-Whitney U test was used in the others. Categorical variables were compared with Yates' corrected chi-square and Fisher's exact probability tests. Where appropriate, possible correlations between the variables were tested with Pearson's, Spearman's, and partial correlation tests. We used logistic regression analyses to assess independent factors associated with FSD and ED. Statistical significance was accepted at two-sided $p<0.05$.

RESULTS

Findings of female participants

The demographic characteristics: The average age of 119 females was 39.72±6.64 (24.00-50.00) years, weight was 99.25±25.62 (52.70-179.80) kg, BMI was 38.34±9.77 (19.40-63.70) kg/m^2, FM was 42.80±18.79 (10.30-89.32) kg. According to the participants BMI categories, 8.4% were normal weight, 15.1% were overweight, and 76.5% were obese (of them 9.2% were super obese; 33.6% were class III-morbidly obese, 16.8% were class II-severely obese, 16.8% were class I-obese). The demographic characteristics of the participants are presented in Table 1.

Results of BDI: According to the BDI score, moderate and severe depression was detected in 25% of women. There is no significant difference between the FSFI scores of those who were depressed and those who were not.

Results of SF-36 assessment: Subparameter scores of SF-36 were found to be below the norm values determined for Turkish women (29). In addition, the subparameter scores decreased as the degree of obesity increased. Correlations between SF-36 and FSFI domains are presented in Table 2.

Findings of smoker women: The rate of smokers was 25.6% and does not create a substantial difference in FSD.

FSFI and its domain findings: Arousal (3.70±1.44 vs. 2.76±1.69; p=0.003), orgasm (17.86±5.61 vs. 15.56±6.63; p=0.040), and the total FSFI scores of 59 working women were found to be significantly higher than those of unemployed women. The average total FSFI score of the participants was 16.70±6.23 (3.00-26.30), and all of them had SD since the cut-off score of the scale was less than 26.55. The FSFI cut-off <23 was classified as " SF-poor," 23-29 as "SF-moderate," and ≥30 as "SF-good," while 83.2% of the participants had "SF-poor," and 16.8% had "SF-moderate."

All female patients had SD. The mean BMI (38.49±10.14 vs 37.68±8.06 kg/m2) and FM (43.52±19.68 vs 39.51±14.05 kg) of those with poor SF were found to be higher than those with moderate SF (p=0.477; p=0.804), and their ages were significantly older (40.41±6.39 vs. 36.55±7.02 years; p=0.033). Of those with SF-poor, 75.8% were obese, 15.2% were overweight, and 9.1% were normal weight.

Effects of obesity on female participants: The total FSFI scores were lower in those with obesity than those without (p=0.476). The FSFI domains were also found to be lower in those with obesity than those without obesity, including arousal (p=0.021), lubrication (p=0.016), and pain (p=0.001) scores. However, satisfaction scores were higher in women with obesity (p<0.001) (Table 2).

Satisfaction disorders were found in 52.5% and 90.9% of those with and without obesity, respectively (p=0.021); Pain disorder was 72% and 34.6% (p=0.003). It was observed that obesity did not create a statistically significant difference in the evaluation of the other FSFI domains. When the average scores of BMI categories and the FSFI domains were analyzed, the arousal (p=0.011), lubrication (p=0.015), and pain scores (p<0.0001) decreased significantly as BMI increased, while satisfaction scores (p<0.0001) increased significantly (Table 3).

A weak negative correlation was observed between both BMI and obesity severity and arousal (p=0.010, r=-0.239 and p=0.042, r=-0.190), lubrication (p=0.023, r=-0.211 and p=0.047, r=-0.136), and pain (p=0.000, r=-0.334 and p=0.002, r=-0.278). Figure 1 shows the average scores of FSFI domains in normal, overweight, and obese women. A weak negative correlation was found between the FM and FSFI scores: arousal (p=0.003, r=-0.276), lubrication (p=0.020, r=-0.217), orgasm (p=0.046, r=-0.172), and pain (p=0.003, r=-0.273).

Sexual satisfaction showed a weak positive correlation with BMI and FM and a moderate positive correlation with the severity of obesity (p<0.001, r=0.380; p<0.001, r=0.513 and p=0.011, r=0.280).

Effects of MetSynd on female participants: MetSynd was present in n=58 participants. Sexual desire (p=0.017), arousal (p=0.047), pain (p=0.016), and total FSFI score (p=0.042) were found to be lower in women without MetSynd than in women with. Additionally, 91.8% of those with MetSynd had a total FSFI score of <23 and were considered SF-poor.

In logistic regression analysis, it was observed that age alone (OR: 1.087, 95% CI: 1.008–1.172; p=0.030) and the presence of MetSynd alone (OR: 4.257, 95% CI: 1.291–14.038; p=0.017) had significant relationships with moderate or poor impairment of SF.

Findings of male participants

The demographic characteristics: The average age of the 94 males was 37.84±6.83 (23-50) years, weight 118.88±34.91 (60.20-217.80) kg, FM 41.58±25.46 (4.40-118.14) kg and BMI 38.48±10.58 (20.00-63.10) kg/m^2.

According to the participants' BMI categories, 76.5% were obese (13.6% super obese, 27.2% class III-morbidly obese; 13.6% class II-severely obese, 23.5% class I-obese), 14.8% overweight and 8.6% normal weight. The demographic characteristics of the participants are presented in Table 1.

BDI assessment findings in men: According to the BDI score, moderate and severe depression was detected in 16% of men. The sexual desire scores of these patients

Table 1: Demographic characteristics of participating women and men by body mass index categories

	Normal		Overweight		Class I (Moderate) obesity		Class II (Severe) obesity		Class III (Morbid) obesity		Super obesity	
	Women (n=10)	Men (n=10)	Women (n=18)	Men (n=12)	Women (n=20)	Men (n=21)	Women (n=20)	Men (n=14)	Women (n=40)	Men (n=26)	Women (n=11)	Men (n=11)
Age (year)	35.30 ±8.32	35.57 ±6.50	41.76 ±5.73	37.27 ±8.10	40.33 ±7.83	38.23 ±7.11	39.52 ±4.96	38.20 ±5.34	40.11 ±6.75	38.10 ±6.17	39.50 ±5.60	38.50 ±9.00
Weight (kg)	60.24 ±4.71	74.50 ±8.93	73.81 ±9.48	85.19 ±8.96	84.19 ±6.50	98.73 ±8.60	96.92 ±4.10	114.01 ±11.04	114.04 ±11.33	140.34 ±15.12	146.12 ±13.94	180.30 ±28.01
Fat mass (kg)	14.59 ±3.62	12.89 ±4.75	27.16 ±6.06	21.11 ±4.90	31.97 ±5.81	27.06 ±3.35	38.79 ±6.24	70.41 ±105.73	52.67 ±8.89	59.58 ±14.75	79.85 ±6.02	78.48 ±28.58
BMI (kg/m²)	22.64 ±1.72	22.74 ±1.39	28.06 ±1.49	28.23 ±1.99	32.52 ±1.37	32.07 ±1.25	37.61 ±1.34	37.62 ±1.42	44.31 ±3.04	45.56 ±2.82	56.20 ±3.71	57.97 ±3.59
Married (%)	80.0	71.4	92.3	72.7	86.7	70.6	100.0	60.0	82.9	20.0	90.0	12.5
Employed (%)	90.0	71.4	61.5	90.9	40.0	100.0	29.4	100.0	60.0	95.5	50.0	100.0
Education level (%)												
Primary school	N/A	28.6	23.1	9.1	26.7	5.9	5.9	20.0	22.9	NA	10.0	N/A
Secondary high school	N/A	14.3	23.1	45.5	40.0	35.3	76.5	70.0	45.7	60.0	80.0	62.5
University	100.0	57.1	53.8	45.5	33.3	58.8	17.6	10.0	31.4	40.0	10.0	37.5
Smoker (%)	20.0	28.6	16.7	54.5	33.3	23.5	11.1	60.0	30	40.0	25.0	50.0
Moderate- severe depression (%)	10.0	14.3	25.0	9.1	N/A	17.6	33.3	20.0	42.9	15.0	N/A	12.5
MetSynd (%)	N/A	N/A	53.8	45.5	60.0	52.9	29.4	70.0	62.9	95.0	60.0	87.5

BMI: Body Mass Index, MetSynd: Metabolic Syndrome, N/A: Not Available

Table 2: Correlations between 36-Item Short Form Survey (SF-36) domains and Female Sexual Function Index (FSFI) and International Index of Erectile Function (IIEF) domains

SF-36 domains	Female Sexual Function Index (FSFI) domains						International Index of Erectile Function (IIEF) domains				
	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain	Erectile function	Orgasmic function	Sexual desire	Intercourse satisfaction	Overall satisfaction
Physical functioning		p=0.031 r=0.260	p=0.003 r=0.363		p=0.000 r=-0.632	p=0.000 r=0.454					
Role limitation due to physical problems			p=0.011 r=0.303		p=0.000 r=-0.546	p=0.003 r=0.354					
Role limitation due to emotional problems		p=0.046 r=0.240	p=0.027 r=0.266		p=0.000 r=-0.501	p=0.004 r=0.341	p=0.042 r=0.255	p=0.036 r=0.263	p=0.044 r=0.232		p=0.022 r=0.295
Energy and vitality			p=0.024 r=0.274		p=0.000 r=-0.674	p=0.000 r=0.483					
Mental health			p=0.005 r=0.334		p=0.000 r=-0.673	p=0.000 r=0.557					
Social functioning			p=0.000 r=0.414	p=0.012 r=0.301	p=0.000 r=-0.695	p=0.000 r=0.558					
Bodily pain			p=0.001 r=0.385		p=0.000 r=-0.689	p=0.000 r=0.593					
General perception of health			p=0.011 r=0.311		p=0.000 r=-0.615	p=0.001 r=0.388					

Table 3: Female Sexual Function Index and 36-Item Short Form Survey Field Scores in women classified based on body mass index categories

FSFI domains	Min-Max Scores	Non obese	Class I (Moderate) obesity	Class II (Severe) obesity	Class III (Morbid) obesity	Super obesity
Desire	1.2-6.0	3.51±1.07	3.33±1.22	2.91±1.56	3.00±1.28	3.00±1.22
Arousal	0-6.0	3.80±1.58	3.50±1.65	3.12±1.77	3.09±1.51	2.12±1.49
Lubrication	0-6.0	3.38±1.49	3.39±1.37	2.77±1.43	3.00±1.16	2.26±1.65
Orgasm	0-6.0	3.51±1.50	3.41±1.46	2.75±1.70	3.26±1.26	2.36±1.61
Satisfaction	0.8-6.0	3.36±1.33	2.20±2.62	3.60±1.98	3.91±1.51	2.65±1.96
Pain	0-6.0	3.30±1.47	3.10±1.75	1.93±1.66	2.01±1.36	1.89±1.77
Total score	2.0-36.0	17.18±5.50	17.32±5.22	15.81±7.70	17.16±6.11	14.30±7.44
SF-36 domains	**Country (Türkiye) specific scores**	**Non obese**	**Class I (Moderate) obesity**	**Class II (Severe) obesity**	**Class III (Morbid) obesity**	**Super obesity**
Physical functioning	80.6±21.7	74.95±22.19	43.18±17.90	28.85±21.03	27.60±19.53	14.33±2.30
Role limitation due to physical problems	82.9±28.6	64.22±45.94	33.16±41.39	10.06±18.15	21.85±35.17	4.00±0.00
Role limitation due to emotional problems	89.0±22.5	70.01±43.00	20.77±38.16	10.66±24.79	15.26±27.71	4.66±1.15
Energy and vitality	63.4±13.7	53.27±21.91	33.25±14.02	19.53±11.98	22.68±20.23	13.66±3.78
Mental health	70.1±11.4	65.31±21.00	55.16±23.56	29.46±22.68	29.10±26.61	21.00±2.00
Social functioning	90.1±12.9	69.86±29.53	60.79±37.65	18.06±29.01	26.42±37.09	6.00±1.00
Bodily pain	81.0±20.2	66.06±30.78	44.04±30.40	15.00±22.08	22.77±32.98	7.33±1.52
General perception of health	69.1±16.9	56.40±22.71	40.90±21.50	23.53±16.60	23.00±16.95	16.00±1.00

FSFI: Female Sexual Function Index, SF-36: 36-Item Short Form Survey. Scores are given as mean±SD

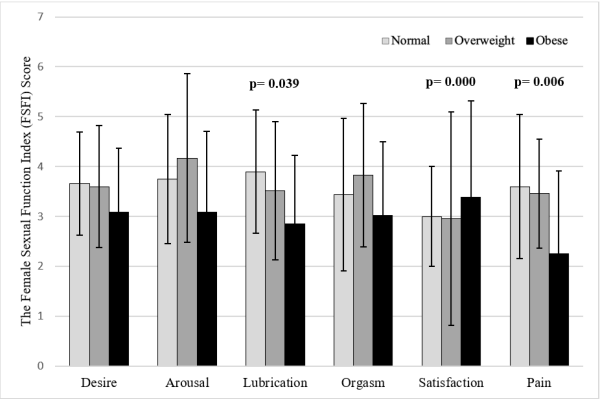

Figure 1: Individual domains of female sexual function in women according to categories of body mass index

were found to be higher than those without depression (p=0.008). Depression and orgasmic function (p=0.032, r=-0.221), sexual desire (p=0.032, r=-0.238), sexual satisfaction (p=0.033, r=-0.221), and general satisfaction (p=0.027, r=-0.234) had weak negative scores; A weak positive correlation (p=0.045, r=0.208) was detected between ED.

SF-36 assessment findings in men: Subparameter scores of SF-36 were below the norm values determined for Turkish men with MetSynd (29). In addition, the scores determined for each domain decreased as the degree of obesity increased. Correlations between SF-36 and IIEF domains are presented in Table 2.

Findings of smoker men: The rate of smokers was 39.5%, and there was no significant difference in terms of ED. However, smokers' sexual satisfaction scores were found to be lower than non-smokers (p=0.047).

IIEF and its domain findings in men: According to the participants' IIEF scores, the rate of men with moderate-severe ED (score <21) was 15.5%, while the rate of men without ED (score ≥21) was 84.5%. When looking at the IIEF domains, orgasmic function scores of 2.8% of the participants, sexual desire scores of 23.6%, sexual satisfaction scores of 5.6%, and general satisfaction scores of 5.6% were below the average.

Effects of obesity on male participants: Although not statistically significant, the probability of having ED was

higher in men with obesity than in those without ED (10.5% vs. 16.4%; p=0.417). According to the IIEF survey, no significant difference existed between the age, weight, and BMI of men with moderate-severe ED (score <21) and those without. A significant difference was found between the FM of men with and without moderate-severe ED (p=0.042). No relationship could be detected between the FM and IIEF domains in men.

Orgasmic function, sexual satisfaction, and general satisfaction scores were below the average in all men with obesity, and sexual desire scores were below the average in 24.1% of men with obesity.

The IIEF domains, orgasmic function scores were less than the average scores in 3.8% of the obese participants, sexual desire in 24.1%, sexual satisfaction in 7.5%, and general satisfaction scores in 13%. The IIEF domain scores according to BMI and obesity severity are presented in Table 4.

It was determined that the incidence of ED increased with increasing BMI (p=0.004, r=0.316) (Figure 2). The incidence of ED increased as the severity of obesity increased (I, II, III.degree and super-obesity 8.3%, 8.3%, 16.7%, and 50%, respectively; p=0.032). However, no relationship was found between them in the logistic regression analysis. When the average scores of the BMI categories and IIEF domains were analyzed, only the ED scores decreased significantly as the BMI increased (p=0.046).

Effects of MetSynd on male participants: The rate of patients with MetSynd is 67.9% and 83.3% of participants with MetSynd had ED (p=0.175). There was a negative relationship between the presence of MetSynd and the general satisfaction scores from IIEF domains; that is, they had lower general satisfaction scores (p=0.035, r=-0.234). We found that the probability of ED in those diagnosed with MetSynd was higher than in those without (18.5% vs. 7.7%; p=0.176). Looking at the IIEF domains of the participants, orgasmic function scores were below average at 4.4%, sexual desire at 23.9%, sexual satisfaction at 8.9%, and general satisfaction scores at 15%.

DISCUSSION

The most important finding of this study, which supports the literature, is that SF in women and men are negatively affected by the presence of MetSynd and obesity. Sexual function worsens as the severity of obesity increases in

Table 4: Male Sexual Function Index and 36-Item Short Form Survey Field Scores in women classified based on body mass index categories

IIEF domains	Min-Max scores	Non obese	Class I (Moderate) obesity	Class II (Severe) obesity	Class III (Morbid) obesity	Super obesity
Erectile function	0-30	26.00±3.36	26.00±3.92	26.09±3.36	24.27±3.71	22.63±3.57
Orgasmic function	0-10	9.00±1.45	9.38±1.03	9.18±1.47	9.63±0.92	8.04±2.01
Sexual desire	2-10	7.44±1.85	7.73±1.19	8.27±1.42	7.36±1.80	7.31±1.83
Intercourse satisfaction	0-15	11.61±1.46	11.27±2.51	11.90±2.30	12.00±2.56	11.27±2.41
Overall satisfaction	2-10	8.05±1.79	8.52±1.50	9.09±0.94	8.18±1.60	7.45±2.34
SF-36 domains	**Country (Türkiye) specific scores**	**Non obese**	**Class I (Moderate) obesity**	**Class II (Severe) obesity**	**Class III (Morbid) obesity**	**Super obesity**
Physical functioning	87.2±17.1	79.88±23.87	83.93±20.73	56.12±23.27	35.38±29.80	24.33±9.81
Role limitation due to physical problems	89.8±19.3	74.93±36.37	68.42±45.58	61.37±47.23	27.84±41.15	29.00±39.88
Role limitation due to emotional problems	92.8±15.1	55.75±38.87	80.40±40.59	59.83±40.41	14.17±27.03	25.88±35.31
Energy and vitality	65.7±11.9	58.88±23.49	61.81±25.03	41.62±21.49	25.42±17.84	35.00±34.87
Mental health	71.0±10.6	73.60±19.98	64.75±21.91	54.62±32.80	25.69±18.35	42.00±39.84
Social functioning	91.7±12.8	68.34±26.40	78.43±28.53	61.00±38.96	22.00±30.79	28.66±40.12
Bodily pain	85.1±16.4	72.73±31.63	79.18±27.74	52.87±37.87	22.61±34.73	23.66±35.79
General perception of health	73.6±14.9	60.56±23.59	60.62±20.88	43.37±31.25	20.58±15.12	32.66±32.34

IIEF: International Index of Erectile Function Questionnaire, SF-36: 36-Item Short Form Survey. Scores are given as mean±SD

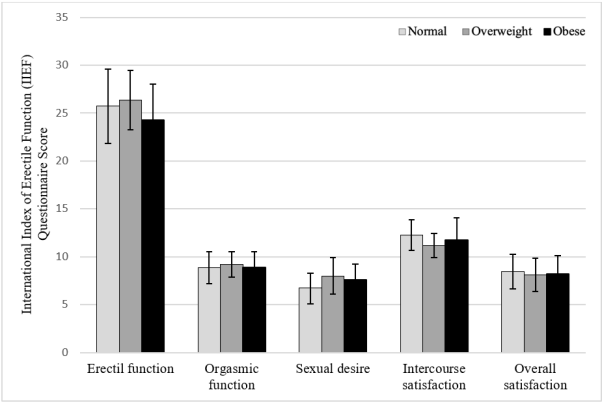

Figure 2: Individual domains of male sexual function in men with different categories of body mass index

women, and the incidence of ED increases in men, but there is no significant change in evaluation scores. On the other hand, sexual satisfaction in women is inversely proportional to the severity of obesity, contrary to expectations. In addition, while SF worsens in women with increasing age, men do not change.

MetSynd is closely associated with both ED and FSD. Esposito et al. showed that the prevalence of ED in men with MetSynd was 96% and that the FSFI score and the number of components of MetSynd were inversely related in women (30). In our study, the prevalence of ED was 83.3%, and the prevalence of poor-SF in women was 4.24 times higher than in healthy women. Other factors associated with FSD are age and BMI (26,34). In men, age is a less important factor than the severity of obesity in ED (15). In the study of Skrypnik et al., the risk of SD is 1.5 times higher in patients with BMI 25-30 kg/m^2 and three times higher in patients with BMI>30 kg/m^2, and the severity of obesity is an independent risk factor for ED (15).

However, no relationship was found between the FSFI scores and BMI in women (10). It is interesting that in our study a significant negative relationship was found between BMI and all domains except in women's sexual satisfaction scores. The sexual satisfaction scores were even higher in women with 2nd and 3rd-degree obesity. While sexual arousal and lubrication were negatively affected by both physical and emotional factors, sexual satisfaction was not. As a matter of fact, research showed there are uncertainties in the relationship between obesity and sexual satisfaction in women. While some studies showed that women of normal weight may be more sexually active, others discovered that women with obesity may also be sexually active (10). This situation makes us think that sexual satisfaction, especially in women, does not show a linear relationship with the presence and degree of obesity. Similarly, we saw that there is a close relationship between emotional negativities and ED, orgasmic function, sexual desire, and general satisfaction in men. Litwin MS et al., reached similar results in their study and therefore emphasized that doctors should consider the emotional impact when evaluating sexual performance in men (31). Another issue they drew attention to is the low correlation coefficients between SD and SF-36 domains, as we observed in our study. The authors note that general health-related quality-of-life measures alone do not adequately reflect disease-specific impairments in patients' quality of life.

Studies conducted in different countries emphasize that the prevalence of sexual desire, arousal, and orgasm disorders varies from country to country, indicating the potential for significant intercultural differences (10). Studies conducted in different provinces of Türkiye have yielded very different results as well. The possible reason for this is our cities' cultural and traditional differences. It can be challenging to predict personal difficulties and their impact on survey results, especially when it comes to questioning and declaring individual behaviors regarding sexuality, which is taboo in our society.

Adolfsson et al. found no significant difference between weight groups in terms of sexual life satisfaction in both men and women. At this point, researchers have touched on the variability of personal expectations regarding what is required for satisfaction (32). That is, overweight and obese people have lower expectations about what is needed for sexual satisfaction than people of normal weight. Social stigma applied consciously or unconsciously to obese individuals may cause these individuals to internalize these negative messages and restrict themselves from enjoying sexual intercourse.

In our study, we found that sexual desire in men was least affected by obesity and MetSynd (24). In contrast, orgasm function and sexual satisfaction scores were 1.5 times lower on average, and general satisfaction scores were 2.5 times lower on average. Corona G et al., found hypoactive sexual desire in 40% of men with MetSynd. They emphasized the importance of not only penile perfusion disorder but also somatized anxiety among the causes of SD (33).

The strength of our study is that men and women were evaluated together at the same center and with the same team. The number of studies with this design is quite limited. The limitations of our study are the small number of participants in the normal BMI group and the fact that the participants' hormonal levels and body images were not evaluated. Therefore, regardless of the factors considered in this study, the effects of male and female SD, obesity-related hormonal imbalance, body image disturbance, and low self-perception could not be evaluated.

CONCLUSION

As a result, the relationship between FSD and obesity with and without MetSynd has been investigated less

in the literature than ED, and the results are contradictory. The hypothesis that FSD increases with increasing obesity severity is compatible with our study. In men, the presence of obesity±MetSynd obesity with and without MetSynd has been associated with ED primarily on physiological grounds and, in some studies, on psychological foundations. Our analysis supports this finding. In our study, while FSD was present in all women, ED was detected in only 15% of men, which calls into question the applicability of research in this field and the reliability of the participants' statements (12). Because sexuality is seen as a taboo and a male-dominated activity in our culture, new studies with similar designs and more participants are needed to eliminate uncertainties in our country and in other similar cultures.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 14.08.2015, No: 13).

Informed Consent: Written informed consent was obtained from each participant.

Peer Review: Externally peer-reviewed.

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SINGLE CENTER EXPERIENCE OF LIVER RE-TRANSPLANTATION: INDICATIONS-TIMING AND COMPLICATIONS

KARACİĞER RE-TRANSPLANTASYONU TEK MERKEZ DENEYİMİ: ENDİKASYONLAR-ZAMANLAMA VE KOMPLİKASYONLAR

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ABSTRACT

Objective: Function loss, for whatever reason, of the graft used for liver transplantation requires re-transplantation. This study is an evaluation of all re-transplantations performed at our center.

Material and Method: All liver re-transplantation patients whose surgeries had been performed at our clinic, whether at an early or late stage, were included in the study. Demographic information, details related to the surgery, and complications were evaluated retrospectively.

Result: From 2018 to 2023, 236 liver transplantations were performed on 228 recipients in our institution. Of these patients, a total of 18 underwent re-transplantation, 10 of whom were from external centers and 8 of whom had had their first liver transplantation performed at our center. Of these patients, 12 were male and 6 were female, with a mean age of 6.7 years (±4.8) for pediatric patients and 49 years (±14.32) for adult patients. The mean weight for pediatric patients was 19.76 kg (±8.86), and for adult patients it was 70.48 kg (±11.83). The mean body mass index for pediatric patients was 17.41 kg/m² (±2.84), and for adult patients it was 22.33 kg/m² (±2.65). Six of these patients underwent early re-transplantation (7.6±5.4 days) and 12 underwent late re-transplantation (7.6±5.3 years). In terms of re-transplantation etiology, primary non-function was prominent for the early period, while secondary biliary cirrhosis, disease recurrence, and chronic rejection were detected for the late period. Seven recipients (39%) died during the perioperative period, and 1-year survival was calculated as 61% in this patient group.

Conclusion: Re-transplantation has high mortality and morbidity rates. Although early re-transplantation seems to overcome

ÖZET

Amaç: Karaciğer transplantasyonu için kullanılan greftin çeşitli nedenlerle fonksiyon kaybı re-transplantasyonu gerektirmektedir. Bu çalışmada merkezimizde gerçekleştirilen tüm karaciğer re-transplantasyon olguları değerlendirilmiştir.

Gereç ve Yöntem: Kliniğimizde erken ve geç dönem olmak üzere karaciğer re-transplantasyonu yapılan tüm hastalar çalışmaya dahil edildi. Demografik bilgiler, ameliyatla ilgili detaylar ve komplikasyonlar retrospektif olarak değerlendirilmiştir.

Bulgular: 2018'den 2023'e kadar kurumumuzda 228 alıcıya 236 karaciğer nakli gerçekleştirildi. Bu hastalardan 10'u dış merkezlerden olmak üzere toplam 18 hastaya re-transplantasyon yapılmıştır. Bu hastaların 12'si erkek, 6'sı kadın olup, yaş ortalaması pediatrik hastalarda 6,7 (±4,8), erişkin hastalarda ise 49 (±14,32) idi; çocuk hastaların ortalama ağırlığı 19,76 kg (±8,86), yetişkin hastaların ortalama ağırlığı 70,48 kg (±11,83); çocuk hastaların ortalama vücut kitle indeksi 17,41 kg/m² (±2,84), yetişkin hastaların ise 22,33 kg/m² (±2,65) olduğu belirlendi. Bu hastaların altısına erken retransplantasyon (7,6±5,4 gün), 12'sine geç retransplantasyon (7,6±5,3 yıl) uygulandı. Re-transplantasyon etiyolojisi açısından erken dönemde primer non-fonksiyon ön plana çıkarken, geç dönemde sekonder biliyer siroz, hastalık nüksü ve kronik rejeksiyon saptandı. Perioperatif dönemde yedi alıcı (%39) öldü ve bu hasta grubunda 1 yıllık sağkalım %61 olarak hesaplandı.

Sonuç: Re-transplantasyon yüksek mortalite ve morbidite oranlarına sahiptir. Erken re-transplantasyon, özellikle primer non-fonksiyon vakalarında yüksek ölüm oranlarının üstesinden

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high mortality rates, especially in primary non-function cases, organ shortage and the need for living donors are significant problems.

Keywords: Liver transplantation, chronic graft dysfunction, liver re-transplantation

geliyor gibi görünse de, kadavra organ eksikliği ve canlı donör ihtiyacı önemli sorunlardır.

Anahtar Kelimeler: Karaciğer nakli, kronik greft disfonksiyonu, karaciğer re-transplantasyonu

INTRODUCTION

Liver transplantation (LT) surgery, which started in the 1960s, has shown an increase in graft and patient survival and a decrease in complication and mortality rates due to the improvement of surgical techniques and technological developments in gastroenterology, endoscopic procedures, immunology, microbiology, pharmacology and especially interventional radiology (1, 2).

Graft and patient survival are the most important goals in LT. The most important factors affecting graft and patient survival are surgical technique, primary non-function (PNF), recurrence of primer disease, rejection (acute or chronic), and bile duct anastomosis complications (3-5). When the graft is irreversibly severely affected and becomes dysfunctional, re-transplantation (Re-Tx) becomes a life-saving option if the clinical condition of the patient is appropriate.

For both surgical and medical reasons, liver Re-Tx has a lower success rate than the initial transplant, and a 1-year survival rate has been reported to be around 77% for adult patients and 89% for pediatric patients (6-8). The worldwide average Re-Tx rate among all liver transplants varies between 7% and 23% (9).

In this study, liver Re-Tx cases performed at our clinic were retrospectively evaluated, and the results obtained are shared.

MATERIALS and METHODS

Patients who underwent Re-Tx from July 2018 to February 2023 were included in this study. The patient group was divided into two categories, "early" and "late", and their demographic data, etiology of LT (first LT and Re-Tx), graft type and characteristics, vascular and biliary anastomosis types, amount of replaced blood during surgery, length of hospital stay, and complications/mortality were noted. Re-Tx performed within the first month after LT is defined as early Re-Tx, and Re-Tx performed one month later is defined as late Re-Tx (10).

Recipient and donor preparation (if a living donor was used), postoperative immunosuppression treatment, and long-term patient follow-up were performed according to clinical protocols (11).

This study was approved by Koç University Ethic Committee (Date: 21.06.2023, No: 2023.223.IRB1.073).

Statistical analysis

IBM SPSS 21 statistical package program was used for data evaluation (IBM SPSS Corp., Armonk, NY, USA). As the data did not follow a normal distribution, median (minimum-maximum values) and mean±standard deviation were provided. Kaplan-Meier was used for survival statistics.

RESULTS

Between July 2018 and February 2023, 236 LTs were performed at our center on 228 patients (103 children, 125 adults). Seventeen patients underwent a first Re-Tx surgery, and one patient underwent a second Re-Tx. Of these Re-Tx patients, six were female and 12 were male, and there were 12 pediatric and six adult patients.

The mean age for the pediatric patients who underwent a Re-Tx was 6.7 years (±4.8), and for adult patients it was 49.08 years (±14.32). The mean weight for pediatric patients who underwent a Re-Tx was 19.76 kg (±8.86), and for adult patients it was 70.48 kg (±11.83). The mean body mass index for pediatric patients was 17.41 kg/m² (±2.84), and for adult patients it was 22.33 kg/m² (±2.65). Re-Tx was performed urgently on 6 patients, and electively on 12 patients. All of the six patients who underwent an early urgent Re-Tx and two of the 12 patients who underwent a late Re-Tx had had their first LT at our clinic.

The patients' demographic information, initial transplant indications, and re-transplantation reasons are detailed in Table 1. Vascular thrombosis and PNF were the prominent etiologies in patients who underwent early urgent Re-Tx, while chronic rejection and secondary biliary cirrhosis were more common in patients who underwent late surgery.

The mean time between the initial transplant and Re-Tx was 8.3 days (±5.1) for early Re-Tx and 7.7 years (±5.4) for the late group. Preoperatively, all the cases of the early group and one patient of the late group were followed in the intensive care unit. The liver grafts used in Re-Tx included two whole livers from deceased donors (11%), three split left lateral segments from deceased donors (16%), one split right lobe from a deceased donor (5.5%), six living donor left lateral segments (33%), five living donor right lobes (27%), and 1 living donor left lobe (5.5%). The graft weights were a mean of 607 g (±436) with a body weight-to-graft weight ratio of 1.6% (±0.6).

Cadaveric allograft vein replacement was performed in two of the portal vein anastomoses. Hepatic artery anastomosis was performed under a microscope (Leica M530 OHX,

Table 1: The patients' demographic information, initial transplant indications, and Re-Tx reasons. The first six patients are early Re-Tx patients, the others are late Re-Tx patients

	Age (Year)	Gender (M/F)	Weight (kg)	BMI (kg/m²)	Etiology	Reason of Re-Tx
1	48	1	56	18.5	PSC	PNF
2	1.5	1	13.1	20.5	Wolcott - Rallison syndrome	PNF
3	0.5	2	10.8	19.7	Argininosuccinic acidemia	PVT
4	8.5	2	17.6	16.6	Cryptogenic cirrhosis	HAT
5	2.5	1	9.9	13.7	Alagille syndrome	PNF
6	6	2	20	15.7	Biliary atresia/HPS	PV injury/acute liver failure
1	48	1	89.5	26.2	PSC	Secondary biliary cirrhosis
2	6	2	22.5	18.9	Primary Hyperoxaluria	Sekonder Budd Chiari
3	11	1	30	17.8	Biliary atresia	Secondary biliary cirrhosis
4	6.5	2	17.4	15.8	Criggler Najar syndrome	Secondary biliary cirrhosis
5	4	1	12.9	14	Biliary atresia	Chronic rejection
6	66	1	74	24.2	Alcoholic cirrhosis	HCV
7	23.5	1	64.7	20.9	FAH	HBV
8	51	1	75.7	22.1	Wilson/Chronic rejection	Chronic rejection
9	58	1	63	22.1	HBV	Chronic rejection
10	15	2	33	14.7	Primary Hyperoxaluria	Chronic rejection
11	4	1	14	23	Primary Hyperoxaluria	Chronic rejection
12	15	1	36	18.6	PFIC	Chronic rejection

FAH: Fulminant Autoimmune Hepatitis, HAT: Hepatic Artery Thrombosis, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, HPS: Hepatopulmonary Syndrome, PFIC: Progressive familial intrahepatic cholestasis, PNF: Primary non-function, PSC: Primary Sclerosing Cholangitis, PV: Portal Vein, PVT: Portal Vein Thrombosis, M/F: Male/Female

Table 2: Detailed information about patients who underwent early and late Re-Tx is summarized.

	Early Re-tx	Late Re-tx
Age (years)	11.2 (±18.2)	25.7 (±23.3)
Weight (kg)	21.2 (±17.4)	44.4 (±27.2)
BMI (kg/m²)	19.0 (±3.6)	19.9 (±3.9)
Op. Time (minutes)	371 (±122)	516 (±116)
Blood tx (ml)	1379 (±1153)	1445 (±1139)
Re-tx type	Deceased full-sized (1) Deceased split LL (2) Live donor LL (3)	Deceased full-sized (1) Deceased split right (1) Deceased split LL (1) Live donor right (5) Live donor left (1) Live donor LL (3)
1-year survival	33.30%	75.00%
Reason of mortality	Intraabdominal sepsis (2) Postoperative brain death (1) Vascular collapse (1)	Intraabdominal sepsis (3)

BMI: Body mass index, LL: Left lateral, Op: Operation, Re-tx: Re-transplantation.

Singapore) using 7-8/0 polypropylene as continuous-interrupted techniques with 5-10x magnification. Double artery anastomosis was needed in two patients. The biliary reconstruction was completed with duct-to-duct in two adult cases and Roux-en-Y hepaticojejunostomy in other cases.

The mean operation time for all patients was 467 (±134) minutes, and the mean blood transfusion requirement was 1422 (±1102) ml/m². Detailed information on the patients is summarized in Table 2.

The one-year survival rate was 61.1%, with rates of 33.3% for early and 75% for late Re-Tx. All mortalities were seen in the early perioperative period. The reasons for the mortalities were intraabdominal sepsis in five cases, postoperative brain death in one case, and hemodynamic instability and vascular collapse in one.

As for surgical complications, spontaneous intestinal perforation was seen in three patients, diaphragmatic hernia in one, portal vein stenosis in two, and hepatic artery stenosis in one during the early postoperative period. During the late period, bile duct anastomosis stenosis was seen in two patients, PTLD in one, and osteomyelitis in another.

The average length of hospital stay for surviving patients was 31.3 days (±24.7), and the mean follow-up period was 2.5 years (±1.3).

DISCUSSION

Liver Re-Tx, which was first applied in 1981, has developed over the years and success rates have increased. As a result, the need for Re-Tx has decreased and survival rates of Re-Tx have increased. 5-year survival rates have been reported to vary between 60% and 80% (6-8). Re-Tx rate after the first LT varies between 7% and 23% according to different sources (9, 12, 13).

Re-Tx performed within the first month after LT is defined as early Re-Tx, while Re-Tx performed after one month is called late Re-Tx (10). The most common causes of early Re-Tx are primary non-function and vascular complications, whereas disease recurrence and biliary complications are the most common causes of late Re-Tx (14, 15).

Both technical and medical problems increase morbidity and mortality in Re-Tx and have a higher complication rate compared to initial LT (6). The combination of adhesions and fibrosis caused by previous operations, the length and quality of the remaining inferior vena cava, hepatic artery, portal vein and bile ducts, and portal hypertension caused by previous operations may particularly increase the rates of bleeding and complications (16, 17). However, elective surgery in late Re-Tx cases, especially those performed with a living donor, leads to more satisfactory haemodynamic and metabolic control (9).

Although early Re-Tx does not have many of the same surgical challenges, metabolic and haemodynamic problems in emergency LT may lead to complications. Therefore, although early Re-Tx has a shorter operative time, for patient-related reasons, mortality is higher than in patients who undergo early Re-Tx (9, 18, 19).

In some cases, depending on the severity of graft liver necrosis, the metabolic and haemodynamic status of the recipient may deteriorate. This is caused by cytokines and vasoactive agents released from the necrotic liver into the systemic circulation. This clinical picture, also known as "Toxic Liver Syndrome", may lead to multiorgan dysfunction (20). In such patients, graft hepatectomy may be necessary to remove the toxic liver from the body. This allows time for the patient to undergo Re-Tx. In the an-hepatic period, the patient is supported with plasma exchange and haemodiafiltration/haemodialysis and monitored in the intensive care unit (21). One of our patients required graft hepatectomy. The "an-hepatic period" lasted approximately 18 hours and the patient benefited from liver Re-Tx.

In continents where organ donation is low, such as Central Asia and the Far East, deceased donor organ restrictions affect the survival of patients requiring urgent Re-Tx. According to the data from the Turkish Ministry of Health, the organ donation/brain death rate in 2022 is around 16.8% (22). Due to insufficient organ donations, living donor LT becomes mandatory, especially in cases requiring urgent Re-Tx. The willingness of family members to donate organs for a second living donation, finding a suitable donor and preparing the donor may cause significant time loss. In cases of acute liver failure with severe haemodynamic and metabolic problems, lost hours increase patient mortality.

In our clinical experience, when emergency Re-Tx is planned with a living donor, the time required to complete the investigations is 4 hours, but the actual time loss depends on the decision of the family and the voluntary donation of the living organ. In two cases in which emergency surgery was required from living donors, one case resulted in postoperative brain death due to delayed preparations, and the other case resulted in early postoperative death due to haemodynamic instability and metabolic problems.

One of the most important disadvantages of this study is its retrospective and single-center design. Also, the sample size of the study is too small to allow a statistical comparison. Nevertheless, the results of the study provide valuable information for liver Re-Tx.

CONCLUSION

Re-Tx has a higher mortality and complication rate compared to initial LT especially in emergency Re-Tx cases.

The scarcity of organ donations and the need for living donors cause loss of time and seem to be the most important mortality factors. In late Re-Tx cases, despite surgical technical difficulties, metabolic and haemodynamic stabilization of the patient and planning the operation under elective conditions result in positive outcomes. Re-Tx with a living donor is advantageous due to appropriate timing and patient preparation.

Ethics Committee Approval: This study was approved by Koç University Ethic Committee (Date: 21.06.2023, No: 2023.223. IRB1.073).

Informed Consent: This is a retrospective archive study that does not include live animals or humans. Therefor informed consent was not sought.

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ENHANCING SURGICAL OUTCOMES IN BRONCHIECTASIS: PREDICTING EARLY SURGICAL COMPLICATIONS WITH THE BRONCHIECTASIS SEVERITY INDEX

BRONŞİEKTAZİ TEDAVİSİNDE CERRAHİNİN YERİ: BRONŞİEKTAZİ ŞİDDET İNDEKSİ İLE ERKEN CERRAHİ KOMPLİKASYONLARIN ÖNGÖRÜLMESİ

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ABSTRACT

Objective: Bronchiectasis is defined as the irreversible dilation of the large and smaller airways. This study is a retrospective data analysis of patients with localized bronchiectasis who underwent anatomical resection at our institution. The aim of the study was to detect quality of life improvements after lung resection in localized bronchiectasis patients.

Material and Method: 68 patients were evaluated between the years 2001 and 2019. Patient demographics, pathological data, preoperative period, Bronchiectasis Severity Index (BSI) score, and long-term outcomes were reviewed. We selected patients who had undergone anatomical resection. Cases of unrelated deaths or of lost data during the follow-up period were excluded.

Result: The median age was 26, and the female and male ratio was nearly even. Pediatric patients are defined as individuals under the age of 17 and 26 patients were in the pediatric group. The preoperative BSI score was calculated on each patient. Seven patients had expected high readmission rates and high mortality rates, according to their high BSI score, but after the surgery period none of those patients needed to be re-hospitalized due to bronchiectasis. 14 patients had VATS procedures and 54 patients were operated on via thoracotomy. The average postoperative hospital stay was 13 days for all patient groups. Patients who had had VATS stayed in the hospital for eight days, but those who had had open surgery remained for 14 days (p=0.167). Based on the subgroup analysis, it was observed that

ÖZET

Amaç: Bronşiektazi, büyük ve küçük hava yollarının geri dönüşümsüz olarak genişlemesi olarak tanımlanır. Bu çalışmada, anatomik rezeksiyon uygulanmış lokalize bronşiektazi tanılı hastaların retrospektif veri analizi yapılmıştır. Çalışmanın amacı, lokalize bronşiektazi hastalarında akciğer rezeksiyonu sonrası yaşam kalitesindeki iyileşmeyi belirlemektir.

Gereç ve Yöntem: 2001 ile 2019 yılları arasında 68 cerrahi hastanın değerlendirmesi yapılmıştır. Hastaların demografik verileri, preoperatif dönem Bronşiektazi şiddet indeksi (BŞİ) skoru hesaplanmış, postoperatif erken dönem sonuçlar ve uzun dönem cerrahi sonuçlar incelenmiştir. Bronşiektazi nedeniyle anatomik rezeksiyon geçiren hastalar çalışmaya dahil edilmiştir. Bronşiektazi dışında sebeplerle ölen hastalar ve takip süresinde verilerine ulaşılamayan hastalar çalışma dışı bırakılmıştır.

Bulgular: Ortalama yaş 26 olup, kadın ve erkek oranı arasında anlamlı fark izlenmedi. Pediatrik yaş grubu 17 yaş altı hastalar olarak kabul edildi ve 26 hasta bu grupta değerlendirildi. Pediatrik grup 26 hastadan oluşmaktaydı. Her bir hasta için preoperatif BŞİ skoru hesaplandı. Yüksek oranda tekrar hastaneye yatış ve yüksek mortalite oranları beklenen yedi hastada, yüksek BŞİ skoruna rağmen ameliyat sonrası dönemde bu hastaların hiçbirinin bronşiektazi nedeniyle yeniden hastaneye yatışa ihtiyaç duymadığı görüldü. 14 hasta video yardımlı torakostopik cerrahi ile ve 54 hasta torakotomi ile opere edildi. Tüm hasta grubunda ortalama ameliyat sonrası hastanede kalış süresi 13 gün olup, VATS işlemi uygulanan hastalarda bu süre sekiz gün, açık cerrahi uygu-

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patients with a severity score of nine or higher experienced increased complication rates (p=0.35).

Conclusion: Even for patients with a high BSI score, surgery is a reliable option if clinical parameters are compatible. BSI shows the predictive value of postoperative complications. Patients should be evaluated in multidisiplinary centers. In making surgical decisions, experienced pulmonologists and thoracic surgeons are needed so that the best time for surgery is decided upon.

Keywords: Bronchiectasis, thoracic surgery, VATS, Bronchiectasis severity index score

lanan hastalarda ise ortalama 14 gün olarak bulundu (p:0,167). Alt grup analizine göre, BŞİ skoru dokuz veya daha yüksek olan hastalarda postoperative erken komplikasyon oranlarının arttığı gözlemlendi (p:0,35).

Sonuç: Yüksek BŞİ skoruna sahip hastalarda bile, klinik parametreler uygunsa cerrahi güvenilir bir seçenektir. Bronşiektazi şiddet indeksi, ameliyat sonrası komplikasyonların tahmin edilmesinde öngörü değerine sahiptir. Hastalar multidisipliner merkezlerde değerlendirilmelidir. Cerrahi karar verme sürecinde deneyimli göğüs hastalıkları hekimleri ve göğüs cerrahlarına ihtiyaç vardır.

Anahtar Kelimeler: Bronşektazi, göğüs cerrahisi, VATS, Bronşiektazi şiddet indeks skoru

INTRODUCTION

Bronchiectasis is a chronic lung disease characterized by recurrent airway infections and inflammation, resulting in irreversible structural damage to the small airways and often affecting the surrounding lung parenchyma. In 1819, Theophile Hyacinte Laennec provided the first clinicopathological description of bronchiectasis based on the case of a 72-year-old woman who died after experiencing chronic recurrent productive cough and hemoptysis (1). Autopsy findings revealed the presence of saccular bronchiectasis in the pulmonary parenchyma (2).

Advancements in non-invasive diagnostic methods have facilitated the identification of bronchiectasis in patients with asymptomatic clinical progression. Computed tomography (CT) features of bronchiectasis include bronchial dilatation, with a bronchioarterial ratio greater than 1 (presumably comparing the internal airway lumen to the adjacent pulmonary artery). Other indirect CT signs of bronchiectasis involve bronchial wall thickening, mucus impaction, and a mosaic perfusion pattern in the lung parenchyma (2). However, surgical intervention is typically recommended for patients who exhibit clinical symptoms (3).

Regarding recurrent pulmonary infections in the progress of bronchiectasis, developing countries remain at high risk. Despite this fact, children in developed countries with cystic fibrosis remain at high risk (4-8). The most commonly known pathologies are idiopathic, post-recurrent infection, immunodeficiency, chronic obstructive pulmonary disease, connective tissue disease, allergic bronchopulmonary aspergillosis, primary ciliary dyskinesia, asthma, non-TBC mycobacteria (9). The number of new patients currently under any stage of treatment is not definite. The patient count has risen over the last few years according to global statistics. Bronchiectasis can exist in any individual group. However, it generally occurs in childhood during the pre-antibiotic period (10). Recent evidence shows that bronchiectasis disproportionately affects women and older individuals and may be contributing to an increasing healthcare burden. Age-standardized incidence has declined from 13.9 per 100,000 persons in 2007 to 10.6 per 100,000 persons in 2017 (an average decline of 2.7% per year). This decline was steeper among men (15.6 per 100,000 in 2007 to 9.9 per 100,000 in 2017, an average decline of 4.4% per year) than women (12.4 per 100,000 in 2007 to 11.2 per 100,000 in 2017, an average decline of 1.0% per year), and the age-standardized incidence rate of bronchiectasis in women was slightly higher than that of men in 2017 (11).

The presence of sputum production alone or isolation of a pathogen without clinical signs of active infection is not always an indication for antibiotic treatment. The absence of clinical signs and symptoms, production of sputum, and isolation of pathogen microorganisms is not always an indication of antibiotic treatment. In cases of high fever, shortness of breath, or clinical deterioration, empiric antibiotic treatment should be started and continued for at least 14 days, after sending the sputum culture of optimal antibiotics. Antibiotics are used when the clinical picture deteriorates as demonstrated by an increased cough or sputum production, high fever, shortness of breath, and hemoptysis. Treatment should be started empirically (immediately after the sputum sample is sent for microbiological analysis) based on the previous isolation and continue for 14 days. Due to recommendations and rising antibiotic resistance, we do not advise starting 'routine' antibiotherapy (12).

The most commonly accepted surgical indication for surgery is resistance to medical treatment. Surgical resection must be considered after running out of all conservative treatment options, but in some cases like periodic or massive hemoptysis, proceeding to surgical resection can be a more suitable option. For patients in high-risk groups, intensive hospital care and bronchial artery embolization should be considered (13). Surgical treatment may be considered for certain patients with bilateral localized bronchiectasis. All types of pulmonary resections can be conducted on patients with the right types of clinical progress. The most commonly seen area is the left lower lobe (14). The modern era of thoracic surgery dictates video-assisted thoracic surgery (VATS) on most

patients with suitable surgical conditions. In this study, there are patients who underwent a VATS procedure (15).

This article evaluates the clinical severity of surgery-candidate patients with bronchiectasis using the Bronchiectasis Severity Index (BSI). It also examines early complication rates and long-term outcomes in surgically treated patients.

MATERIALS and METHODS

In this article, we selected 68 patients who were operated on at the Department of Thoracic Surgery, Istanbul University, School of Medicine, from 2001 to 2019 to determine clinical changes in a follow-up period of at least two years. The study was approved by the Local Human Ethics Committee (Date: 14.04.2023, No: 8). All patients underwent preoperatively a series of clinical and radiological tests. Complete medical background, presence of cystic fibrosis, family history, incidence of pulmonary infections and antibiotic usage per year collected from all patients. Dynamic respiratory function tests were performed for all patients, and in selected patients, quantitative perfusion tests were done to predict the results of surgery. We performed high resolution computerized tomography on each patient. Bronchoscopy was performed on each patient by pulmonology specialists. The multifactorial bronchiectasis severity index was calculated preoperatively to determine the average severity of planned surgery patients: the Bronchiectasis Severity Index (BSI).

The BSI corresponds to a scale that evaluates the severity and prognosis of NCFB by analyzing nine parameters/variables: age, body mass index (BMI), FEV1% predicted, hospitalization and exacerbations before the study, degree of dyspnea, chronic colonization by P. aeruginosa and other microorganisms and radiological extension of the disease. The BSI score is shown in Table 1. Clinical parameters were calculated according to the BSI scoring system, and one to four-year mortality and hospitalization rates are shown on Table 2.

Before surgery, all patients had strict pulmonary exercise periods. Antibiotherapy were used according to the "British Thoracic Society Bronchiectasis (non-CF) Guideline Group, British Thoracic Society guideline for non-CF bronchiectasis" (11).

Table 1: Bronchiectasis Severity Index (BSI)

Bronchiectasis Severity Index Parameter	Score	Description
Age (years)	0	<50
	2	50-69
	4	70-79
	6	≥80
Body Mass Index (kg/m^2)	2	Less than 18.5
	0	18.5-25
	0	26-29
	0	≥30
FEV1 (%)	0	>80
	1	50-80
	2	30-49
	3	<30
History of previous hospital admission	0	None
	5	Present
Exacerbations before study (times)	0	0
	0	1-2
	2	≥3
mMRC dyspnea score	0	1-3
	2	4
	3	5
Pseudomonas colonization	0	Absent
	3	Present
Colonization with other microorganisms	0	Absent
	1	Present
Radiological severity (bronchiectasis present on lobes)	0	<3 lobes
	1	≥3 lobes

FEV1: Forced expiratory volume in 1 second, mMRC: Modified Medical Research Council

Table 2: Severity of bronchectasis (BSI score) and one year outcomes

Mild (0-4)	
0-4 Mild Bronchiectasis	0-2.8
Moderate (5-8)	0.8-4.8
Severe (≥9)	7.6-10.5

BSI: Bronchiectasis severity index

The surgical technique differs from patient to patient. However, if available we prefer the VATS technique. In the VATS patient group, we prefer uniportal and bi-portal surgery if viable. Segmentectomy, lobectomy, and pneumonectomy were performed in all cases because of the selection nature of anatomically limited disease. Early mortality, morbidity, and late mortality were noted. Patients with lost data in the follow-up period, those who had an unrelated cause of death, and patients with a secondary unrelated, medically deteriorating disease were excluded as well as patients with cystic fibrosis due to the nature of disseminated lung involvement. We also excluded patients with detected pulmonary foreign bodies. During the preoperative period, both rapid invasive and non-invasive sputum collection methods revealed no evidence of pathogenic bacterial growth. Cardiovascular anesthesiology specialists evaluated all patients preoperatively for clinical status and general anesthesia risks. Left-side selective intubation was applied to all patients for selective lung ventilation and to prevent aspiration on the non-diseased side.

Statistical analysis

Statistical analysis was conducted using IBM SPSS version 26.0 for Windows (IBM Corp., Armonk NY, USA). Descriptive data were presented as median ± standard deviation (SD), median (min.–max.), number, and frequency. The distribution of variables and their adherence to a normal distribution were assessed using the Kolmogorov-Smirnov test. Group comparisons were performed using Student's t-test. Pearson correlation analysis was employed to evaluate the relationship between variables. Receiver operating characteristic (ROC) analysis was employed to determine the optimal cut-off values. A significance level of $p<0.05$ was used to determine statistical significance. Sensitivity and specificity analyses were performed for the platelet-to-lymphocyte ratio (PLR) using three different cut-off values, aiming to identify the values that maximize specificity and sensitivity. The primary focus of the survival analysis was overall survival (OS), defined as the time interval from the date of initial surgery to the date of death. IBM SPSS version 21 was used for the statistical analyses. Group relationships based on categorical variables were assessed using the $\chi 2$ test. The Kaplan-Meier method was employed to compute the OS of the groups. Cox regression analysis was used to analyze the impact of factors on OS and calculate the hazard ratio with a 95% confidence interval.

RESULTS

The age range was 5-63 with a median age of 26 (±15.62) years. A total of 68 patients were evaluated and classified by declaration; 37 were male and 31 were female. Body mass index values were 21 (±5.05) with a minimum of 13 and a maximum of 32.3. The patients were divided into two groups, adults (n=42) and children (n=26). The lower FEV1 ratio observed in the pediatric group compared to the adult group might suggest a potential greater impact of bronchiectasis on the pediatric group. However, it is important to note that this difference did not indicate a statistical significance. Among all the patients, 8 (11.8%) patients had shortness of breath, but according to the mMRC scoring system, none of the patients reached more than 3 points on the dyspnea score. 21 patients (30.9%) demonstrated sputum presence but, according to the surgical selection criteria, none of the patients had more than 50 ml of sputum daily. Eleven patients (16.2%) had no history of antibiotic usage due to lower airway infections, and 15 patients (22%) had a non-anti-tuberculosis type of antibiotherapeutics. 37 patients had a history of antibiotic usage due to lower airway infections and 37 patients (54%) had a hospitalization history due to lower lobe infections. Even though all patients were negative for acid-resistant staining on sputum, 5 (7.4%) had a history of anti-TB antibiotics. No pathogenic microorganisms, including Pseudomonas, were detected in the multiple sputum cultures conducted before the operation. 19 patients (27.9%) had a history of minor hemoptysis, and no patient had a history of massive hemoptysis.

According to BSI, 29 patients (42.6%) got 0 to 4 points, which showed mild bronchiectasis, 32 patients (47.1%) got BSI score 5 to 9 points, showing moderate bronchiectasis and seven patients (10.3%) had 10 plus points which was described as severe bronchiectasis. Four patients (5.9%) underwent embolization due to recurrent hemoptysis. Fourteen patients (20.6%) had a VATS procedure and 54 (79.4%) were operated on via thoracotomy. Resection types and ratios are shown in (Table 3). Three patients underwent thoracomyoplasty due to lung expansion insufficiency and one patient needed plication due to complications related to diaphragmatic paralysis. All these surgical interventions were performed in the early postoperative period.

The mean postoperative hospital stay was 13 (±11) days for all patient groups. VATS patients spent 8 days in the hospital, and open surgery patients were there for 14.89 days (p:0.167). Patients with higher BSI score had a longer hospital stay. The median hospital stay for higher and lower scored patients was 22.7/12.4 (p:0.002). No patients experienced mortality within 30 days after surgery. Out of the 24 patients, 22 developed intrathoracic complications, while two patients developed postoperative atrial

Table 3: Distribution of the study group according to the resection type

Resection type	n	%
	Left sided resections	
Left upper lobectomy	4	5.9
Left lower lobectomy	25	36.8
Lingulectomy	8	11.8
Left common basal segmentectomy	4	5.9
Left pneumonectomy	4	5.9
Left trisegmentectomy	1	1.5
	Right sided resections	
Right upper lobectomy	3	4.4
Right lower lobectomy	11	16.2
Right middle lobectomy	7	10.3
Right pneumonectomy	1	1.5
Total	68	

Table 4: Major intrathoracic and extrathoracic complications

Complications	n	%
Acute miyocardial infarction	2	2.9
Empyema	4	5.9
Prolonged air leak	4	5.9
Pleural effusion	1	1.5
Pneumonia	9	13.2
Wound infection	4	5.9
Total	24	

fibrillation, which was effectively managed with medical intervention within the first 48 hours. No significant differences were found between the gender groups on complications (p=0.47). Major intrathoracic and extrathoracic complications are listed on table (Table 4). The most common postoperative complications were pneumonia (5.9%), local wound infection (5.9%), and prolonged air leak (5.9%). No patient reported late-period readmission and surgery-requiring complications. The median follow-up period was 147 months (Least follow up period mentioned). According to subgroup analysis, if the severity score is nine or higher, patients are faced with higher complication rates (p=0.035). No disease-related mortality occurred during the follow-up period. Seven (10.3%) patients had severe bronchiectasis during the preoperative clinical approach according to BSI, but after surgery, none of those patients were reported as having mortality or re-hospitalization due to bronchiectasis.

DISCUSSION

In our study, there were no differences in the overall follow–up period, VATS/open surgery ratios, and median hospital stay days. Male gender tended to be slightly younger although this age difference did not reach statistical significance. According to the WHO, average BMI values are 27.8 kg/m² for both gender but in our study, they were 21 (±5.05) kg/m². This may be due to recurrent infectious periods of the patient's lifespan. The BSI score is an accepted scoring system for clinical severity. The scoring system anticipated that patients with more than 9 points (indicating severe bronchiectasis) would have hospitalization rates of up to 52.6% within one year. However, in our study, no readmissions were observed within the one-year period. Nonetheless, in our study, we found that a higher BSI score was associated with increased early postoperative complications and a longer hospital stay. Differences between adult and pediatric patients on FEV1 ratios were not statistically significant but the overall adult population had higher rates of FEV1 ratios.

Despite pediatric-term lung infections becoming less and less common, bronchiectasis incidence is expected to rise due to improvements in chest imaging and diagnostic testing, plus improvements in thoracic surgical methods leading to more minimally- invasive surgery. Likewise we prefer the VATS technique for all viable patients. However in some cases, considering the general anesthesia period, extensive adhesions, and VATS complications, open surgery is still a reliable and considerable model.

In our study, median hospital stays for VATS and thoracotomy procedures were statistically not significant, but

overall they were longer than other studies in the literature Alban et al. reported that the main hospital stays for both groups were four to five days. This may be attributed to the fact that bronchiectasis patients experienced more prolonged early postoperative complications (17).

Accordingly to previous studies, we recommend that bronchiectasis patients being considered for surgery should undergo examination and be assessed by experienced thoracic surgeons and chest disease specialists (18,19). In the British Thoracic Surgery Guideline for Bronchiectasis, surgical treatment is described as lacking high-quality randomized control studies, and the advantages of surgery over conservative management remain unclear. Additionally, there is a reporting bias evident in the available case series.

CONCLUSION

In this research, our objective was to assess postoperative complications in bronchiectasis surgery using the BSI scoring system, which delineates clinical severity. Surgical intervention and patient evaluation are anticipated to yield optimal surgical outcomes.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 14.04.2023, No: 8).

Informed Consent: Written informed consent was obtained.

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THE MANAGEMENT STRATEGIES IN THE PLACENTA ACCRETA SPECTRUM IN TERTIARY CENTERS IN TÜRKİYE

TÜRKİYE'DEKİ ÜÇÜNCÜL MERKEZLERDE PLASENTA AKRETA SPEKTRUMUNUN YÖNETİM STRATEJİLERİ

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ABSTRACT

Objective: To determine the differences and consensus points in managing patients with placenta accreta spectrum (PAS) disorder in a nationwide survey.

Material and Method: Forty-seven items were asked via an online survey. Seventy-seven percent responded to the survey (37/48). Consensus/strong consensus was predefined as 75%–89% (28–33/37)/>90% (≥34/37) of panelists agreeing on an answer.

Result: In a few areas, consensus or strong consensus was achieved. These are the absence of interventional radiology (89.2%) and cell-saver in the institution (94.6%), a rare selection of magnetic resonance (83.8%), and frequent use of transvaginal sonography (94.6%) as an adjuvant diagnostic tool. Penetrative sexual intercourse is prohibited (78.4%); perineal shaving (81.1%) and rectal enema (94.6%) are not used; general anesthesia (75.7%) is the preferred technique; hypothermia control (97.3%) is not omitted; and administration of oxytocin (75.7%) is similar to routine cesarean section; vascular injuries are managed by vascular surgeons (78.4%); gynecologic oncologists are not a regular part of the surgical team (86.5%); routine insertion of a central venous cannula (78.4%) is not considered and placement of an abdominal drain (89.2%) is usually performed. Surgery is often performed through a median abdominal incision (83.8%), and a total hysterectomy (81.1%) is chosen. Routine hypogastric artery ligation (91.9%) is not performed. In the postoperative period, the patients are allowed to have early mobilization (91.9%) and oral intake (83.8%). They are habitually discharged on the 3rd-4th postoperative day (75.7%). Psychiatric needs are often neglected (94.6%).

Conclusion: These consensus points could help obstetricians manage this complicated condition. These results also demon-

ÖZET

Amaç: Plasenta akreta spektrumunun (PAS) yönetimindeki ortak ve farklı yaklaşımların ulusal çapta bir anket çalışmasıyla belirlenmesi.

Gereç ve Yöntem: Çevrim içi bir anket ile 47 soru yöneltildi. Katılımcıların %77'si ankete cevap verdi (37/48). Katılımcıların cevaplarında uyum için %75-89 (28–33/37), kuvvetli uyum için ≥ %90 (≥34/37) fikir birliği arandı.

Bulgular: Az sayıda konuda uyum ve kuvvetli uyum sağlanabildi. Bunlar girişimsel radyoloji imkânı olmaması (%89,2), hücre kurtarıcı olmaması (%94,6), manyetik rezonansın nadiren kullanılması (%83,8), yardımcı görüntüleme yöntemi olarak sıklıkla transvajinal sonografi (%94,6) kullanılmasıdır. Penetran cinsel ilişkinin yasaklanması (%78,4), perine traşı (%81,1) ve lavman kullanılmaması (%94,6), genel anestezi kullanılması (%75,7), hipotermi kontrolünün ihmal edilmemesi (%97,3), oksitosinin sezaryende kullanılan dozda uygulanması (%75,7), damar yaralanmalarında damar cerrahisinden yardım alınması (%78,4), jinekolojik onkoloji uzmanlarının ameliyatlara rutin olarak çağrılmaması (%86,5), santral venöz kateterin rutin olarak rutin olarak takılmaması (%78,4) ve ameliyat bitiminde genellikle dren konulması (%89,2) ise diğer noktalardır. Katılımcılar arasında insizyon tercihi genellikle orta hat kesidir (%83,8) ve ameliyat şekli total histerektomidir (%81,1). Ameliyat sonrası dönemde hastaların hareket etmesi (%91,9) ve beslenmesi (%83,8) kısıtlanmamaktadır. Genellikle ameliyat sonrası 3.-4. günlerde taburcu edilmelerine (%75,7) karar verilmektedir. Psikiyatrik ihtiyaçları genellikle ihmal edilmektedir (%94,6).

Sonuç: Görüş birliği elde edilen noktalar bu karmaşık sorunun yönetiminde doğum hekimlerine yardımcı olabilir. Bu sonuçlar

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strate the need for evidence-based data for implementing proper treatment strategies for PAS disorder. Future research is sought for these points.

Keywords: Perinatology, placenta accreta, postpartum hemorrhage, surveys and questionnaires

aynı zamanda PAS'ın doğru yönetimi için kanıta dayalı bilgi açığını ortaya koymaktadır. Bu konular için gelecekte yapılacak çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Perinatoloji, plasenta akreta, postpartum kanama, anket

INTRODUCTION

The placenta accreta spectrum (PAS) disorder is an iatrogenic disease and an essential risk factor for maternal health. Currently, the incidence of the disease is reported as 3 in 1000, and the mortality may be as high as 6-7% (1). As the denominator of maternal mortality is 100,000, the estimated number of maternal deaths due to PAS disorder may be as high as 18 in 100,000 deliveries. The morbidity and mortality could be lowered significantly by antenatal diagnosis and proper management (2). The "centers of excellence" briefly define the hospitals where the multi-disciplinary, experienced clinical staff and supporting facilities are present. The management of these cases in the centers of excellence is praised, but the minimum requirements for defining these centers and the level of clinical expertise are unclear. The clinical practice in managing PAS disorder varies significantly in these centers, and few evidence-based data exist. The combination of the differences between the institutions regarding facility and staff with the heterogeneous nature of the disease makes it difficult to dispel these gaps. Surveys are candidates for creating at least experience-based data in such situations. We analyzed the literature and found recent surveys from high-income countries. We aimed to evaluate the trends in managing PAS disorder in a developing country where the cesarean rate is more than 50%.

MATERIAL and METHODS

We conducted a nationwide survey among 48 experts in complicated obstetric surgery from 26 cities in Türkiye. A questionnaire was prepared using the Google Forms tool. The survey was available for one month in August of 2022. During this interval, three remainder surveys were sent to candidate participants. The candidates were senior obstetricians or consultants suggested by senior physicians in tertiary hospitals. In addition, the participants have published papers in international or national journals or have presented their experiences at international or national scientific meetings. The participants received an e-mail with a link to the survey, and the authors contacted them personally to invite them to fill it out. The Ethics Committee of Çukurova University approved the study protocol (Date: 30.06.2022; No: 48).

The topics selected in the survey are determined from the points in which the heterogeneity is apparent and evidence-based data is hard to find. The survey contains five chapters: department and surgeon description, diagnosis of PAS, preparation for surgery, intraoperative management of PAS, and postoperative care. In sum, participants were asked 47 questions. Less than 75% accepted as no consensus, 75-89% (28-33/37) taken as consensus, and >90% (≥34/37) accepted as strong consensus.

RESULTS

We identified 34 units from 26 cities. The population of these cities is 53.3 million, constituting 63.5% of the country's population. The survey was sent to 48 experts, and 37 responded (77%). Survey data were collected using Google Forms. The demographic characteristics of survey participants and the different management approaches reported by participants are presented as numbers and percentages in Table 1. In addition, the consensus points are depicted in an iconography shown in Figure 1.

DISCUSSION

Proper management of PAS disorder compromises antenatal diagnosis, anti-anemic support before the surgery, coordination and collaboration of experienced partners, and adequate facilities in the hospital. By performing this nationwide questionnaire, we aimed to demonstrate the consensus points in order to find a standardized way. The survey participants were experts from hospitals with a high number of operations in high-population cities. While the number of towns is 26 out of 81 provinces, the population of these cities represents 63% of the entire country.

In our survey population, most of the participants practiced for more than ten years and practiced PAS surgery for more than five years. More than 90% of the participating institutions had more than 10 PAS surgeries annually. Although the strong recommendation is consistently stated in recent publications, regular conversation before surgery with other departments is performed by nearly half of our participants. Support for interventional radiology is not sought by international organizations and is absent in most institutions. While the predetermined transfusion policy ratio did not reach a consensus level, nearly 65% preferred a combination of fresh frozen plasma and thrombocyte with erythrocyte in a ratio 1:1:1. Early restoration of the coagulation system is defined as "*damage control*

Table 1: Management practices for PAS disorders among the participants (n=37)

Description of the hospital and the physician	
Questions	**n (%)**
Years in practice	
<10 years	4 (10.8)
<10 years	33 (89.2)
Years in PAS surgery	
<5 years	8 (21.6)
<5 years	29 (78.4)
Number of PAS surgeries per year in the institution	
<10	3 (8.1)
<10	34 (91.9)
Presence of other institutions occupying PAS surgery in the city	
Yes	23 (62.1)
No	14 (37.8)
Presence of a predetermined transfusion policy in the institution	
1 ES/1 FFP/1 TS	24 (64.9)
1 ES/2 FFP/4 TS	2 (5.4)
Other	6 (16.2)
Not predetermined	5 (13.5)
Preoperative meeting with blood bank staff	
Yes	16 (43.2)
No	21 (56.8)
Preoperative meeting with anesthesiology staff	
Yes	18 (48.6)
No	19 (51.4)
Preoperative meeting with neonatology staff	
Yes	16 (43.2)
No	21 (56.8)
Preoperative meeting with operating room staff	
Yes	23 (62.1)
No	14 (37.8)
Presence of interventional radiology in the institution	
Yes	4 (10.8)
No	33 (89.2)
Presence of cell saver in the institution	
Yes	2 (5.4)
No	35 (94.6)
Prenatal diagnosis	
Questions	**n (%)**
The role of MRI	
Never	26 (70.3)
Rarely selected	5 (13.5)
Frequently	6 (16.2)
The role of transvaginal ultrasound	
Never	2 (5.4)
Rarely selected	7 (18.9)
Frequently	28 (75.7)
Operation time (weeks)	
34	4 (10.8)
34-35	9 (24.3)
35	4 (10.8)
35-36	3 (8.1)
36	8 (21.6)
36-37	3 (8.1)
37	5 (13.5)
<37	1 (2.7)

Table 1: Continue

Preoperative	
Questions	**n (%)**
Preoperative hospital stay	
1 day before	14 (37.8)
Within 7 days	9 (24.3)
<7 days	10 (27)
Not standardized	4 (10.8)
Routine corticosteroid use <34 weeks	
Yes	17 (45.9)
No	20 (54.1)
Strategy for preventing anemia	
Oral iron	12 (32.5)
IV iron	10 (27.0)
Oral + IV iron	14 (37.8)
Erythropoietin	1 (2.7)
Tubal ligation is an option in your institution	
Yes	34 (91.9)
No	3 (8.1)
Routine intestinal cleaning	
Yes	2 (5.4)
No	35 (94.6)
Routine perineal shaving	
Yes	7 (18.9)
No	30 (81.1)
Prohibition of penetrating sexual intercourse during pregnancy	
Yes	29 (78.4)
No	8 (21.6)
Intraoperative	
Questions	**n (%)**
Anesthesia	
General	28 (75.7)
Regional	9 (24.3)
Routine cystoscopy and ureteral stents	
Yes	2 (5.4)
No	35 (94.6)
Repair of non-complicated urinary injuries	
Obstetrician	24 (64.9)
Urologist	13 (35.1)
Repair of injury of great vessels	
Obstetrician	8 (21.6)
Vascular surgeon	29 (78.4)
Routine admission of gynecological oncologist	
Yes	5 (13.5)
No	32 (86.5)
Routine arterial cannulation	
Yes	20 (54.1)
No	17 (45.9)
Routine central venous cannulation	
Yes	8 (21.6)
No	29 (78.4)
Patient position during surgery	
Supine	17 (45.9)
Dorso-lithotomy	20 (54.1)

Table 1: Continue

Intraoperative	
Questions	**n (%)**
Abdominal incision	
Low abdominal transverse	6 (16.2)
Median	31 (83.8)
Bladder insufflation before dissection	
Yes	17 (45.9)
No	20 (54.1)
Tool for hemostasis during bladder dissection	
Suture	14 (37.8)
Electrocautery	13 (35.1)
Vessel sealing systems	10 (27)
Uterine incision	
Low transverse	4 (10.8)
High transverse	10 (27)
Classical	23 (62.2)
Principal surgical approach	
Cesarean hysterectomy	21 (56.8)
Placenta left in situ	1 (2.7)
Segmental resection	10 (27)
Pelvic devascularization and tamponade after placental removal	5 (13.5)
Type of hysterectomy	
Subtotal	7 (18.9)
Total	30 (81.1)
Routine hypogastric artery ligation	
Yes	3 (8.1)
No	34 (91.9)
Routine antibiotic prophylaxis	
<24 hours	23 (62.2)
<24 hours	14 (37.8)
Oxytocin policy	
As is in routine cesarean	28 (75.7)
Higher than routine	5 (13.5)
No uterotonic	4 (10.8)
Intraoperative blood analysis	
Blood gas	24 (64.9)
Blood count	8 (21.6)
Thromboelastography 1	(2.7)
None	4 (10.8)
Body heat stabilization	
Pre-anesthetic heating	5 (13.5)
Passive isolation	15 (40.5)
Active heating	10 (27)
Heating of fluids	6 (16.2)
None	1 (2.7)
Routine drain placement	
Yes	33 (89.2)
None	4 (10.8)
Late cord clamping or milking	
Yes	20 (54.1)
No	17 (45.9)

Table 1: Continue

Postoperative	
Questions	**n (%)**
Prophylaxis for venous thromboembolism	
Anti-embolism socks	1 (2.7)
Early mobilization	6 (16.2)
Anti-embolism socks + early mobilization	2 (5.4)
Early mobilization + low-molecular-weight heparin	7 (18.9)
Anti-embolism socks + low-molecular-weight heparin	4 (10.8)
All	17 (45.9)
Time of mobilization	
≤24 hours	34 (91.9)
<24 hours	3 (8.1)
Time of oral intake	
≤24 hours	31 (83.8)
Following normal bowel function	6 (16.2)
Time for discharge	
48 hours	3 (8.1)
72-96 hours	28 (75.7)
<96 hours	6 (16.2)
Routine evaluation for need of psychiatric support	
Yes	2 (5.4)
No	35 (94.6)

PAS: Placenta accreta spectrum, ES: erythrocyte suspension, FFP: fresh frozen plasma, TS: thrombocyte suspension, MRI: Magnetic resonance imaging, IV: Intravenous

resuscitation." It is recommended in massive transfusion to treat hypovolemia, tissue oxygenation, dilutional coagulopathy, and decreasing the crystalloid requirement (3). There is no consensus in the literature on the composition of blood products. Holcomb et al. compared the 1:1:1 to 1:1:2 in severely injured people. They found no difference in mortality in 24 hours and 30 days (3). Cell-saver technology is not present in the great majority of institutions. New filtering technologies reduce the risk of the transmission of fetal blood and debris in maternal circulation. Liu et al. compared cell salvage and allogeneic blood transfusion in obstetric patients. Nearly 65% had PAS disorder and blood loss of more than 3000mL. They found less allogeneic transfusion, infection, hospital stay, and hypoproteinaemia in the cell salvage group (4).

Transabdominal ultrasonography markers of PAS disorder are well-defined and useful. However, some practitioners need adjuvant imaging modalities to diagnose or determine the prognosis. Faralli et al. found that careful and standardized use of ultrasonography is superior to magnetic resonance imaging (MRI) (5). Similarly, other reports often found the routine MRI unnecessary (6, 7). However, many surveys collecting expert attitudes use MRI as an adjunct tool (8-10). The participants in our study agreed on using transvaginal ultrasound and not MRI. It may be attributed to limited sources.

The gestational age at delivery has two sides: prematurity and risk of emergency surgery. Prematurity is a leading cause of perinatal mortality and morbidity. However, surgery under emergency conditions brings additional risks. The perinatal mortality and morbidity are apparent before the 34th week. Our study participants have no agreement on delivery time, but none offered elective surgery before the 34th week of gestation. The *American College of Obstetricians and Gynecologists* consensus report strongly recommends (grade of recommendation 1A) to schedule the delivery in PAS disorder between 34–36 weeks of pregnancy (6). An evidence-based report proposes to create a risk-based grouping. In the absence of bleeding, rupture of membranes, or regular uterine contractions, postponing the delivery until 36 weeks is recommended (grade of recommendation D) (1). Other expert surveys are aligned to perform scheduled surgery at the 34th week of gestation or later (7, 9-12).

Another option for preventing prematurity and decreasing the risk of urgent surgery is early admission to the hospital. This may increase nosocomial infections, hospital charges, and anxiety but not ameliorate maternal and perinatal outcomes. There is no evidence nor consensus seeking the benefits of early admission in asymptomatic women. Even in placenta previa, ambulatory management is acceptable (1). One-third of our survey group believe that entry one day before would be sufficient. Others propose hospitalization of less than one week or more than a week. This diversity may be attributed to the variations in transportation availabilities.

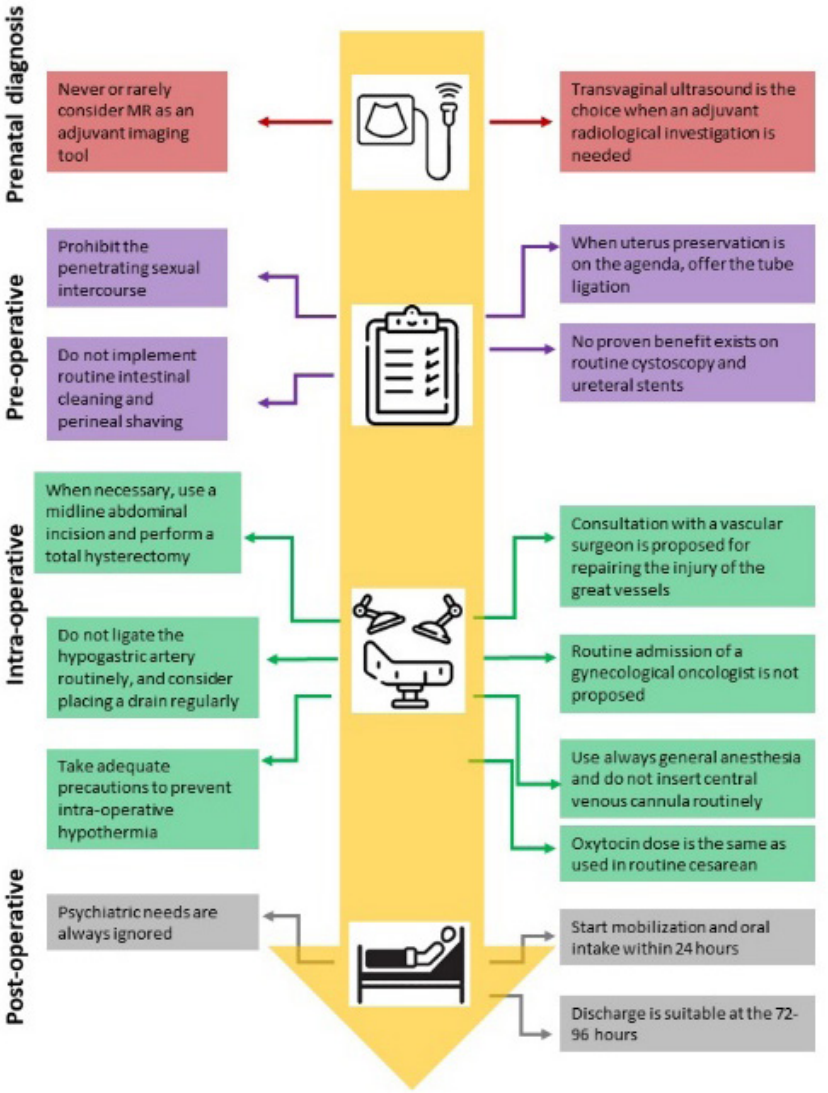

Figure 1: Consensus reached bullets in prenatal diagnosis, preoperative, intraoperative, and postoperative management of PAS disorder.
PAS: Placenta accreta spectrum

Even after 34 weeks, routine use of corticosteroids is also a subject of debate. There is no data or consensus on using antenatal steroids in scheduled PAS surgery. Due to intermittent episodes of vaginal bleeding, most of these women had received corticosteroid prophylaxis previously. Meta-analyses show higher rates of neonatal hypoglycemia, neurocognitive disorders, mental and behavioral disorders when using antenatal corticosteroids after the 34th week (13). Our participants demonstrate similar confusion, with nearly half using antenatal corticosteroids after 34 weeks of gestation.

Preventing anemia before surgery is another critical issue in managing PAS disorder. Anemia is present in nearly half of pregnancies. Prevention of anemia before the delivery will help to reduce the need for blood products. Except for the rare instance, it can be prevented by supplementing iron. While oral iron supplementation is the easiest and cheapest, it requires patient compliance. Close monitoring of hemoglobin and patient education are essential factors. When anemia is detected shortly before the delivery, the time would not be sufficient for oral treatment. Despite the higher cost and rare but severe side effects, intravenous iron can be considered for fast recovery (14). Our participants prefer equally using oral, intravenous, or both to prevent anemia.

Many patients wish to preserve their uterus for many reasons. However, the risk of recurrence of PAS disorder is considerably high in subsequent pregnancies (15). If

the point of uterine preservation is not fertility conservation, tubal ligation is a reasonable option. There is strong consensus among our participants for planning tubal ligation.

Many women have increased anxiety during a pregnancy complicated by PAS. Failure to provide respectful care and interventions with unproven efficacy may exacerbate them. Although current knowledge argues against their use, preoperative enemas and perineal shaves are routine in many maternity units (16). Our survey group was aligned against intestinal cleaning and consensus against perineal shaving.

A recent review demonstrated that expert opinions strongly restrict sexual intercourse for many obstetric complications, though evidence is lacking (17). This review addressed many obstetric complications, including placenta previa, but not PAS disorders. While there is no data about the effects of penetrative sexual intercourse on the prognosis of PAS disorder, our contributors agree that penetrative intercourse should be prohibited.

Some suggest using general anesthesia for better hemodynamic control. Others believe that even large amounts of blood loss in these patients could be managed with regional techniques (6-10). Ioscovich et al. conducted a survey study among the anesthesiologists assessing the condition's intensity. They found that in aggressively adherent cases, the anesthesiologists tend to use general anesthesia (12).

In a case study, the authors stated that even in macroscopic hematuria, preoperative cystoscopy did not add information other than obtained from radiologic works (1, 6). Determining the role of ureteral stents is more complex. Current evidence highlights that the identification of ureters is easier with stents. However, the evidence on ureteral injury reduction is scarce. Our participants do not use routine cystoscopy or ureteral stents in asymptomatic patients. They usually repair non-complicated bladder injuries themselves. They ask for the assistance of a urologist for complicated bladder and ureteral damages and a vascular surgeon for those of great vessels.

The patient's position during PAS surgery depends on many factors. These include visualization of the amount of vaginal bleeding, preventing joint injury due to an uncomfortable position, and manipulating the cervix. There is no agreement on this topic in the literature, and our participants also could not have a consensus (1, 6).

The primary surgical approach among participants is hysterectomy, and if they choose to do so, they agree to perform a total rather than a subtotal hysterectomy. Leaving the placenta in situ was an option only for one participant. Others preferred segmental resection or pelvic devascularization and tamponade after placental removal. These results are concordant with other surveys (1, 8, 10, 11). The main problem with surgery during PAS disorder is the bladder dissection from the lower uterine segment and control of bleeding. Both issues require a wide sight of the surgical field. Our participants and many others agreed that a midline incision is necessary. However, Collins et al., have noted no evidence on this topic (1). Recently, Ghaleb et al. published their experience with PAS surgery. They made a segmental excision with uterine devascularization through a Pfannenstiel incision on 62 women (18). We previously presented our data on the surgical treatment of PAS. We performed a total abdominal hysterectomy on 161 women having placenta increta or percreta with very low transfusion and complication rates (19). Like abdominal incisions, many prefer a corporal incision on the uterus for preventing iatrogenic placental damage. This incision may be vertical or transverse fashion over the uterine corpus. While a low transverse incision over the uterus would lead to placental injury, it could only be a choice when segmental myometrial excision is the target for uterine preservation. Bladder injury is the most typical complication of PAS surgery. It occurs in nearly one in ten. Çelik et al. stated that preoperative bladder filling with 200 mL of saline solution prevents the risk of bladder injury in PAS surgery and diminishes the volume of blood loss (20). Our survey members are nearly equally divided on retrograde filling the bladder. Turan et al. proposed using a hand-held vessel sealing system for hemostasis during bladder dissection (21). Only a few of our participants chose this. Others stated that they used sutures and/or electrocautery. The preference for ligating, coagulating, or sealing the vessel depends on the availability and the size of the vessel. New technologies promise speed but may not be available in all settings.

The efficacy of hypogastric artery ligation in obstetric hemorrhage is not proven. It may be attributed to the excessive pelvic anastomotic connections. Therefore, routine use is not recommended (1, 6). However, any of the previous surveys did not investigate this topic. Our survey participants are aligned on this topic and do not perform routine hypogastric artery ligation.

Cesarean section is the leading risk factor for postpartum infection, and the benefits of single-dose antibiotic prophylaxis have been demonstrated (22). Re-dosing during surgery was evaluated in a meta-analysis and was found beneficial if administered within 240 minutes (23). Dose adjustment was defined in cesarean regarding the maternal weight but not for operation length or blood loss, which are common in PAS surgery. Furthermore, no antibiotic regimen was determined when the placenta remained in situ. All of our participants use antibiotic prophylaxis but disagree on the duration. Some prefer to continue antibiotics beyond 24 hours.

While the evidence is apparent in non-complicated cases, prophylactic oxytocin for preventing postpartum bleeding has not been studied in PAS disorder (24). Potential problems may be seen in the presence of a partially invasive placenta. In such cases, oxytocin infusion could cause incomplete separation and excessive bleeding. However, oxytocin is proposed for preventing uterine atony generated from the mass effect of the placental remaining in the uterus until the termination of the hysterectomy. Finally, the cardiovascular effects of oxytocin could trigger arrhythmia, decrease myocardial contractility, and cause hypotension (25). The cardiovascular effects of oxytocin on physiologic and supraphysiological doses during a surgery in which acute volume depletion is expected require further research. Using minimal effective doses seems to be safe instead of higher dosages. Our participants opted for a similar dosage as used in non-complicated cesarean in most cases.

Intraoperative blood analysis may determine hemoglobin level (blood gas, complete blood count), type and severity of coagulopathy (complete blood count, coagulation tests, fibrinogen level, thromboelastography), and electrolytes (blood gas, biochemical analysis). Thromboelastography is a quick test for the specific assessment of the affected component. A recent study that did not include obstetric patients found that its use reduces bleeding or transfusion (26). Despite this advantage, many institutions do not have this facility, and the most used only during the operation is blood gas in our survey group. Determining the deficient blood compartment using these tests will reduce the use of blood products.

Body heat stabilization is a critical but neglected issue during major surgeries. It has been demonstrated that many easy and cheap methods are available, but healthcare professionals' compliance is poor (27). In our survey group, there is a strong consensus on using one of these measures to prevent perioperative hypothermia. This high compliance may be attributed to the qualification of our group selection. No previous surveys have taken this matter into account, according to our review of the literature.

Late cord clamping has positive effects on the adaptation of the newborn; this is more apparent in preterm infants (28). However, there has yet to be a consensus on this topic among our participants. Nearly half agree, but others do not. While almost all of these infants are premature, this subject was outside the scope of any other previous surveys.

Thromboembolism is a silent enemy during the perinatal period. Prolonged hospital stay, decreased activity, hypercoagulable state of pregnancy, and triggered coagulation due to pelvic surgery are the stimulants of thromboembolism. This fact requires meticulous and balanced prophylaxis between thromboembolism and drug-induced iatrogenic bleeding. To our knowledge, no evidence-based recommendation or expert opinion is present for venous thromboembolism prophylaxis in PAS surgery. In non-complicated cesarean, early mobilization, anti-embolism socks, and low-molecular-weight heparin are preferred concomitantly (29). Nearly half of our survey participants practice this as well. Our participants have a strong consensus on mobilization within one day and a consensus on oral intake within one day. They also have a consensus on discharging the patient on the third or fourth day. While enhanced recovery after surgery guidelines on cesarean delivery similarly propose these items, the evidence level is low (30).

Pregnancy and the postpartum period itself cause different psychiatric disturbances. Loss of fertility and life-threatening surgery would likely increase the intensity of these disorders. Bartels et al. have demonstrated that PAS surgery has long-lasting effects on women's mental health (31). Despite this result, our participants do not systematically evaluate the need for psychiatric support.

Study limitations

This survey has some strengths and limitations. To our knowledge, this is the first study conducted in a developing country where sources may be limited. While the number of participants is limited, the urban population represents more than 60% of the country. In addition, the group is homogeneous in many respects, including experience, age, and institutional setting.

CONCLUSION

In conclusion, our study shows significant differences in treating PAS in Türkiye, which has high PAS rates, as the cesarean section rate is more than 50%. Considering the high mortality of this condition, we need more evidence-based data on the effectiveness of the different treatment strategies used. The consensus points identified in this paper will guide healthcare providers, and the points highlighted by the lack of evidence would stimulate the design of new clinical trials.

Ethics Committee Approval: The Ethics Committee of Çukurova University approved the study protocol (Date: 30.06.2022, No: 48).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.B., R.M.; Data Acquisition- S.B., İ.H.; Data Analysis/Interpretation- S.B., R.M.; Drafting Manuscript- S.B., İ.H.; Critical Revision of Manuscript- S.B., R.M.; Final Approval and Accountability- S.B., R.M., İ.H.

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THE ROLE OF BETA-CATENIN AND FOXP1 IN THE PATHOGENESIS OF POLYPOID ENDOMETRIOSIS

POLİPOİD ENDOMETRİOZİS PATOGENEZİNDE BETA-KATENİN VE FOXP1'İN ROLÜ

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ABSTRACT

Objective: To investigate whether beta-catenin and Forkhead box protein P1 (FOXP1) play a role in pathogenesis of polypoid endometriosis (PE).

Material and Method: Our study included fifteen cases of PE. Clinical findings were gathered from archived files of relevant clinics and pathology reports. All glass slides were re-examined for confirmation of the diagnosis and the detection of additional microscopic findings. An immunohistochemical examination was performed using anti beta-catenin and FOXP1 antibodies in fifteen cases of PE, and in a control group that contained nine cases of endometrial polyps (EP) and nine cases of conventional ovarian endometriosis (OE).

Result: Stromal nuclear beta-catenin expression was observed in six cases in PE, five cases in EP and one case in the OE group. Stromal FOXP1 staining in PE and EP was significantly reduced as compared to OE. Five PE and two EP cases showed stromal FOXP1 staining while all the OE cases showed stromal FOXP1 staining. The Stromal FOXP1 staining was statistically significant between PE vs OE (p=0.002) and EP vs OE (p=0.023) cases. There was no difference between PE and the control cases in terms of nuclear beta-catenin staining (p=0.69). There was no correlation between these two antibodies and histologic features.

Conclusion: The loss of stromal FOXP1 is another biological difference of PE and the overall similarity of expression of FOXP1 between PE and EP could be regarded as a contributing factor for polyp formation.

Keywords: Endometriosis, polyp, immunohistochemistry, FOXP1, beta-catenin

ÖZET

Amaç: Polipoid endometriozis (PE) patogenezinde Forkhead box protein P1 (FOXP1) ve beta-katenin'nin rolünün araştırılması.

Gereç ve Yöntem: Çalışmaya 15 PE olgusu dahil edilmiştir. Klinik bilgiler hastaların tıbbi kayıtlarından ve patoloji raporlarından elde edilmiştir. Tüm mikroskopik preperatlar tanının doğrulanması ve ek mikroskopik özelliklerin tanımlanması amacıyla tekrar değerlendirilmiştir. FOXP1 ve beta-katenin antikorları kullanılarak 15 PE ve kontrol grubu olarak dokuz endometrial polip (EP) ve dokuz ovarian endometriozis (OE) olgusuna immünhistokimyasal inceleme yapılmıştır.

Bulgular: Stromal nükleer beta-katenin boyanması altı PE, beş EP ve bir OE olgusunda gözlenmiştir. Stromal FOXP1 boyanması OE olgularına göre PE ve EP olgularında belirgin şekilde azalmış olup tüm OE olgularında stromal FOXP1 boyanması izlenirken beş PE ve iki EP olgusunda stromal FOXP1 boyanması saptanmıştır. PE ile OE ve EP ile OE olguları arasındaki stromal FOXP1 boyanması farkı anlamlıdır (sırasıyla p=0,002 ve p=0,023). Beta-katenin ile PE ve kontrol grubu olguları arasında anlamlı fark bulunmamıştır (p=0,69). Histolojik özelliklerle bu antikorların pozitifliği arasında ilişki yoktur.

Sonuç: PE olgularındaki FOXP1 kaybı PE ve konvansiyonel endometriosis arasındaki bir diğer biyolojik fark olarak tanımlanabilir. Ayrıca PE ve EP olgularındaki stromal FOXP1 boyanmasındaki benzerlik FOXP1'in polip oluşumunda rolü olduğunu düşündürmektedir.

Anahtar Kelimeler: Endometriozis, polip, immünhistokimya, FOXP1, beta-katenin

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INTRODUCTION

Endometriosis is a condition characterized by the presence of endometrial-like glands and stroma outside the uterine corpus. It usually affects women in reproductive age and its prevalence ranges between 5-10% (1-2). Polypoid endometriosis (PE) is a rare form of endometriosis which resembles endometrial polyps microscopically (3). It can form mass lesions that can be misdiagnosed as tumors clinically.

The forkhead box protein P1 (FOXP1) is a member of the forkhead box family of proteins that belongs to the P subfamily. It is a master regulator of embryonic stem cells pluripotency and acts as a tissue specific tumor suppressor or oncogene (4,5).

Beta-catenin is the key transcriptional factor of the canonical Wnt/beta-catenin pathway (6). Wnt signaling increases the stability of the beta-catenin and allows it to translocate to the nucleus where it acts as a transcriptional co-activator of the T cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors (5).

As the transcription factor FOXP1 potentiates Wnt signaling via acetylation of beta-catenin which increases the transcription of beta-catenin target genes (5). In endometriosis, this interplay is evident in stromal cells as FOXP1 increases fibrosis in endometriotic lesions through the Wnt/beta-catenin pathway (7).

Pathogenesis of endometriosis is complex and not fully understood but the pathogenesis of PE is largely unknown and few case series were available (8,9,10). In this study we built upon our previous work and examined whether FOXP1 and beta-catenin played a role in the pathogenesis of PE (11).

MATERIALS and METHODS

The computer archives of the Pathology Department, Istanbul Faculty of Medicine, were searched for cases diagnosed as PE. Fifteen cases were identified between 2005 and 2019. Surgical procedures of the cases are as follows: four total abdominal hysterectomy, one unilateral or bilateral salphingo-oophorectomy, one salphingectomy, one cystectomy, one mass excision, two low anterior resection, three total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy and lymph node dissection, one total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy, lymph node dissection and low anterior resection, and one total abdominal hysterectomy with bilateral salphingo-oophorectomy, parametrial resection, nephroureterectomy. Glass slides were reexamined, and immunohistochemistry was performed on cases using monoclonal antibodies against FOXP1 (Cell Marque SP133, dilution: 1/200) and beta-catenin (Biocare, dilution: 1/250). Nine cases of ovarian endometriosis (OE) and nine cases of endometrial polyp (EP) cases were selected as control groups.

Stromal and glandular staining were evaluated as: extent, intensity and cellular compartment stained with FOXP1 and beta-catenin. Membranous staining for beta-catenin was accepted as normal (N) and nuclear beta-catenin staining was accepted as aberrant (A). The staining intensity for FOXP1 and aberrant beta-catenin were graded as 0: no staining, 1+: weak, 2+: moderate, 3+: strong.

The Chi-square test, Kruskal-Wallis test and Fischer Exact test were used for comparing the positivity of FOXP1 and beta-catenin nuclear positivity between groups. The P value less than 0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS) version 27.0 was used for statistical analysis.

RESULTS

Clinical and demographic findings

Patient ages ranged from 29 to 58 (mean: 41.93, median: 40) years. Only seven of their presenting symptoms were known. These symptoms were menometrorrhagia, vaginal bleeding, rectal bleeding, and inguinal pain. Polypoid masses were usually multiple. In five cases the masses were found in multiple anatomic sites. In remaining ten cases the lesions were detected in only one anatomic site. The most common sites of involvement were the ovary and rectosigmoid colon. Details of the clinical findings of PE cases are presented in Table 1.

Pathologic features of PE, EP and OE cases

All PE cases consisted of glandular and stromal components. Most of the cases showed features consistent with proliferative and secretory phase endometrium. Two ovarian PE cases showed glandular proliferation consistent with atypical complex hyperplasia (borderline endometrioid tumor) and the International Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid carcinoma arising within a polypoid lesion respectively. The stromal components of PE cases were typical for regular endometrial polyps. No features consistent with Müllerian adenosarcoma were observed. The most common feature was predecidual change. Six cases showed features of aggressive endometriosis, which had involvement of the colon and pelvic soft tissue. Extensive pelvic involvement led to hydroureter and hydronephrosis in one PE case (Figure 1).

EP cases showed varied morphological features. One of the cases showed atrophic glands. The rest of the cases showed glandular features consistent with proliferative phase. Four cases showed marked and two showed mild hypercellular stroma. Decidual change was observed in one case (Figure 1).

Table 1: Clinicopathologic features of PE cases.

Clinicopathologic features of PE cases	
Patient age	41.93±8.77 (min-max: 29-58)
Presenting symptom	Menometrorrhagia (1) Inguinal pain (1) Rectal bleeding (1) Vaginal bleeding (4)
Surgical procedure	Total abdominal hysterectomy (4) Unilateral or bilateral salphingo-oophorectomy (1) Salphingectomy (1) Cystectomy (1) Mass excision (1) Low anterior resections of the colon (2) Total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy and lymph node dissection (3) Total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy, lymph node dissection and low anterior resection (1) Total abdominal hysterectomy with bilateral salphingo-oophorectomy, parametrial resection, nephroureterectomy (1)
Location of the lesion*	Ovary (6) Salpinx (3) Uterinecorpus (2) Douglas pouch (2) Rectosigmoid colon (4) Cervix (1)
Number of the lesion (Solitary/multiple)	Solitary (10) Multiple (5)
Size of the lesion	Macroscopic (12) Microscopic (3)
Glandular features	Atrophic (1) Proliferative (5) Secretory (3) Cystic change (1) Focal hyperplasia without atypia (1) Focal complex hyperplasia with atypia (1) Nonspecific (3)
Stromal features	Hypercellular (3) Hypercellular with decidualization (2) Hypocellular (1) Decidualization (2) Myomatous (2) Nonspecific (5)
Growth direction of the polyp	Peritoneal cavity (6) Neolumen (5) Peritoneal cavity and neolumen (2) Intestinal lumen and neolumen (1) Vagina and neolumen (1)

PE: Polypoid endometriosis, *: Number of involved locations is greater than 15 because 5 cases have multiple PE lesions in different locations.

In OE cases tubal ciliated metaplasia and fibrosis were the most common features for glands and stroma respectively (Figure 1).

Polypoid endometriosis

Nuclear beta-catenin expression was not observed in the glandular component of the PE cases. For the stromal com-

ponent, six cases showed nuclear beta-catenin expression. Staining intensity for nuclear beta-catenin expression was weak for three cases and moderate for three cases. Staining extent in cases with nuclear expression ranged between 5% and 40% (mean 24.16±14.63) (Table 2) (Figure 1).

FOXP1 showed only nuclear staining for both compartments. Five cases showed no glandular staining. Of the remaining ten cases staining extent was between 5% and 90% (mean 22.5±27.30). Staining intensity was weak for nine cases and moderate for one case. Ten cases showed no stromal staining while four cases showed weak, and one case showed moderate nuclear staining. Staining extent for stromal FOXP1 was between 5% and 70% (mean 33±33.83) (Table 2) (Figure 1).

When nuclear expressions of both antigens were considered, only one of the six cases showing stromal nuclear beta-catenin expression had nuclear stromal FOXP1 expression. In that case both beta-catenin and FOXP1 expression were detected in the same area.

Endometrial polyps

Same as PE cases; nuclear beta-catenin staining was not observed in the glandular component. In the stromal component, nuclear beta-catenin staining was observed in five of the cases. Staining intensity for cases with nuclear beta-catenin expression was weak for two and moderate for three cases. Staining extent for nuclear beta-catenin expression was between 5% and 70% (mean 35±27.38) (Table 2) (Figure 1).

FOXP1 nuclear staining was observed in both the glandular and stromal components. Two cases showed no staining whereas the rest of the cases showed nuclear staining in glandular compartment. Six of the cases showed weak and one case showed moderate glandular FOXP1 staining. Staining extent was between 10% and 40% (mean 27.14±12.53). For the stromal component only two cases showed nuclear staining. Staining intensity was weak and moderate. Staining extent was 10% and 70% respectively (Table 2) (Figure 1).

Only one case showed both nuclear beta-catenin and FOXP1 staining.

Ovarian endometriosis

Nuclear beta-catenin staining was not observed in glandular cells of the OE cases. For stromal cells, only one case showed nuclear staining. Staining extent was 50% and intensity was moderate for the case with nuclear beta-catenin staining (Figure 1).

Glandular and stromal nuclear FOXP1 staining was observed in eight OE cases. One OE case showed only stromal FOXP1 staining. Staining extent was between 5% and 30% (mean 15.62±9.79) in glandular component. Nuclear staining was observed in stromal cells of all OE cases. Staining extent was between 60% and 90% (mean 84.44±10.13). Staining intensity was moderate for all OE cases (Table 2) (Figure 1).

Only one case showed both nuclear beta-catenin and FOXP1 staining.

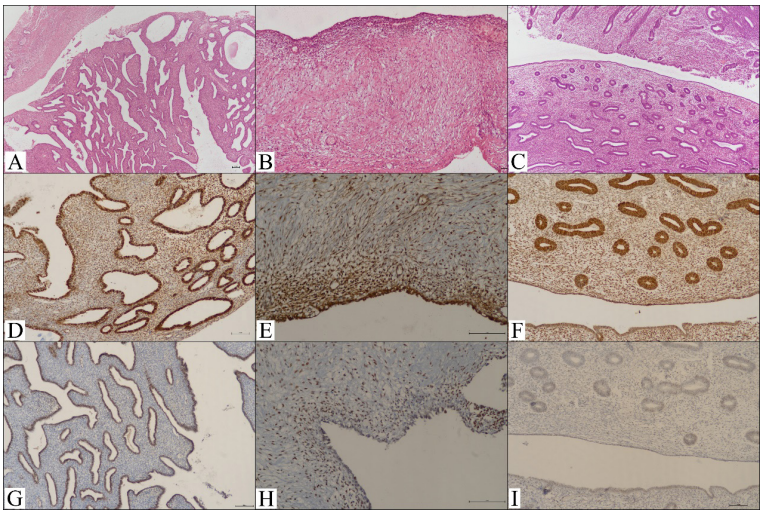

Figure 1: A: Polypoid endometriosis in fallopian tube. HE x40. B: Ovarian endometriosis. Attenuated endometriosis epithelium and stroma is visible at the top. HE x100. C: Endometrial polyp. HE x40. D: Weak and moderate nuclear beta-catenin staining of the stromal cells of polypoid endometriosis. Beta-catenin IHC x100. E: Moderate nuclear staining of the stromal cells of ovarian endometriosis. Beta-catenin IHC x200. F: Beta-catenin staining in endometrial polyp. Both nuclear and cytoplasmic staining is observed. Beta-catenin IHC x100. G: FOXP1 staining in polypoid endometriosis. While stromal cells didn't show FOXP1 expression, there is nuclear FOXP1 staining in glands. FOXP1 IHC x100. H: FOXP1 staining in ovarian endometriosis. Most of the stromal cells show moderate FOXP1 expression. FOXP1 IHC x200. I: FOXP1 staining in endometrial polyp. Weak staining was observed in glands, endothelial cells and inflammatory cells. Staining with FOXP1 was not observed in stromal cells. FOXP1 IHC x100.

Table 2: Beta-catenin and FOXP1 staining of the polypoid endometriosis, ovarian endometriosis and endometrial polyp cases.

Beta-catenin expression of the polypoid endometriosis, ovarian endometriosis and endometrial polyp cases

	Epithelial	Stromal		Epithelial	Stromal		Epithelial	Stromal
PE#1	N	5%,1+	**OE#1**	N	N	**EP#1**	N	40%,2+
PE#2	N	N	**OE#2**	N	N	**EP#2**	N	N
PE#3	N	N	**OE#3**	N	N	**EP#3**	N	50%,2+
PE#4	N	40%,1+	**OE#4**	N	N	**EP#4**	N	N
PE#5	N	N	**OE#5**	N	N	**EP#5**	N	70%,1+
PE#6	N	N	**OE#6**	N	50%,2+	**EP#6**	N	5%,1+
PE#7	N	15%,2+	**OE#7**	N	N	**EP#7**	N	10%,2+
PE#8	N	N	**OE#8**	N	N	**EP#8**	N	N
PE#9	N	30%,2+	**OE#9**	N	N	**EP#9**	N	N
PE#10	N	15%,2+						
PE#11	N	N						
PE#12	N	40%,1+						
PE#13	N	N						
PE#14	N	N						
PE#15	N	N						

Only aberrant (nuclear) staining extent and intensity were considered significant. 0: Negative, 1+: Weak, 2+: Moderate, 3+:S trong, PE: Polypoid endometriosis, OE: Ovarian endometriosis, EP: Endometrial polyp, N: Normal.

FOXP1 expression of the polypoid endometriosis, ovarian endometriosis and endometrial polyp cases

	Epithelial*	Stromal**		Epithelial*	Stromal**		Epithelial*	Stromal**
PE#1	10%,1+	0	**OE#1**	30%,1+	90%,2+	**EP#1**	30%,1+	0
PE#2	10%,1+	0	**OE#2**	30%,1+	90%,2+	**EP#2**	0	10%,1+
PE#3	5%,1+	0	**OE#3**	10%,1+	80%,2+	**EP#3**	10%,1+	0
PE#4	5%,1+	0	**OE#4**	20%,1+	80%,2+	**EP#4**	30%,1+	0
PE#5	10%,1+	10%,1+	**OE#5**	10%,1+	90%,2+	**EP#5**	30%,1+	0
PE#6	0	0	**OE#6**	10%,1+	90%,2+	**EP#6**	0	0
PE#7	10%,1+	0	**OE#7**	10%,1+	90%,2+	**EP#7**	10%,1+	70%,2+
PE#8	0	0	**OE#8**	5%,1+	60%,2+	**EP#8**	40%,2+	0
PE#9	90%,2+	5%,1+	**OE#9**	0	90%,2+	**EP#9**	40%,1+	0
PE#10	40%,1+	0						
PE#11	5%,1+	10%,1+						
PE#12	0	0						
PE#13	0	0						
PE#14	0	70%,1+						
PE#15	40%,1+	70%,2+						

*: Epithelial staining values: 0: Negative, 1+: Weak, 2+: Moderate, 3+: Strong, **: Stromal staining intensity values: 0: Negative, 1+: Weak, 2+: Moderate, 3+: Strong, PE: Polypoid endometriosis, OE: Ovarian endometriosis, EP: Endometrial polyp.

Correlation between histologic features and beta-catenin/ FOXP1 expression

Nuclear beta-catenin staining was observed in three out of six PE cases with aggressive features and three out of five cases with multiple lesions. The PE cases with atypical complex hyperplasia (borderline endometrioid tumor) and endometrioid carcinoma (FIGO Grade I) showed no stromal staining with beta-catenin.

Three cases with >10% glandular FOXP1 staining showed no specific histologic features. Stromal FOXP1 staining was not observed in PE cases with multiple lesions. Only one PE case with aggressive features showed stromal FOXP1 staining, and it was weak and focal (10%). Two cases with glandular proliferations consistent with atypical complex hyperplasia (borderline endometrioid tumor) and endometrioid carcinoma (FIGO Grade I) showed weak and focal (10%) and no FOXP1 staining, respectively. Two cases with extensive (70%) stromal FOXP1 showed proliferative phase glandular features but had no specific stromal features.

For control cases, EPs did not show any specific histologic features with regards to beta-catenin or FOXP1 staining. In OEs stromal sclerosis was a prominent feature in terms of FOXP1 expression.

Statistical analysis

Both beta-catenin and FOXP1 positivity, regardless of extent and intensity, compared as PE vs EP vs OE, PE vs control cases (EP and OE), PE vs EP, PE vs OE and EP vs OE. Beta-catenin staining was analyzed only for stromal components of the PE, EP and OE cases because nuclear staining was not detected in any of the glandular components.

Stromal FOXP1 staining was statistically significant between PE vs EP vs OE (p=0.007), PE vs OE (p=0.002) and EP vs OE (p=0.023) while there was no statistical difference between PE vs EP (p=0.66) and PE vs control group (EP+OE) (p=0.119).

Glandular FOXP1 staining showed no statistical difference between PE vs EP vs OE (p=0.66), PE and control group (EP+OE) (p=0.41), PE vs EP (p=0.66), PE vs OE (p=0.35) and EP vs OE (p=1).

There was no statistically significant beta-catenin staining difference between PE vs EP vs OE (p=0.26), PE and control group (EP+OE) (p=0.69), PE vs EP (p=0.67), PE vs OE (p=0.19) and EP vs OE (p=0.13) found.

DISCUSSION

PE is an uncommon type of endometriosis. With its polyp-like structure it raises the question of which common features it shares with endometrial polyps and with conventional endometriosis. In this study we tried to answer this question on the aspect of beta-catenin and FOXP1 expression.

Many factors contribute to the survival and progression of the ectopic endometrial tissues. Wnt pathway is one of these factors where beta-catenin is the central molecule (8). This molecule is normally located at cell membrane, and it is bound to E-cadherin but when it is uncoupled, beta-catenin is degraded upon phosphorylation by GSK3beta. Stabilization of beta-catenin allows translocation to the nucleus and interacts with TCF-LEF family of transcription factors. It has been shown that the Wnt pathway is activated in endometriosis (12-15). The Wnt pathway is also an oncogenic pathway that is active in different tumors and a potential target in endometrial polyp pathogenesis (16,17). In our study nuclear beta-catenin staining was observed more frequently in PE and EP cases as compared to OE cases but the difference was not statistically significant. We concluded that beta-catenin is not a meaningful contributor to PE pathogenesis.

The FOXP family of proteins are multifunctional transcription factors. They act as both tumor suppressors and oncogenes depending on the neoplasm (18). Two aspects of FOXP1 make it a potential target for PE pathogenesis. First, FOXP1 expression is associated with fibrosis and stromal cell proliferation in endometriosis which is important as stromal cells are the main reason of polyp formation. Second, its organ specific function on cell proliferation is demonstrated in different neoplasms (7,18,19). In our study, OE cases showed results in line with the first the aspect of FOXP1. Fibrosis was the prominent feature of these cases. In PE cases the FOXP1 expression is greatly reduced. When combined with the similar FOXP1 expression of EP cases we assumed that FOXP1 expression was not required for polyp formation. In contrast, the loss of FOXP1 expression in stromal cells in PE and EP cases could be causing stromal cell overgrowth in both groups. We based this assumption on FOXP1's tumor suppressor/oncogenic properties. The reports in literature pointed out that FOXP1 acts as a tumor suppressor in endometrioid carcinoma (20,21). In our PE cohort, the case with endometrioid carcinoma showed no expression of FOXP1 in either the stromal or glandular component. Although PE is not considered a neoplastic entity, the loss of FOXP1's tumor suppressor function could be a contributing factor in polyp formation in PE.

The above-mentioned markers are also interlinked. FOXP1, through acetylation enhances the beta-catenin's transcriptional activity (5). Also, FOXP1's fibrotic activity is reported to be through the Wnt pathway (7). This association was encountered in one PE case. Other than that, we did not find any correlation with nuclear beta-catenin and FOXP1 expression with immunohistochemistry. But there was a similarity between PE and EP cases in their FOXP1 and beta-catenin expression. This raises the question as to whether this immune profile has a role in polyp formation. Endometrial polyp pathogenesis was not investigated in this regard, and this will be an interesting topic for a future study.

CONCLUSION

We investigated FOXP1 and beta-catenin expression in PE and their roles in PE pathogenesis. Significant reduction of FOXP1 in PE and EP stromal cells indicated that FOXP1 could play a role in polyp formation in PE.

Ethics Committee Approval: This is a retrospective archive study that does not include live animals or humans. Therefor ethics approval was not sought.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.Y., S.Ö, A.Y.A.; Data Acquisition- A.Y.A., C.Y., H.S.; Data Analysis/Interpretation- A.Y.A., A.B.; Drafting Manuscript- A.Y.A., A.B.; Critical Revision of Manuscript- E.Y., S.Ö., C.Y., H.S.; Final Approval and Accountability- A.Y.A., E.Y., A.B., C.Y., H.S., S.Ö.

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SCARS MAY INDEED "HAVE THE STRANGE POWER TO REMIND US THAT OUR PAST IS REAL":* A PATIENT REPORTED OUTCOME MEASURES STUDY IN WOMEN WITH POSTMASTECTOMY BREAST RECONSTRUCTION

İZLERİN GERÇEKTEN DE 'ENTERESAN BİR ŞEKİLDE YAŞADIKLARIMIZIN GERÇEK OLDUĞUNU BİZE ANIMSATMA GÜCÜ'* OLABİLİR: MASTEKTOMİ SONRASI MEME REKONSTRÜKSİYONU YAPILMIŞ KADINLARDA HASTA RAPORLU BİR SONUÇ ÇALIŞMASI

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ABSTRACT

Objective: One of the leading causes of death among women is breast cancer. The disease process and treatment journey consume patients' emotional and physical energy, severely affecting mood, self-esteem, body image, sexual functions, commitment, and overall quality of life. Postmastectomy breast reconstruction is known to revert some of these adversarial conditions. This study uses patient-reported outcome measures (PROMs) to investigate the factors influencing the end result and quality of life regarding postmastectomy breast reconstruction.

Material and Method: Thirty-four patients who'd undergone breast reconstruction filled out a questionnaire form including 54 questions pertaining the patients' surgical and oncological history, demographics, mood, self-esteem, body and breast self-image, social and familial support mechanisms, and satis-

ÖZET

Amaç: Meme kanseri kadınlar arasında önde gelen ölüm nedenlerinden biridir. Hastalığın seyri ve tedavisi hastaların duygusal ve fiziksel enerjisini tüketir ve duygu-durumları, özgüvenlerini, cinsel işlevlerini, yaşama bağlılık ve yaşam kalitelerini etkiler. Mastektomi sonrası meme rekonstrüksiyonu bu sorunların bir kısmının giderilmesinde yardımcı olabilir. Bu hasta tarafından raporlanan çıktı ölçütleri çalışmasında sonuçları ve hastaların yaşam kalitelerini etkileyen etmenler araştırılmıştır.

Gereç ve Yöntem: Meme rekonstrüksiyonu geçirmiş toplam 34 hasta cerrahi ve onkolojik öyküleri, demografik verileri, duygu-durumları, beden ve meme öz algıları, sosyal ve ailesel destek mekanizmaları ile yaşam ve rekonstrüksiyondan memnuniyetlerini sorgulayan 54 soruluk bir anket yanıtladı. Sonrasında

* Cormack McCarthy, novelist (in "All the pretty horses", 1992)

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faction with life and reconstruction. The study then collected anthropometric measurements and standardized photographs and had plastic surgery residents assess aesthetic outcome with regard to the photographs.

Result: Half of the patients had immediate while the other half had delayed reconstruction. Of the patients, 10 (29.4%) had reconstructions that only involved an implant, 15 (44.1%) had reconstructions that only involved autogenous tissue, and nine (26.5%) that had both. No significant association could be found for the reconstruction method or timing of the reconstruction with aesthetic results, symmetry, or patient satisfaction. Meanwhile, nipple-areolar complex (NAC) reconstruction contributed to significantly better aesthetic outcomes (p=0.026) and overall patient satisfaction (p=0.029). Scar issues were found to significantly affect satisfaction scores (p=0.008) while not affecting the aesthetic outcome.

Conclusion: Neither symmetry nor aesthetic outcome were found to be major factors influencing patients' overall satisfaction with breast reconstruction. However, scars are relevant as constant reminders of past surgeries. Another significant factor in patient satisfaction was NAC reconstruction.

Keywords: Breast, reconstruction, cancer, mastectomy, scars, nipple

antropometrik ölçümler ve standardize fotoğraflar alındı. Estetik sonuçları bu fotoğrafların üzerinden değerlendirildi.

Bulgular: Hastaların yarısına eş zamanlı, yarısına geç dönemde rekonstrüksiyon yapılmıştı. On hastaya (%29,4) sadece implant ile, 15'ine (%44,1) sadece otojen doku ile ve dokuzuna (%26,5) ikisi de yapılmıştı. Rekonstrüksiyon metodu veya zamanlamasının estetik sonuçlar, simetri veya hasta memnuniyetiyle aralarında anlamlı bir ilişki bulunamadı. Bununla beraber meme başı-areola kompleksi (MAK) rekonstrüksiyonu yapılmış olması hem estetik sonuçları (p=0,026), hem de hasta memnuniyetini (p=0,029) anlamlı derecede olumlu yönde etkilemişti. Ancak nedbe sorunları estetik sonuçları anlamlı derecede etkilemezken hasta memnuniyetini olumsuz yönde etkileyen tek etmen olarak ortaya çıkmıştır (p=0,008).

Sonuç: Meme rekonstrüksiyonunda memnuniyeti anlamlı ölçüde etkileyen etmenler arasında simetri ve estetik sonuç bulunmazken süreci kendilerine anımsatan nedbe sorunları bulunmuştur. Hasta memnuniyetini anlamlı derecede etkileyen bir diğer etmen ise MAK onarımı yapılmış olmasıdır.

Anahtar Kelimeler: Meme, rekonstrüksiyon, kanser, mastektomi, nedbe, meme başı

INTRODUCTION

Regarding cancer-related mortality, breast cancer stands as the most prevalent malignancy among women, second only to lung cancer (1). While the incidence of breast cancer is on the rise, mortality rates have seen a slight decrease in recent decades, attributable to advancements in screening methods and anticancer medications (1-3). Improvements in both overall survival and disease-free survival rates are accompanied by a growing interest in enhancing the quality of life.

With a lifetime risk of one in eight, breast cancer presents a devastating experience for affected women and their loved ones (4). The ominous diagnosis of cancer, the side effects of hormone therapy and chemotherapy, and various forms of mastectomy surgeries collectively impact affected women throughout the course of the disease, affecting their cognitive, sexual, and social identity (5-8). Reconstructive breast surgery is steadily gaining popularity thanks to the increased awareness of its benefits without any compromise on patient safety (9).

Patient satisfaction is influenced by five major sets of factors: 1) medical background (concomitant diseases, breast/body type, and age), 2) patient expectations (self/breast perception, social background, coordination with the surgical team, and education), 3) oncoplastic background (radiotherapy, chemotherapy, hormone therapy, disease stage, ablation technique), 4) reconstructive surgery (timing of reconstruction, technique used, donor site, complications, and pain), and 5) results (symmetry and aesthetic outcome). Several factors stand out in terms of influencing patient satisfaction following breast reconstruction, including the chosen reconstruction technique, timing of the reconstruction, presence of complications, necessity for reoperation, patients' psychosocial backgrounds, body mass indices, and whether nipple-areolar complex (NAC) reconstruction was performed (10-12). While NAC reconstruction is often offered to patients following a removal due to oncologic surgery, it may also be loosely advertised in relation to breast mound reconstruction (13).

These factors, along with their pros and cons, should be thoroughly discussed with patients before undergoing oncologic surgery. The impact of reconstruction on patient satisfaction has been previously studied (14). This study uses patient-reported outcome measures (PROMs) to present the findings from a comprehensive questionnaire aimed at identifying the factors influencing overall patient satisfaction.

MATERIALS and METHODS

This retrospective study was approval from the Istanbul University, İstanbul Faculty of Medicine's Local Ethical Committee for Clinical Research (Date: 05.11.2023, No: 20). All patients participating in this study have undergone surgery conducted by the authors. The authors affirm that the operating techniques that were employed have been scientifically validated and are ethical. Furthermore, the authors confirm their compliance with the World Medical Association's Declaration of Helsinki

(1964), including its 7th revision (2013), thus ensuring adherence to ethical standards. Informed consent was obtained from all participants.

Patients and questionnaire

The study included patients who'd undergone breast reconstruction in our clinic between 2005 and 2009. A total of 48 eligible patients were identified, with 34 agreeing to participate. Face-to-face interviews covered psychosocial backgrounds; pre-disease, post-mastectomy, and post-reconstruction psychosexual statuses; mood; bodily perception; and self-esteem. The questionnaire comprises 55 questions categorized under demographics, disease and reconstruction history, physical examination, psychosocial status, familial and social support, perception of body and priorities, and overall satisfaction with subsidiaries (see the additional files section in the Appendix).

Of the patients, 17 underwent reconstruction at the same time as their oncologic surgery, while a later reconstruction approach was employed over the remaining 17. Selection criteria included women with a minimum nine-month follow-up post-reconstruction, which takes into consideration the significant tissue healing that occurred in the breast tissue during this period (15, 16). Patients provided written informed consent for the use of their medical and photographic data.

The retrospective data analysis covers demographic features; disease characteristics; psychological, social, and familial support mechanisms; patient expectations, and patient satisfaction. The analysis also assesses overall quality of life, emotional status, and sexual well-being, as drawn from the questionnaire. The analysis evaluates the impact of reconstruction type, timing, method, operations for contralateral breast, NAC reconstruction, resultant breast symmetry, aesthetic outcome, and complications (donor site morbidity, radionecrosis, capsule contraction, excessive scarring).

The same pollster conducted a face-to-face survey that involved measurements of height and weight; uniformity was ensured by scheduling interviews at the same time of day (midday, around 12:00 pm) to eliminate diurnal bias.

A Turkish translation of the modified Rosenberg Questionnaire Form was used to assess body self-image and self-esteem (17). The first subsidiary was used for its relevance to self-image. Self-respect levels were categorized as high (0-1 points), average (2-4 points), or low (5-6 points) based on the scoring scheme.

Responses were evaluated concerning the chosen reconstructive technique, complications, necessity for re-operation, and whether NAC reconstruction had been performed.

Assessment of the aesthetic outcome

Standard frontal and lateral photos obtained from 26 consenting patients were anonymized, double-copied, and randomly numbered. These images were presented twice in random order to 10 residents, who assessed the aesthetic outcome using a visual analog scale. Anthropometric analyses using ImageJ™ (NIH, Bethesda, MD, USA) digital software were also performed on these images. Resultant breast symmetry was assessed clinically and through a comparison of breast indices based on breast mound volume/thoracic volume utilizing a method proposed by Bicer et al. (18).

Statistical methods

For the statistical analysis SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA) was used. Correlation analyses were carried out with Spearman's test. For the independent variables, group comparisons were made using Student's t-test for normally distributed data and the Mann Whitney U test for ordinal and non-normally distributed data. A Kruskal Wallis test for ordinal and non-normally distributed data and a one-way ANOVA test for normally distributed data were utilized when testing more than two groups. For the dependent variable analyses and for comparing paired samples, the dependent variable t-test was used for normally distributed dataset and the Wilcoxon signed-rank test for non-parametric comparisons. The Friedman test was utilized when addressing more than one time point. Post-hoc analyses were carried out using Tukey's test, the Mann-Whitney U test, or the Wilcoxon signed-rank test with Bonferroni corrections. Ratios were compared with the chi-square test when applicable or Fisher's exact test. The intraclass correlation coefficient (ICC) test was utilized to determine inter-observer reliability for the aesthetic scores, with the significance level being set at $p<0.05$.

RESULTS

Demographic data

The mean age of the patients (n=34) was 43.4 (±9.0). Four patients (11.7%) had in-situ lesions, while 28 patients (82.3%) had invasive lesions. Two patients (5.9%) had undergone a mastectomy for benign breast lesions. Sixteen patients (47.1%) had their right breast and 15 (44.1%) had their left breast removed. Three patients (8.8%) had bilateral pathology. Twenty-eight patients (82.4%) underwent modified radical mastectomies, while six (17.6%) underwent breast-sparing mastectomies. Table 1 summarizes the patients' demographic backgrounds.

Reconstruction methods

Half of the patients had their reconstruction at the time of their mastectomy surgery, while the other half received a delayed reconstruction. As for the reconstructive technique chosen, 10 (29.4%) had their reconstructions with the implant only, 15 (44.1%) with autogenous

Table 1: Patients' demographic characteristics

Age	43.4 (±9)
Age at diagnosis	40 (±8)
Body mass index	25.53 (±2.73)
Educational background	
Elementary school	5
Middle school	2
High school[a]	15
College/University	12
Occupation	
Housewife	12
Manufacturing	2
Service[a]	14
Retiree	6
Marital status	
Single	4
Married[a]	23
Divorced	7

a: Median value

tissue only, and nine (26.5%) with both implants and autogenous tissue. All the autogenous reconstructions were performed utilizing abdomen-based flaps (pedicled or free transverse rectus abdominis musculocutaneous flap, deep inferior epigastric artery perforator flap), except for one patient who had a superior gluteal artery perforator flap reconstruction and one whose reconstruction involved a freestyle perforator dermoglandular flap harvested from the contralateral breast. For the patients who underwent both autogenous and implant reconstructions, latissimus dorsi flaps (conventional musculocutaneous, open, or endoscopic) were used either to cover the implant or to increase the tissue bulk. Figure 1 exhibits the distribution of the reconstructive method undergone along with the timing, while Figure 2 exhibits the distribution of the method regarding whether pre-expansion of the breast pocket with a tissue expander had been used (Figures 1 and 2). Information on NAC reconstruction was relevant for 30 patients. At the time of the study, 12 (40%) had undergone NAC reconstruction, while 18 (60%) had not.

Complications

Six patients experienced serious complications related to the reconstructed breast, with necessity to reoperate being the determining factor for seriousness. For aesthetic reasons, 14 patients underwent revision surgeries (41.2%). Twelve patients (46.1%) had complications related to the

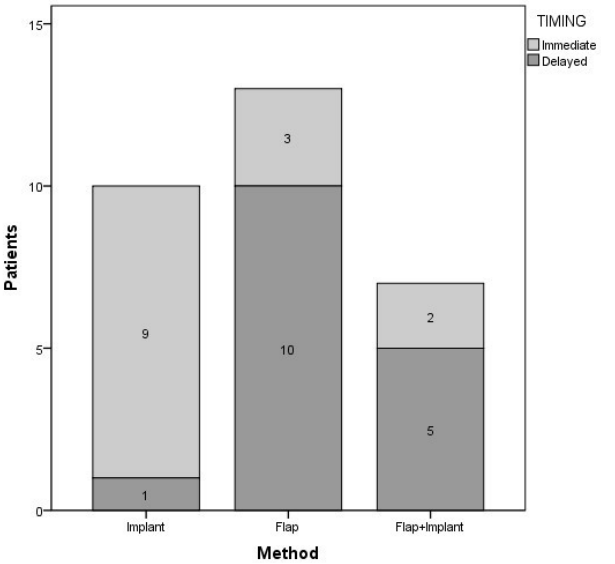

Figure 1: Patients are grouped according to timing and method of reconstruction.

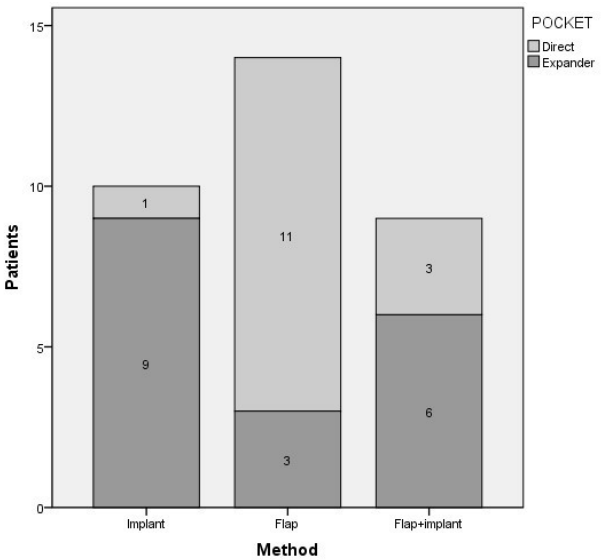

Figure 2: Patients are grouped according to pre-expansion with tissue expanders and method of reconstruction.

donor site, three had delayed wound healing (8.8%), nine patients had hypertrophic or atrophic scars (29%), one patient had an abdominal hernia (2.9%), and one patient experienced intractable pain at the donor site (2.9%).

Concerning the contralateral breast, 20 (5.8%) patients had contralateral breast surgery that included a reduction (n=10; 29.4%), augmentation (n=2; 5.8%), mastopexy (n=2; 5.8%), or mastectomy (n=6; 17.6%).

Social and familial support

With regard to the familial and social support questions,

five (14.7%) of the patients stated having inadequate familial support, 28 patients (82.4%) said it was adequate, and one patient (2.9%) stated it to be neither. All the patients stated receiving adequate support from the health care providers. Eleven patients (32.4%) stated that they had sought psychological help either from a psychiatry clinic or from a clinical psychologist, while 23 patients (67.6%) did not. Only five patients (14.7%) had joined a cancer support group during the disease process.

The patients' perceptions of their body and breast were found to be significantly higher than their perception of their breast image (p=0.011; Figure 3).

Factors affecting the outcome (satisfaction, symmetry, and aesthetic scores)

The type of mastectomy was not found to significantly affect overall patient satisfaction (p=0.727), aesthetic outcomes (p=0.166), or symmetry scores (p=0.208).

An excellent degree of reliability was found among the residents' aesthetic scores. The average ICC measurement was 0.958 (95% CI [0.931, 0.978]; p<0.001).

Having been treated with radiotherapy was associated with more frequent complications (p<0.001). However, neither radiotherapy (p=0.109) nor chemotherapy (p=0.523) significantly affected the aesthetic outcomes.

No significant association could be found between the timing of reconstruction and aesthetic results (p=0.538), symmetry (p=0.443), or patient satisfaction (p=0.830). Likewise, the reconstruction method (autogenous, implant, or both) was not found to affect aesthetic results (p=0.376), symmetry (p=0.205), or patient satisfaction (p=0.963).

As for NAC reconstruction, it contributed to significantly better aesthetic outcomes (p=0.026) and overall patient satisfaction (p=0.029).

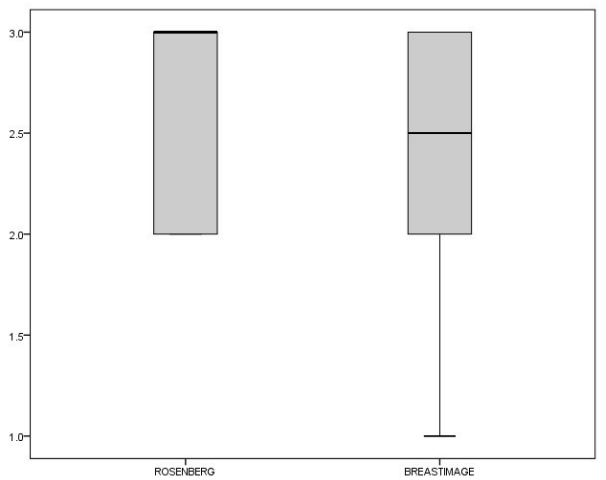

Figure 3: Patients' overall self-image was significantly better than their self-image of breast beauty (Wilcoxon signed-rank test, p=0.011).

Donor site morbidities were not found to be associated with significantly worse aesthetics (p=0.872) or satisfaction scores (p=0.187). However, scar issues were found to be the sole factor significantly affecting overall satisfaction scores (p=0.008) without significantly affecting the aesthetic outcome (p=0.757). Table 2 provides a summary of the factors that might influence satisfaction, aesthetic scores, and symmetry.

The patients described no change in their commitment to life throughout the disease and reconstruction processes (p=1.00). Their overall mood was found to be significantly improved after reconstruction (p=0.04). As for their sex life, patients experienced a decline after their cancer had been diagnosed and their breasts had been removed (p=0.007). However, no significant difference in their intercourse frequency could be found between the pre-diagnosis and post-revision periods (p=0.020, with significance being reset to 0.008 as per the Bonferroni correction while performing the pairwise post-hoc comparisons). Figure 4 presents the change in patients' sexual well-being (in terms of activity) throughout the disease and reconstruction processes.

DISCUSSION

The patients' average age (43.4) was found to be below the average age for mastectomies in the population. However, this average is comparable to the average age of patients who've undergone breast reconstruction (19). Rodby et al. found the average age for undergoing breast reconstruction to be 47 in the Caucasian population, 45.2 in the African American population, and 47.9 in the Hispanic population in their review study focusing on ethnic trends in breast reconstruction (20). Even in industrialized countries women requesting breast reconstruction tend to be younger than those who do not.

Working or retired workers comprised 64.7% of this study' patients. Due to the labor participation rate in an urban population in Turkey being 27.6%, women seeking breast reconstruction were found to be more likely to be involved in the workforce (21). Along with the female labor participation, the reverse pyramid seen in the education level of the women who participated in the study can be seen as another indicator that socioeconomic development level is a major factor for patients seeking or simply having the means to access breast reconstruction options.

Flap-related complications were seen in 16% of the patients, 25% of which resulted in flap loss necessitating proceeding with a salvage flap. The overall flap survival rate of 96% was found to be slightly higher than in the literature (22, 23). However, implant reconstructions result-

Table 2: Patient features with a potential to influence the outcome of breast reconstruction

	n (%)	Satisfaction score		Symmetry score		Aesthetic score	
Mastectomy type							
Breast sparing	6 (17.6%)	4 (IQR: 1)	p=0.727[a]	0.93 (IQR: 0.12)	p=0.208[a]	5.16 (±0.66)	
Modified radical mastectomy	28 (82.4%)	5 (IQR: 2)		0.85 (IQR: 0.27)		4.13 (±1.33)	
Radiotherapy							
Yes	12 (37.5%)	4 (IQR: 2)	p=0.381[a]	0.95 (IQR: 0.17)	p=0.317[a]	3.63 (±1.60)	p=0.109[b]
No	20 (62.5%)	5 (IQR: 3)		0.86 (IQR: 0.29)		4.56 (±1.10)	
Chemotherapy							
Yes	20 (60.6%)	5 (IQR: 2)	p=0.883[a]	0.86 (IQR: 0.29)	p=0.931[a]	4.44 (±1.61)	p=0.523[b]
No	13 (39.3%)	4 (IQR: 2)		0.89 (IQR: 0.28)		4.12 (±0.79)	
Timing							
Immediate	17 (50%)	4 (IQR: 2)	p=0.830[a]	0,83 (IQR: 0.25)	p=0.443[a]	4,18 (±0.99)	p=0.538[b]
Delayed	17 (50%)	5 (IQR: 2)		0.94 (IQR: 0.23)		4.51 (±1.59)	
Technique							
Autogenous	15 (44.1%)	4 (IQR: 3)	p=0.963[c]	0.94 (IQR: 0.19)	p=0.205[c]	4.88 (±1.57)	p=0.376[d]
Implant	10 (29.4%)	4 (IQR: 2)		0.74 (IQR: 0.28)		3.79 (±0.94)	
Implant+autogenous	9 (26.4%)	5 (IQR: 2)		0.85 (IQR: 0.27)		4.56 (±1.02)	
Recipient site preparation							
Direct	16 (47%)	5 (IQR: 2)	p=0.860[a]	0.94 (IQR: 0.19)	p=0.149[a]	4.85 (±1.51)	p=0.400[b]
Expander	18 (53%)	4 (IQR: 2)		0.85 (IQR: 0.28)		4.13 (±0.97)	
Nipple-areolar complex							
Not reconstructed	18 (60 %)	3 (IQR: 2)	**p=0.029[a]**	0.83 (IQR: 0.32)	p=0.250[a]	3.98 (±1.11)	**p=0.026[b]**
Reconstructed	12 (40 %)	5 (IQR: 1)		0.91 (IQR: 0.17)		4.98 (±1.20)	
Complications							
Scar problems	9 (29%)	3 (IQR: 1) **p=0.008[a]**		0.87 (IQR: 0.18) p=0.949[a]		4.84 (±1.14) p=0.757[b]	
Flap problems	4 (17.3%)	5 (IQR: 1) p=0.599[a]		0.95 (IQR: 0.02) p=0.233[a]		4.87 (±2.20) p=0.436[b]	
Donor site issues	12 (46.1%)	4 (IQR: 1) p=0.187[a]		0.90 (IQR: 0.16) p=0.191[a]		4.48 (±1.28) p=0.872[b]	
Implant problems	6 (33%)	4 (IQR: 2) p=0.817[a]		0.91 (IQR: 0.17) p=0.673[a]		4.39 (±0.76) p=0.702[b]	

a: Mann-Whitney U test, b: Two-samples t test, c: Kruskal-Wallis test, d: One-way ANOVA test
Statistically significant results are emphasized in bold print. Bu cümle ikici satıra kaydırılsın

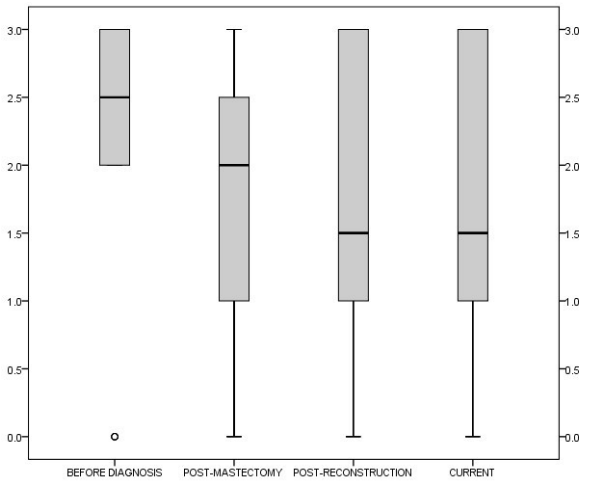

Figure 4: Patients experienced a decline after their cancer had been diagnosed and their breast(s) removed (Student's t test, p=0.007). However, no significant difference in their sexual intercourse frequency could be found between the pre-diagnosis and post-revision periods (ANOVA, p=0.020; significance was reset to 0.008 as per the Bonferroni correction while performing the pairwise post-hoc comparisons).

ed in serious complications in 24% of the patients. The reoperation rate with implant-based reconstructions was higher (16% vs. 24%). On the other hand, donor site morbidity and scar problems were mostly seen in patients who'd undergone autogenous reconstruction.

The patients exhibited a high perception of self-image, making this a pivotal factor in their decision-making process for reconstructive surgery. However, their self-image regarding breast appearance was comparatively lower, possibly influenced by the hindsight bias associated with the breast cancer diagnosis, leading some patients to associate their breasts with the cause of cancer.

Upon investigating the effects of reconstruction on patients' psyche, 88.2% reported a positive impact on their overall mood. Reconstructive surgery has been well established to be able to alleviate the negative emotional impact resulting from organ loss and the psychological burden of a cancer diagnosis (24-26). The main psychosocial drivers for women seeking reconstruction were identified as regaining self-image, eliminating external prosthetics, and a sense of regaining what had been lost (24).

Family bonds were found to be the main social support mechanism for the women in our study (82.4%). While social support is acknowledged as an effective tool in alleviating cancer-related stress and enhancing emotional well-being and self-esteem, access to support groups was notably low at 14.7% (25, 27, 28). This finding aligns with studies indicating varied preferences for social support groups among women from different countries and ethnic groups (29).

Regarding the four time points (i.e., pre-cancer diagnosis, post-mastectomy pre-reconstruction, post-reconstruction, and post-final revisions), patients noted a significant decline in the quality of their sex life which they attributed to the mutilating effects of the mastectomy compounded by radiotherapy, chemotherapy, and hormone therapy. With breast reconstruction, however, the patients reported a recovery to pre-cancer diagnosis levels over time, highlighting the positive impact of reconstruction (30, 31).

Among the factors determining patient satisfaction, NAC reconstruction and scar issues emerged as significant influencers. Notably, scar issues significantly affected patient satisfaction, contrary to patients' expectations, as only 11.8% had considered the absence of scar issues among their priorities. This discrepancy emphasizes the importance of addressing scar-related concerns during the reconstructive surgery decision-making process (32, 33).

The study revealed only 40% of the patients in our group to have opted for NAC reconstruction, with this factor significantly influencing patient satisfaction, which is in line with the existing literature (13, 34-36). Strikingly, scar issues also played a pivotal role in affecting patient satisfaction, emphasizing the significance of careful consideration and management of scarring issues in breast reconstruction. These findings concur with the current literature, which has recently explored the problem more and more. This issue is especially important as one of the most appreciated aspects of breast reconstruction, with abdomen-based flaps offering a bonus abdominoplasty (37). When patients are provided with the reconstruction options, they prefer abdomen-based flaps as they consider the donor site to be a dispensable bulk of tissue (38). However, this also yields the worst outcomes in terms of scar location (38). Even the more conspicuous scars of latissimus dorsi flaps were found to be preferable in a comparative study (39). This discrepancy can be explained by the differences in the tissue excised between abdomen-based flaps and abdominoplasty. In a study comparing the scar perceptions regarding abdominoplasty, conventional abdominal free flap harvest, and a hybrid approach, Li et al. found the hybrid approach to yield results comparable to abdominoplasty, both of which were significantly better than that of the conventional flap harvest (38). Reasonable explanations for this finding may involve how the high-riding scar placement includes sizable perforators located superior or around the umbilicus, as well as an inevitable undue tension at the suture lines due to the need for as much soft tissue as possible. The hybrid approach seems to circumvent this through the addition of an implant.

Neither timing nor method of reconstruction were found to influence patient satisfaction or aesthetic outcome. Although these findings appear a little controversial, they are in harmony with the results of similar studies (32). While autogenous abdominal-based options outweigh implant-based techniques regarding patient satisfaction rates, this trend tends to wane over time, thus diminishing any difference among groups (12, 40, 41).

Although the effects of NAC reconstruction on patient satisfaction could not be proven statistically, this factor was found to significantly influence the aesthetic outcomes. Another factor influencing this aspect was found to be radionecrosis. In this study, we found the presence of radionecrosis to significantly affect the aesthetic outcome.

This study has been able to make a detailed analysis of the outcome of breast reconstruction surgery. Patients seeking reconstruction have been able to be demographically profiled and their expectations from life, perception of body image, and mood mapped in detail.

The study's limitations include not being able to use comprehensive forms specifically targeting breast surgery, such as the Breast Reduction Assessed Severity Scale (BRASS), or BREAST-Q. However, BRASS is specific to breast reduction and not reconstruction, so its use was not warranted (42). Meanwhile, BREAST-Q has a module specifically targeting breast reconstruction (43). However initial reports with BREAST-Q were first published in 2009. Moreover, it was not translated into Turkish until recently, and our patients in this study had been polled before the this adapted form was introduced. We instead used a non-validated but nevertheless comprehensive form we invented. Future studies using the assessment scales mentioned above should be conducted to verify our results. Additionally, our survey was conducted after the cancer diagnosis, mastectomy, reconstruction, and their revisions had been experienced. A clearer image of these patients' psyches can be drawn if these surveys had been conducted before initiating treatment. Another shortcoming involves the limited number of patients in the study.

CONCLUSION

Every day, many women unfortunately face the diagnosis of breast cancer. Besides an undeniable sense of apprehension and fear for their lives, most of them have to undergo mastectomies, chemotherapy, radiotherapy, and hormonal therapy. Most of these therapeutic interventions alone or in combination are capable of damaging one's self-esteem, sense of self, sexuality, mood, commitment to life, and joy. Breast reconstruction is an integral part of the healing process. The appearance of the reconstructed breast may not be as important for the patients as the scars that remind them of their bitter past with cancer. Gaining insight into the expectations of women prior to undergoing reconstruction and listening to those who have already experienced the process are crucial steps in customizing a thoughtful and intentional approach to reconstruction.

Ethics Committee Approval: This study was approved by Istanbul University İstanbul Faculty of Medicine's Local Ethical Committee for Clinical Research (Date: 05.11.2023, No: 20).

Informed Consent: Informed consent was obtained from all participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.B., H.A., Ö.B.; Data Acquisition- A.B., Ç.D.A., E.G., B.Ç.Ö.; Data Analysis/Interpretation- A.B., H.A.; Drafting Manuscript- A.B.; Critical Revision of Manuscript- H.A., E.G., B.Ç.Ö.; Final Approval and Accountability- H.A., E.G., A.B., B.Ç.Ö., Ö.B.; Material or Technical Support- Ç.D.A., A.B., E.G.; Supervision- E.G., B.Ç.Ö., H.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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Appendix

ADDITIONAL FILE LEGENDS

Additional file. This survey contains 55 questions pertaining to the patients' demographic data, history, social and familial support, mood, sexual well-being, self-image, and satisfaction.

ADDITIONAL FILE

Additional File
Date:
Pollster:

DEMOGRAPHICS	
1. Name, Surname	
2. Age	
3. Occupation	
4. Marital Status	
5. Education Status	
6. Address	
7. Contact Number	
8. Height, Weight	

MEDICAL HISTORY-1				
9. Date of cancer diagnosis				
10. Diagnostic history	**10a.** Institution			
	University	Public	Private	
	10b. Mode of diagnosis			
	Self	Routine screening	Other	
	10c. Side			
	Right		Left	
	10d. Tumor location			
	Upper medial	Upper lateral	Lower medial	Lower lateral
11. Tumor type				
12. Mastectomy	Breast preservation	Skin preservation	Radical	
13. Axillary dissection Sentinel lymph node biopsy (SLNB)	+		-	
	SNB+	SLNB -	SLNB +	SLNB -
14. Chemotherapy	Yes		No	
15. Tamoxifen	Yes		No	
16. Radiotherapy	Yes		No	
17. Paramedical	Yes Type/Agent		No	
18. Prophylactic Mastectomy	Yes		No	

MEDICAL HISTORY-2		
19. Concommitant disease	Yes	No
	Type	
20. Menopause Status	Yes	No
	20a. Duration	
	20b. At time of diagnosis	
	Yes	No
	20c. Hormone replacement	
	Yes	No
21. Parity Status	**21a.** Number of children	
	21b. Age at first birth	
	21c. Birth method	
	C/S	Normal
	21d. Desire to have children	
	Present	Not present
22. Breast size before mastectomy	Cup: Size:	
23. Weight before mastectomy		

FORM 2

RECONSTRUCTION HISTORY				
24. Operator				
25. Timing	Simultaneous		Delayed	
26. Reconstruction	**26a.** Implant Expander, then implant			
	26b. Flap Expander ( ), latissimus dorsi and implant ( )			
	Open		Endoscopic	
	Expander ( ), Pedicled TRAM, implant ( ), delay ( ), muscle sparing ( )			
	Ipsilateral		Contralateral	Bilateral
	Expander ( ), Free TRAM, implant ( ), muscle sparing ( ), delay ( )			
	IMA		TDA	
	Expander ( ), Free DIEAP, implant ( )			
	IMA		TDA	
	Expander ( ), Free SGAP, implant ( )			
	IMA		TDA	
27. Revisions	**27a.** Flap Revision Timing Number **27b.** Fat grafts Timing Number **27c.** NAR ( ) Timing Number			

28. Contralateral breast	**28a.** Reduction ( ) Timing Technique Mastopexy ( ) **28b.** Augmentation ( ) Timing			
29. Complications	**29a.** Implant related			
	Capsule formation Rippling		Exposition, extrusion Infection	
	Solution			
	29b. Flap related			
	Total Flap Loss		Partial Loss	
	Arterial	Venous	Arterial	Venous
	Solution **29c.** Donor site morbidity Wound problems Solution Scar problems Solution Hernia, bulging Solution Contracture Solution Other Solution **29d.** Systemic complications **29e.** ICU Stay ( )			

PHYSICAL EXAMINATION			
30. Breast type	Glandular	Tuberous	Lipomatose
31. Scar	Atrophic		Hypertrophic
32. Radionecrosis			
33. Aesthetics			

FORM 3

PSYCHOSOCIAL			
34. Affective state before diagnosis	Good	Medium	Low
35. Psychiatric illness before diagnosis	Present	Non-present	
36. Overcoming the stress of diagnosis	Within a year		
	1-2 years		
	>2 years		
37. Current affective state	Good	Medium	Low
38. Effect of reconstruction on affective state	Positive		
	Negative		
39. Commitment to life before diagnosis	Good	Medium	Low
40. Commitment to life (current)	Good	Medium	Low

41. Awareness method for breast reconstruction	Oncologic team		
	Support groups		
	Breast Cancer Foundation of Turkey	The Turkish Federation of Breast Diseases Societies	
	Relatives		
	Media		
	Internet/Research		
42. Paternalism vs self-determining medical process	Self-determined		
	Paternalised		
43. Sexual well being	**43a.** Before diagnosis		
	Good	Medium	Low
	43b. Before reconstruction after mastectomy		
	Good	Medium	Low
	43c. Before final revision after reconstruction		
	Good	Medium	Low
	43d. After final revision		
	Good	Medium	Low

SUPPORT		
44. Family	Satisfactory	Not satisfactory
45. Medical personnel	Satisfactory	Not satisfactory
46. Psychiatry	Consulted	Not consulted
47. Support groups	Breast Cancer Foundation of Turkey	
	The Turkish Federation of Breast Diseases Societies	
	Other	

(PERCEPTION OF BODY AND PREDISPOSITIONS)

48. Body image, RBSO	Good	Medium	Low
49. Body image before diagnosis	Good	Medium	Low
50. Expectations	Likeness to unaffected breast		
	Larger than unaffected breast		
	Smaller than unaffected breast		
51. Predispositions	Scar problems, and lack thereof		
	Form of reconstructed breast without clothing		
	Form of breast with a dress		
	No aesthetic predispositions, just regaining what was lost		

SATISFACTION		
52. Are expectations met after final revisions?	Largely	
	Some	
	Near to none	
53. Overall satisfaction	Yes	No
	* Scars ( ), Form/aesthetics ( ), Size Large ( ), Size Small ( )	
54. Donor site content	Content	
	Discontent	
55. Offer breast reconstruction to others?	Yes	
	No, because…	

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THE EVALUATION OF MALNUTRITION WITH PREOPERATIVE Z SCORE ANALYSES IN PATIENTS WITH VEAU TYPE 1 AND TYPE 2 CLEFT PALATE

VEAU TİP 1 VE TİP 2 DAMAK YARIĞI OLGULARINDA AMELİYAT ÖNCESİ Z SKORU ANALİZİ İLE MALNUTRİSYONUN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Cleft lip and palate are the most common congenital anomalies of the head and neck region. According to studies, 13.5% of children under 5 years of age were reported to be underweight. When compared with the global data, this ratio was found to be higher in patients with isolated cleft lip, isolated cleft palate, and cleft lip with cleft palate. This study aimed to evaluate the frequency of malnutrition in isolated Veau type 1 and type 2 cleft palate in an institutional patient group.

Material and Methods: Patients with isolated Veau type 1 and type 2 cleft palate who were operated between November 2019 and February 2022 were included in the study. The age (month), height (centimeters), and weight (kilograms) of the patients were noted one day before the surgery, and Z scores were calculated for malnutrition assessment.

Result: A total of 40 patients were included in this study. The mean age of the patients was 16.82±2.73 months (7-48 months). Fourteen patients were male whereas 26 patients were female. Malnutrition was not observed in nine patients. Eight patients had chronic mild malnutrition, 5 patients had chronic moderate malnutrition and 13 patients had chronic severe malnutrition. In addition, chronic mild obesity was observed in two patients,

ÖZET

Amaç: Dudak ve damak yarıkları baş boyun bölgesinin en sık görülen konjenital anomalisidir. Çalışmalara göre 5 yaş altı çocukların %13,5'u normalden zayıf olarak bildirilmiştir. Bu veri ile global veriler kıyaslandığında izole dudak, izole damak ve hem dudak hem damak yarığı nedeniyle ilk kez ameliyat edilecek hastalarda bu oran daha yüksek bulunmuştur. Bu çalışmanın amacı izole Veau tip 1 ve tip 2 damak yarıklarında malnütrisyon görülme sıklığının kurumumuzun hasta grubunda değerlendirilmesidir.

Gereç ve Yöntem: Çalışmaya Kasım 2019 ve Şubat 2022 tarihleri arasında Anabilim Dalımıza başvuran izole Veau tip 1 ve tip 2 damak yarığı olan hastalar dahil edilmiştir. Hastaların ameliyattan bir gün önceki yaşı (ay), boyu (santimetre), ağırlığı (kilogram) değerleri not edilmiş olup malnütrisyon değerlendirmesi için Z skorları hesaplanmıştır.

Bulgular: Çalışmaya toplamda 40 hasta dahil edildi. Hastaların ortalama yaşı 16.82±2.73 (7-48 ay) idi. Hastaların 14'ü erkek ve 26'sı kızdı. Dokuz hastada malnütrisyon izlenmedi. Sekiz hastada kronik hafif malnütrisyon, beş hastada kronik orta malnütrisyon, on üç hastada kronik ağır malnütrisyon izlendi. Ayrıca iki hastada kronik hafif şişmanlık, iki hastada kronik orta şişmanlık ve bir

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chronic moderate obesity was observed in two patients, and chronic severe obesity was observed in one patient. In total, malnutrition was observed in 65% of the patients.

Conclusion: One of the most important problems in patients with cleft palate is feeding. Inadequate nutrition predisposes to malnutrition in the preoperative period. To prevent this situation, the patients should be referred for prompt professional nutritionist care and early follow-up.

Keywords: Cleft lip, growth restriction, malnutrition, secondary cleft palate, Z score

hastada kronik ağır şişmanlık izlendi. Toplamda %65 hastada malnütrisyon izlendi.

Sonuç: Damak yarığı olan hastalarda karşımıza çıkan en önemli sorunlardan biri beslenmedir. Yeterli beslenmenin yapılamaması cerrahi öncesi dönemde malnütrisyona zemin hazırlamaktadır. Bu durumun önüne geçilmesi için hastalar hemen profesyonel beslenme uzmanı desteğine ve erken takibe yönlendirilmelidir.

Anahtar Kelimeler: Büyüme geriliği, dudak yarığı, malnutrisyon, sekonder damak yarığı, Z skoru

INTRODUCTION

Cleft lip and palate are the most common congenital anomalies of the head and neck region. They may be associated with syndromes; however, isolated cleft lip and palate are seen more frequently. Although the incidence varies depending on race, cleft lip and palate are seen approximately one in every thousand births (1). While multifactorial causes are observed in the etiology, genetic and physical factors play a significant role. Although different systems are used in the classification of cleft palate, the Veau classification is the most preferred one (Table 1).

Table 1: Veau Classification

Type 1	Incomplete, cleft of soft palate
Type 2	Incomplete, cleft of soft and hard palate
Type 3	Complete unilateral cleft of primary and secondary palate
Type 4	Complete bilateral cleft of primary and secondary palate

Children with cleft lip and palate should be followed up with a multidisciplinary approach beginning from birth. Patients with cleft lip and palate should be followed up by plastic reconstructive and aesthetic surgeons, otorhinolaryngologists, pediatricians, dentists, orthodontists, and speech therapists. Their anomalies predispose these children to difficulties in feeding. Due to the patients' inability to create sufficient oral competency, inability to create negative pressure during breastfeeding, and predisposition to upper respiratory tract infections; malnutrition and related growth retardation may be observed.

According to studies, 13.5% of children under five years of age were reported to be underweight (2). When compared with global data, this rate was found to be higher in patients with isolated cleft lip, isolated cleft palate, and cleft lip and cleft palate (3,4). Also, there is a higher incidence of postoperative complications in children with malnutrition. Studies have shown that fistula formation which is a complication of the cleft palate operation is more common in malnourished children (5).

Cleft palate anomaly is frequently seen both in our country and in the world and patients with cleft palate are followed up preoperatively and postoperatively. This study aimed to evaluate the frequency of malnutrition in isolated Veau type 1 and type 2 cleft palate in an institutional patient group.

MATERIALS and METHODS

Patients with isolated Veau type 1 and type 2 cleft palate who were operated between November 2019 and February 2022 were included in the study. Patients with an associated syndrome and patients with cleft lip were not included in the study. Age (month), height (centimeters), and weight (kilograms) of the patients were noted one day before the surgery, and Z scores were calculated for malnutrition assessment. The child growth standards of the World Health Organization (WHO) were taken into consideration in the calculation of the Z scores (6).

The study protocol was approved by the Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 28.04.2023, No: 09). All data were anonymized, and the informed consents of the patients were recorded.

The Z Scores (height for age) of 0 to +1 and -1 were considered normal (2). The values of -1 and -2 were considered mild malnutrition and the values of -2 and -3 were considered moderate malnutrition (2,3). Severe malnutrition was accepted as value that were below -3. The values of +1 and +2, +2 and +3, and +3 and above were considered as chronic mild, chronic moderate, and chronic severe obesity respectively (2,3).

RESULTS

A total of 40 patients were included in the study. Fourteen of the patients were male and 26 patients were female. Demographic characteristics of the patients are shown in Table 2. Malnutrition was not observed in nine patients. Eight patients had chronic mild malnutrition, five patients had chronic moderate malnutrition and 13 patients had chronic severe malnutrition. In addition, chronic mild obesity was observed in two patients, chronic moderate obesity was observed in two patients, and chronic severe obesity was observed in one patient. In total, chronic

Table 2: Patients' demographic characteristics and Z-Score results

Patient number	Age (month)	Weight (kg)	Height (cm)	Weighing by age	Height by age	Weighing by height	Z-Score for chronic malnutrition (Height by age)	Z-Score for acute malnutrition (Weighing by height)
1	20	10	67	-0.6	-5.33	2.96	Severe	Normal
2	19	6.8	67	-3.74	-5.18	-1.14	Severe	Mild
3	19	10	70	-1.05	-4.93	2.02	Severe	Normal
4	22	9	73	-2.43	-4.56	-0.12	Severe	Normal
5	11	8	63	-0.83	-4.11	2.01	Severe	Normal
6	11.5	8	64	-0.94	-3.93	1.65	Severe	Normal
7	16	12	71	1.1	-3.73	3.84	Severe	Normal
8	18	9	71	-1.15	-3.49	0.79	Severe	Normal
9	26	7	79	-4.79	-3.41	-4.66	Severe	Severe
10	13	9	67	-0.26	-3.34	1.9	Severe	Normal
11	11	8.3	65	-0.53	-3.32	1.69	Severe	Normal
12	7	7	61	-0.9	-3.02	1.42	Severe	Normal
13	48	13	90	-1.63	-3.02	0.31	Severe	Normal
14	16	10	74	-0.55	-2.59	0.87	Moderate	Normal
15	22	12	79	0.1	-2.54	1.83	Moderate	Normal
16	16	10.5	75	-0.11	-2.2	1.18	Moderate	Normal
17	30	12.5	84	-0.2	-2.19	1.42	Moderate	Normal
18	13	7	72	-3.11	-2.05	-2.99	Moderate	Moderately
19	11	8	69	-0.89	-1.89	0.06	Mild	Normal
20	10	6.7	68	-2.18	-1.83	-1.64	Mild	Mild
21	19	10.8	79	-0.36	-1.7	0.61	Mild	Normal
22	9	8	69	-1.13	-1.64	-0.3	Mild	Normal
23	17	12	78	0.92	-1.41	2.03	Mild	Normal
24	18	10.5	78	0.08	-1.2	0.87	Mild	Normal
25	48	18	98	0.76	-1.17	2.18	Mild	Normal
26	17	12	77	1.35	-1.11	2.47	Mild	Normal
27	13	10.2	75	0.29	-0.81	0.84	No malnutrition	Normal
28	14	8.5	75	-0.91	-0.71	-0.83	No malnutrition	Normal
29	4	6.5	62	-0.23	-0.53	0.21	No malnutrition	Normal
30	18	10	80	-0.27	-0.42	-0.1	No malnutrition	Normal
31	8	8	69	-0.1	-0.21	0.06	No malnutrition	Normal
32	18	13	83	1.41	-0.03	1.92	No malnutrition	Normal
33	14	11	80	0.69	0.56	0.61	No malnutrition	Normal
34	14	9	74	0.69	0.56	0.61	No malnutrition	Normal
35	18	10	84	-0.27	0.94	-1.07	No malnutrition	Mild
36	10	9.5	75	0.79	1.12	0.42	Mild Obesity	Normal
37	14	11.8	82	1.33	1.36	1.02	Mild Obesity	Normal
38	15	12	84	1.68	2.14	0.98	Moderate Obesity	Normal
39	15	12.5	85	1.99	2.5	1.19	Moderate Obesity	Normal
40	11	11.5	85	1.72	4.15	0	Severe Obesity	Normal

malnutrition was observed in 65% of the patients. Also, Z score evaluation was performed by calculating weight-for-height values to determine acute energy malnutrition. Thirty-five children were found to be normal. However, three children had mild, one child had moderate, and one child had severe acute malnutrition.

DISCUSSION

Cleft palate is a common anomaly worldwide and one of the most important problems of these patients is feeding. These children have difficulty in sucking and they cannot create sufficient intraoral negative pressure. For these reasons, alternative methods have been designed for feeding patients with cleft palate. Some special feeding bottles, bowls, and syringes may facilitate feeding in these babies in the preoperative period (7,8).

The patients' parents should be informed about this anomaly both prenatally and postnatally and the patients should be referred to a multidisciplinary center. In the preoperative period, the family should be informed about specific conditions such as feeding difficulties and growth restriction. The patients should be referred to plastic, reconstructive, and aesthetic surgery for the surveillance of the maxillofacial development, orthodontics for dental development, otorhinolaryngology for hearing problems and possible otitis and upper respiratory tract infections, speech therapist for articulation, and Pediatrics for growth monitoring and follow-up.

The development of the child plays an important role in the surgical timing of the cleft palate repair. The weight, the hemoglobin level, and the age of the patient are considered for the timing of the surgery. In general, cleft palate surgery should be performed before 12 months of age; in fact, the timing is determined by the speaking ability of the children. For this reason, nutritional support is important to avoid any delays in the operation.

Z-score analysis is a WHO-recommended method that is frequently used to monitor the growth and development of children. It is recommended to calculate and evaluate the population-based Z scores by assessing anthropometric measurements such as height, weight, and BMI. These Z scores help the physicians in evaluating the development and detecting the malnutrition of the pediatric group (9).

In the preoperative period, patients with insufficient nutrition are susceptible to comorbidities such as upper respiratory tract infections and otitis (10). These recurring clinical conditions may deepen the malnutrition of the patients (10). Some studies show that preoperative malnutrition causes an increase in postoperative complications (5).

The underweight ratio was found to be higher in patients with cleft palate. According to the results of this study, chronic malnutrition was observed in 65% of the patients with isolated cleft palate. Thus, the prevalence of malnutrition was four-fold higher in the cleft palate population compared to the general population. However, 66% of the children were in the normal range for acute energy malnutrition. These children are prone to chronic rather than acute malnutrition and this finding may be attributed to the growth hormone deficiencies in cleft lip and palate patients (11). This finding underscores the significance of preoperative nutritional counseling for these patients.

The syndromic patients and cleft lip patients were excluded from this study to avoid the confounding effects of their comorbidities. Future studies may be performed with a larger cohort and with other Veau types; in fact, the Veau types may be compared according to the severity of malnutrition.

Cleft lip and cleft palate are significantly more prevalent in impoverished communities. However, a population-matched correction and a maternal nutritional status assessment were not performed in this study. They may be regarded as the limitations of this study.

CONCLUSION

To prevent chronic malnutrition during the presurgical period, the patients should be followed up in a multidisciplinary manner, and the patients should be referred to professional nutritionists.

Ethics Committee Approval: This study was approved by İstanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 28.04.2023, No: 09).

Informed Consent: All data were anonymized, and the informed consents of the patients were recorded.

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EFFECTS OF MOBILE- AND FIXED-BEARING TIBIAL INSERTS ON CLINICAL RESULTS OF KNEE ARTHROPLASTY: A RETROSPECTIVE STUDY

TOTAL DİZ ARTROPLASTİSİNDE, HAREKETLİ VE SABİT TASARIMLI TİBİAL İNSERT KULLANIMININ KLİNİK SONUÇLARA ETKİSİ: RETROSPEKTİF ÇALIŞMA

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ABSTRACT

Objective: Total knee replacement (TKR) procedures are widely used in cases of advanced knee osteoarthritis, and satisfactory results are achieved. Although the fixed-bearing (FB) design has been reported as the gold standard by many authors, the mobile-bearing (MB) design has been argued to have more harmonious articulation and to cause less contact stress on the joint surface. This study aims to compare mobile-bearing and fixed-bearing total knee replacement designs and presenting the clinical outcomes.

Material and Methods: The study includes 212 patients who've undergone MB and FB implants with identical design, had at least three years of follow-ups, and had their range of motion, pain scores, implant survival, and functional scores recorded.

Result: When comparing the MB and FB designs, the MB group has 106 cases with an average age of 63.1±8.0, and the FB group has 116 cases with an average age of 63.9±7.0 years; no significant difference was observed between the groups. Also, no significant difference was observed regarding Knee Society scores (KSS), range of motion (ROM), or visual analogue scales (VAS) between the first year and last follow-up. The mean follow-up times of the two groups are 62.4 months (range=38-92) for the MB group and 66.8 months (range=40-88) for the FB group. Each group also had similar complication rates.

Conclusion: The clinical and functional results for both the MB- and FB-design total knee prostheses are excellent. Despite the many theoretical advantages of MB total knee replacement, this study shows little significant difference in the early functional outcomes between MB and FB prostheses. The study concludes neither MB- or FB-design TKR to have clinically superiority.

Keywords: Total knee replacement, mobile bearing, fixed bearing, prosthesis loosening, prosthesis survival

ÖZET

Amaç: Total diz replasmanı prosedürü ileri evre diz osteoartriti vakalarında yaygın olarak kullanılmakta ve tatmin edici sonuçlara ulaşılmaktadır. Sabit tasarımlı dizaynlar birçok yazar tarafından altın standart olarak bildirilmişken, hareketli tasarımlı dizaynların daha uyumlu eklemleşmesi ve buna bağlı eklem yüzeyinde düşük temas stresinin olduğu düşünülmektedir. Bu çalışmanın amacı, mobil ve sabit insert total diz protezi tasarımlarını karşılaştırmak ve klinik sonuçları bildirmektir.

Gereç ve Yöntem: Çalışmaya hareketli ve sabit tasarımlı özdeş implantlar uygulanan ve en az üç yıl takip edilen 212 hasta dahil edildi. Hastaların eklem hareket açıklığı, ağrı skorları, implant sağ kalımı ve fonksiyonel skorları kaydedildi.

Bulgular: Hareketli ve sabit tasarımlı dizaynlar karşılaştırıldığında sırasıyla gruplardaki olgu sayısı 106 ve 116 iken, ortalama yaş 63,1±8,0 ve 63,9±7,0 idi ve anlamlı fark izlenmedi. Birinci yıl ve son takipte Diz Cemiyeti skoru (KSS), eklem hareket açıklığı and vizuel analog skala (VAS) açısından anlamlı fark izlenmedi. İki grubun ortalama takip süreleri sırasıyla 62,4 (38-92) ve 66,8 (40-88) ay idi. Komplikasyon oranları her grup için benzerdi.

Sonuç: Hareketli ve sabit tasarımlı total diz protezlerinin klinik ve fonksiyonel sonuçları mükemmeldir. Hareketli insert tasarımlı total diz protezinin birçok teorik avantajına rağmen, bu çalışma iki grup arasında erken fonksiyonel sonuçlarda çok az anlamlı fark gösterdi. Çalışma sonucunda, hareketli ve sabit tasarımlı total diz protezlerinin klinik olarak birbirinden üstün olmadığı görüşüne varılmıştır.

Anahtar Kelimeler: Total diz protezi, hareketli insert, sabit insert, protez aşınması, protez sağkalımı

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INTRODUCTION

Total knee replacement (TKR) applications are widely used in cases of advanced knee osteoarthritis, and satisfactory results are achieved (1). The literature reports a 20+ year survival rate of up to 90-95% (2). While the TKR procedure has been supported by many studies in which satisfactory results were obtained in patients, which type of design is more successful remains unclear.

The clinical success of fixed-bearing (FB) design total knee arthroplasty has been reported as the gold standard by many accepted authors in the literature. Publications are found to have reported excellent results for FB prostheses of various condylar designs, different tibial surfaces, and with or without patellar surface changes, as well as cases in which the posterior cruciate ligament was cut or preserved in situ (3). Meanwhile, fewer publications are found to provide similar results for mobile-bearing (MB) design TKRs (4-6). However, MB designs have some theoretical advantages over FB designs. MB tibial inserts are considered to have a more harmonious articulation and therefore cause less contact stress at the articular surface. This mobility also results in a reduction of stress at the bone-implant interface. Therefore, polyethylene has been argued to be able to wear down slower and primary prosthesis survival to last longer. Polyethylene has also been argued to be able to tolerate mild femoral and tibial rotation errors without adverse effects on patellar alignment. Based on this, knee pain has also theoretically been predicted to be less (4).

Despite these theoretical advantages MB prostheses have, no documented improvement appears to exist regarding functional outcomes compared to FB designs (5-9).

The aim of this study is to reveal the clinical and radiological short-term results of knee replacement surgery in two mostly identical ways, the only difference being whether the tibial insert is mobile or fixed and which is better in terms of prosthesis survival.

MATERIALS and METHODS

Study population

The study population comprises an archive of total knee arthroplasties performed in the orthopedics and traumatology clinic of the third-level hospital where the study has been conducted.

Study design and participants

This study is a retrospective study that includes a total of 278 patients who underwent total knee arthroplasty in an orthopedics and traumatology clinic between January 2015-January 2020. The participants were selected according to standard protocols, and those who did not meet the criteria were excluded from the study. The study includes 212 patients who underwent MB or FB implants of identical design and had at least three years of follow-ups. One week before surgery, a physical exam occurred after the pre-operative anesthesia exam. The participants' demographic information, implant selection, and measurement planning were recorded before the operation.

Inclusion criteria

- 40-80 years old
- Having undergone MB- or FB-design total knee prosthesis due to last stage gonarthrosis.

Exclusion criteria

- Less than three years of follow-ups
- Unmanaged neurological/psychiatric disorder(s)
- Chronic renal insufficiency
- Presence of drug addiction or substance abuse for any reason

One day before surgery, informed consent was obtained from the participants after being briefed on the surgical, rehabilitation, and treatment protocols. Standard inpatient evaluations were followed on the first, second, and third days of the postoperative period. The surgical results of the patients were reevaluated, and the patient study also recorded control data.

The files of the patients who underwent TKR surgery in the clinic between 2015-2020 were reviewed and evaluated according to the inclusion and exclusion criteria. The data of the patients who continued their follow-ups regularly for one year after surgery and who had at least three years of follow-ups were analyzed.

This retrospective study has identified two groups:

Group 1: MB tibial insert design implant group following standard TKR surgical procedures.

Group 2: FB tibial insert design implant group following standard TKR surgical procedures.

Surgical technique

Participants were prepared for surgery under spinal anesthesia in the supine position with the application of lateral support. A midline incision was made following standard sterilization procedures, and the skin and subcutaneous tissue were dissected. Arthrotomy was initiated 5 mm lateral to the vastus medialis muscle of the joint capsule and 3 cm above the patella and completed by leaving a 5 mm tissue layer between the patella and capsule. The tourniquet, prepared before the operation, was not used at the start of the surgery but was inflated after the completion of the incisions, and the washing procedure was then begun. Cruciate ligaments were excised. For both prostheses, intramedullary alignment was used for the femur and extramedullary alignment for the tibia. Tibial and femo-

ral cuts are made according to a previously determined design. Appropriate soft tissue releases were applied to adjust the alignment in both groups. These are inflated once the cuts are completed, and the washing process begins. Following the implantation and completion of the cement reaction, the tourniquet is deflated, and bleeding control is achieved. No drain is used. Following implantation, the capsule and soft tissues are closed up. All patients receive 24 h of antibiotics. Low-dose warfarin is used for thromboprophylaxis.

After the operation, the first outpatient clinical follow-up occurs in the third month, the second in the sixth month, and the third one year later after the standard inpatient evaluation on the first day, with standard follow-ups then occurring annually.

The patients are provided range of motion (ROM) therapy on the joint on the 1st, 2nd, and 3rd days post-operation using the standard rehabilitation program.

Superficial and deep soft tissue complications and treatments performed during the 1st, 2nd, and 3rd days of the patients' post-operation hospitalization are recorded in the same system.

Primary outcomes involve the Knee Society score (KSS) and prosthesis survival. Secondary outcomes involve visual analogue scales (VAS), ROM, and complications.

The patients' functional KSS, ROM, and VAS values are recorded during the annual checkups during the postoperative period (10).

Patients who are called in for their final checkup have anteroposterior x-rays taken. A bone defect classification is assessed based on this and according to the Aori classification, and the stability between the components and the bone interface are evaluated. The prosthesis survival times of patients who lose stability and undergo revision are recorded (11).

This study was approved by the Kirsehir Ahi Evran Faculty of Medicine Clinical Research Ethics Committee (Date: 05.09.2023, No: 15/98).

Power analysis

Power analysis was performed to determine the sample size, with an effect size of d=0.75, Power (1-β)=0.90, and allocation ratio=1 being assumed. As a result, the minimum sample size has been calculated as 39 people in each group.

Statistical analysis

The analyses were conducted using the software program SPSS ver. 26 (IBM SPSS Corp., Armonk, NY, USA). The variables' normality of the data was examined using the Kolmogorov-Smirnov test. The Mann–Whitney U test was used to compare two independent groups, while the Friedman test was used for repeated measurements of more than two groups. In the case of significant differences, Bonferroni-corrected p-values were considered for multiple comparisons. Relationships between categorical variables were examined using chi-square tests. A significance level of $p<0.05$ is considered statistically significant for all analyses.

RESULTS

According to the research groups, no significant difference was observed among the patients in terms of age, gender, or the side operated upon ($p>0.05$) However, the body mass index (BMI) values were determined to be dissimilar between the groups. A statistical difference was found between the groups, with BMI being significantly higher in the FB group ($p<0.05$). The mean follow-up times of the two groups are 64.4 (38-92) and 66.8 (40-88) months, respectively. The mean follow-up times are similar for the two groups (Table 1).

Table 1: Demographic data

	MB	FB	p
Male **Female**	42 64	48 68	0.403
Side - Right **Side - Left**	56 50	56 60	0.339
Age	63.1±8.0	63.9±7.0	0.266
BMI	31.2±2.1	37.2±1.9	<0.001
Mean (range) number of Follow-up months	64.4 (38-92)	66.8 (40-88)	0.078

MB: Mobile bearing, FB: Fixed bearing, BMI: Body mass index

According to the research groups, no significant difference was observed in terms of the VAS and KSS values measured during the 1st year and final follow-up post-surgery. However, significant differences were identified between the ROM values measured during the 1st year and final follow-up post-surgery ($p<0.05$). Prosthesis survival was similar in the MB and FB groups, both at 103/106 (97.1%; Table 2).

When examining the osteolysis areas in the femur and tibia according to the Aori classification in the final checkups, the two groups were found to be similar (Table 3).

The complication rates are similar for each group (Table 4). Revision surgery was performed in two patients in the FB group as a result of persistent pain. Revision surgery was needed in 1 patient in the MB group due to per-

Table 2: Clinical results at first year and last follow-up

	MB group	FB group	p
VAS score, mean ± SD (1st year checkup)	1.7±1.4	1.8±1.5	0.922
VAS score, mean ± SD (last follow up)	1.5±1.3	1.7±1.5	0.783
KSS score (1st year)	91.8±2.1	91.4±1.8	0.846
KSS score (last follow up)	93.4±1.8	92.8±1.5	0.821
ROM (1st year)	114.9±1.8°	105.6±1.6°	0.004
ROM (last follow-up)	116.8±2.2°	108.8±1.4°	0.006
Prosthesis survival	103/106 (97.1%)	113/116 (97.4%)	0.893

MB: Mobile bearing, FB: Fixed bearing, VAS: Visual Analogue Scale, SD: Standard deviation, KSS: Knee Society score, ROM: Range of motion

Table 3: Radiographic results

Radiolucent lines	MB	FB
Overall, n (%)	10 (9%)	9 (8%)
Tibia (n)		
0–4 mm	6	7
5–9 mm	3	2
≥ 10 mm	1	-
Aori classification		
Type 1	4	5
Type 2a	3	3
Type 2b	2	1
Type 3	1	-

MB: Mobile bearing, FB: Fixed bearing, n: number

Table 4: Complications

	MB group	FB group
Overall, n (%)	3 (2.8%)	3 (2.5%)
Aseptic loosening	1	-
Deep infection	1	1
Persistent pain	1	2

MB: Mobile bearing, FB: Fixed bearing, n: number

sistent pain. While revision was performed in one patient because of aseptic loosening, one patient had significant loosening findings in radiology (Aori type 3). A periprosthetic joint infection (PJI) occurred in one patient from each group, as well as one case where someone had undergone two-stage revision surgery due to this.

DISCUSSION

FB-designed TKR has been used for many years, and publications are found in the literature to have reported excellent long-term results with follow-up periods of 10 to 17 years (12-15). However, aseptic loosening developments still occur at an undesired level (16-18). To make up for this, MB-designed knee arthroplasty was promoted in the late 1970s with several potential advantages over conventional FB (19, 20).

Despite the many theoretical advantages of MB total knee replacement, this study has shown little significant difference in early functional outcomes between MB and FB prostheses. These results are supported by several other studies showing no significant difference in outcomes between FB and MB implants (4-8).

Another theoretical advantage of the MB prosthesis is the improved functional performance of the knee. This study found no difference between the two groups in terms of residual pain, functional outcome, or range of motion, which is consistent with similar studies in the literature (21-25).

Similar to Harrington et al.'s study, the current study noted ROM values to be slightly better in the MB group at the 1st year checkup. Contrary to Harrington et al., however, although the difference in the final checkup had decreased, it did not become statistically insignificant (26).

Ranawat et al.'s short-term follow-up study found that, after the bilateral TKR procedure, no significant difference occurred in terms of clinical or functional results. These results are largely consistent with those of the current study (7). However, another multicenter study found better results in MB designs regarding functional knee scores during the 1st-year checkup (24).

Another advantage of the MB design is that the tibia can be aligned under the femur by itself, thus minimizing malposition in the tibial component. This has been hypothesized to be able to improve patellofemoral tracking and reduce patellofemoral pain; however, the current study was unable to prove this.

Another hypothesis is that MB TKRs minimize component loosening and polyethylene wear. The present study found no significant difference regarding polyethylene wear or related osteolysis and component loosening, and the literature generally reports results in line with this (5, 22). In fact, Huang et al. reported significantly more osteolysis to have occurred in their MB design patient group They argued that, as a possible cause of this osteolysis, which is more prominent on the femoral side, smaller polyethylene particles may occur due to abrasion between both the compatible articular surface and

the tibial baseplate surface, and that they may undergo phagocytosis (27).

When evaluated in terms of postoperative late period pain, studies have examined many scores such as the KSS pain score, Oxford knee pain score, Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scale, and VAS and generally found no significant differences between the MB and FB designs (5, 8, 23, 24, 30-34).

The potential disadvantages of the MB design include higher implant costs and insert dislocations (28, 29). This dislocation has been reported in the literature, but no significant differences could be detected (24, 35, 36). The current study did find insert dislocation to have occurred in one patient in the MB group, but the problem was solved with one large insert change without the need for component revision.

The major limitation of this study is its retrospective nature. The second major limitation is the use of similar types of prostheses from different brands. In addition, although the groups in this study had an average follow-up of five years, even longer follow-up periods may be required to understand whether one design is more successful against loosening.

CONCLUSION

In conclusion, the current study's participants had a mean follow-up period of five years, no significant difference found regarding function, pain, ROM, or signs of radiological loosening between the MB- and FB-design total knee arthroplasty. The study feels that having the surgeon synthesize the patient's characteristics and experience when choosing the appropriate implant would be appropriate.

Ethics Committee Approval: The study has ethical approval from the Kırşehir Ahi Evran Faculty of Medicine Clinical Research Ethics Committee (Date: 05.09.2023, No: 2023-15/98).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer Review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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CASE REPORT / OLGU SUNUMU
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METHEMOGLOBINEMIA WITH NEUROLOGICAL MANIFESTATIONS: A CASE OF RECESSIVE CONGENITAL METHEMOGLOBINEMIA TYPE II

NÖROLOJİK BULGULARLA BİRLİKTE OLAN METHEMOGLOBİNEMİ: TİP II KONJENİTAL RESESİF METHEMOGLOBİNEMİ OLGUSU

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ABSTRACT

Congenital methemoglobinemia is a rare cause of cyanosis that is characterized by increased methemoglobin levels and caused by mutations in the cytochrome B5 reductase 3 (CYB5R3) gene resulting in deficiencies of the nicotinamide adenine dinucleotide-cytochrome b5 reductase enzyme. The congenital disease has two types: type I, in which the enzyme deficiency occurs only in the erythrocytes, and type II, in which all tissues are affected. Accordingly, cyanosis is the sole clinical manifestation in type I, whereas cyanosis is accompanied by such severe neurological findings as intellectual disability, microcephaly, generalized dystonia, and movement disorders. In this study, a case who presented with respiratory distress was found to have high methemoglobin levels and was diagnosed with type II congenital methemoglobinemia due to the presence of neurological findings was presented. The patient's treatment was adjusted, the methemoglobin level was reduced, and cyanosis regressed, but no change was observed in neurological findings. This untreatable, rare condition must be included in the differential diagnosis of patients with unexplained cyanosis and high methemoglobin levels, and genetic counseling must be provided to the family, because of its severity and 25% recurrence rate.

Keywords: Methemoglobinemia, congenital, cyanosis, neurological development

ÖZET

Konjenital methemoglobinemi, methemoglobin düzeyinde artışla seyreden, nadir siyanoz sebeplerindendir. Hastalıktan sorumlu olan nikotinamid adenin dinükleotit sitokrom b5 redüktaz enzimi eksikliğine sebep olan sitokrom B5 redüktaz 3 (*CYB5R3*) gen mutasyonlarıdır. Konjenital hastalığın iki tipi vardır; tip I'de sadece eritrositlerde enzim eksikliği görülürken, tip II'de tüm dokular etkilenir. Buna bağlı olarak tip I'de siyanoz görülen tek klinik bulgu iken tip II'de hafif siyanozun yanında bilişsel yetersizlik, mikrosefali, jeneralize distoni, hareket bozuklukları gibi ciddi nörolojik bulgular eşlik eder. Bu çalışmada, solunum sıkıntısı yakınması ile başvuran, methemoglobin düzeyi yüksek saptanan, nörolojik bulguların eşlik etmesi sebebi ile tip II konjenital methemoglobinemi tanısı alan olgu sunuldu. Hastanın tedavisi düzenlendi, methemoglobin düzeyi düşürüldü, siyanoz geriledi, ancak nörolojik bulgularda değişiklik görülmedi. Tedavisi olmayan bu nadir hastalık, açıklanamayan siyanozu olup methemoglobin düzeyi yüksek saptanan hastaların ayırıcı tanıları arasında yer almalı ve hastalığın şiddeti ve %25 nüks oranı nedeniyle aileye genetik danışmanlık verilmelidir.

Anahtar Kelimeler: Methemoglobinemi, konjenital, siyanoz, nörolojik gelişim

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INTRODUCTION

Methemoglobinemia is a rare condition characterized by elevated methemoglobin (metHb) levels in the blood. Under normal conditions, a small amount of metHb is produced in the erythrocytes upon exposure to various free radicals, and the nicotinamide adenine dinucleotide-cytochrome b5 reductase (NADH-CYB5R) enzyme plays a protective role by reducing 99% of the metHb to hemoglobin A, thus maintaining a metHb level of 1–2%. If this protective mechanism is impaired, the metHb level increases. The reason for metHb level increase can be congenital, resulting from enzyme deficiency; or acquired, such as through exposure to various chemicals (1-3). The congenital form that is inherited in an autosomal recessive fashion has two types: in type I, NADH-CYB5R enzyme deficiencies occur only in the erythrocytes; while in type II, all tissues are affected. The disease can be attributed to mutations on the 22q13 gene chromosome. Clinical manifestations vary depending on the metHb level. Although cyanosis is the only clinical manifestation in recessive congenital methemoglobinemia (RCM) type I, which is the benign form of the condition; RCM type II presents with cyanosis accompanied by neurological findings (1,3,4). Due to the rarity of the disease, it may not be considered in differential diagnoses of patients with cyanosis. The current report presents a patient with RCM type II which presented with respiratory distress.

The patient's guardian provided informed consent.

CASE PRESENTATION

A 9-year-old female presented to our hospital with respiratory distress and involuntary movements. The patient was born to consanguineous parents (first-degree relatives) with no complications after a normal pregnancy. There was no remarkable family history. The patient had normal development in the first six months of life but then encountered delays in reaching developmental milestones and growth retardation. She developed microcephaly (43 cm, < 3 percentile, -6.5 SDS) in the first year, while other anthropometric measurements remained within normal ranges. Psychomotor retardation had become prominent, and opisthotonus attacks and choreoathetotic movements had increased for the last two years. She had frequent fits of crying and prominent agitation. At age four she was making simple utterances and would smile at familiar faces. It was learned from the mother that she had episodes of cyanosis when she had a fever. During these periods, a slight increase in the methHb level was observed, but it was stated that this was not significant.

A physical examination revealed central cyanosis and neurological findings such as microcephaly, hypertonia in the trunk and extremities, hyperactive deep tendon reflexes, widespread dystonia that became prominent upon physical contact, intense choreoathetotic movements, growth retardation, intellectual disability and delay in speech development. A diagnosis of methemoglobinemia was first considered due to the observation of central cyanosis that was unresponsive to oxygen therapy, chocolate-colored blood (Figure 1), and metHb levels of 17–18.6% measured from an arterial blood gas analysis. No exposure to any toxic substances was detected. Cardiac and respiratory examinations revealed normal findings; chest X-ray and echocardiography showed normal findings; and cranial magnetic resonance imaging study revealed cerebral atrophy and ventricular dilation (Figure 2). Routine laboratory examinations and metabolic screening tests were normal. Electroencephalography was normal. A genetic analysis was conducted with a prediagnosis of RCM based on the clinical and laboratory findings, and revealed a homozygous pathogenic mutation in the *CYB5R3* (c.489C>G) gene, as a result of which, the patient was diagnosed with RCM type II. The patient was placed on a treatment of ascorbic acid 500 mg/day and riboflavin 120 mg/day. Despite the improvement in the cyanosis and metHb level (5.3-6.5%), no change was observed in the neurological symptoms at the 3-6 months follow-up. The patient died six months after the diagnosis in a different center, where she applied with respiratory distress and was diagnosed with pneumonia. During this period, the patient continued her medication.

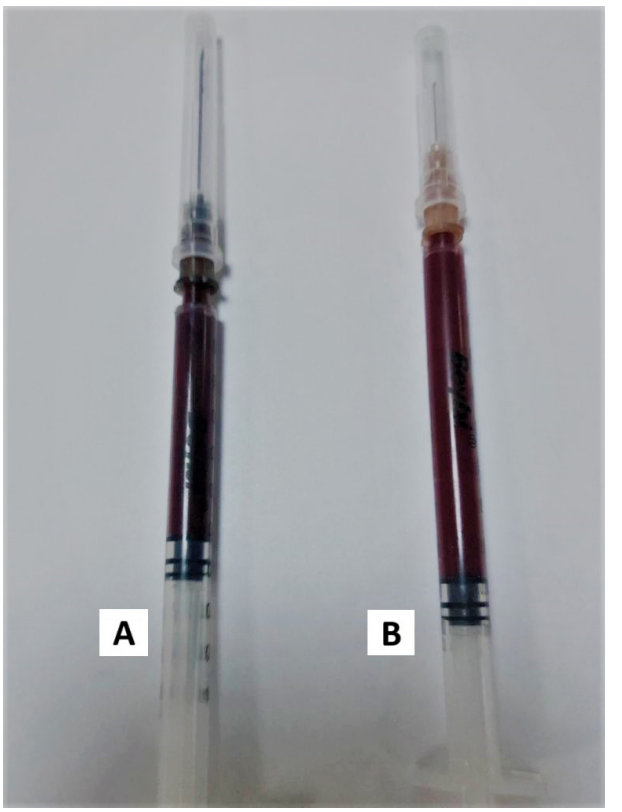

Figure 1: Arterial blood gas samples; A: Chocolate brown colored blood sample of the patient, B: Blood sample from a normal person

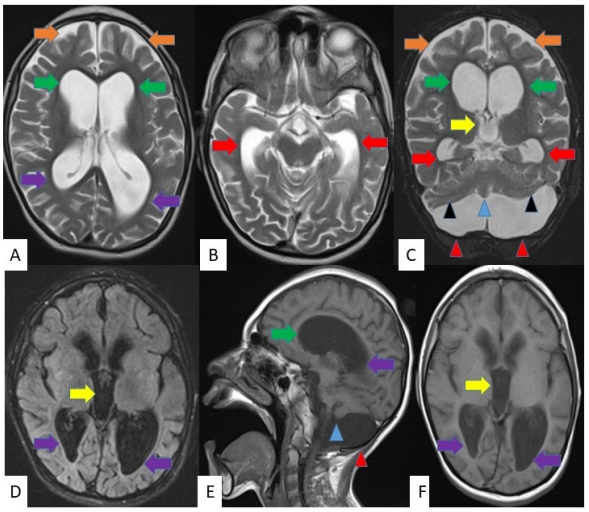

Figure 2: From left to right from top to bottom (A-F); on axial T2-weighted (A-B), coronal fat-suppressed T2-weighted (C), FLAIR (D), sagittal T1-weighted (E) and axial T1-weighted (F) images; In both lateral ventricles, more prominent on the left frontal (green arrows), temporal (red arrows) and occipital horns (secondary to atrophy of white matter especially at this level) (purple arrows), in the 3rd ventricle (yellow arrow), extraaxial CSF distance (to be less) (orange arrows) marked dilatation is observed. There is also cystic dilatation of the 4th ventricle towards the posterior fossa (red arrowheads), and hypoplasia of the cerebellar vermis (blue arrowhead) and cerebellar atrophy (black arrowheads) (Dandy-Walker variant). There is also cerebral atrophy inconsistent with the patient's age.

DISCUSSION

Methemoglobinemia refers to the abnormal elevation of metHb levels in the blood resulting from a defect in the pathways that maintain metHb within normal ranges. In this form of hemoglobin, ferrous iron is oxidized into a ferric form, leading to a decrease in the oxygen-carrying capacity of erythrocytes, and resulting in cyanosis and hypoxia (1). Clinical manifestations vary depending on the rate of increase in metHb levels and the half-life of the responsible agent in an acquired form. But in the congenital form, compensatory erythrocytosis occurs and a milder presentation is observed in response to chronic increases in metHb levels (5,6). RCM type I is a benign form of the condition in which the enzyme deficiency involves only erythrocytes, and cyanosis is the only clinical manifestation. Whereas in type II, enzyme deficiency occurs in all tissues, and the most distinctive feature is cyanosis accompanied by neurological impairment in those aged 6–9 months, resulting in death in the first years of life (7). Central cyanosis that is unresponsive to oxygen therapy and arterial blood that is darker than normal suggests the possible diagnosis, which can be supported by a measurement of metHb levels. The presence of neurological findings such as progressive intellectual disability, microcephaly, opisthotonus, athetotic movement, and generalized hypertonia accompanying methemoglobinemia suggests the diagnosis of RCM type II. Confirming the diagnosis is easy in the presence of methemoglobinemia with accompanying neurological findings, as was the case in our patient; although it may be more challenging to recognize the condition clinically in the early periods when neurological manifestations have not yet developed. For this reason, acquired factors must first be ruled out in a patient with methemoglobinemia, and the work-up should then proceed with genetic subtyping (3,7,8).

The homozygous mutation identified in our patient, c.489C>G, is one of a few identified mutations causing RCM type II. Up to 80 mutations have been identified in the *CYB5R3* gene that are responsible for the condition; with the mutations that cause enzyme instability resulting in type I, and the mutations that cause enzyme inactivation resulting in the type II form (7-9).

There have been a few case reports presenting the cranial imaging findings of patients with RCM type II, brain atrophy was noted in our patient, similar to previously reported cases. The most commonly reported findings include brain atrophy, delayed myelination, and thinning of the corpus callosum, which are non-specific and have limited diagnostic contribution (3,4,9,10).

High-dose ascorbic acid (200–500 mg/day) therapy effectively reduces metHb levels in RCM, and it has been reported that riboflavin (120 mg/day) therapy is also effective in some cases. Methylene blue treatment can be used when the metHb level is very high or when the patient is severely symptomatic. Despite this therapy, patients have a poor prognosis, and the treatment has no effect on any neurological impairments that have already been acquired. Since the pathophysiology of the disease is unknown, the reason for the ineffectiveness of the treatment on neurological findings is also unknown (1,3,4).

CONCLUSION

Recessive congenital methemoglobinemia is a rare disease, with the type II form of the condition being particularly rare and seldom taken into consideration in the differential diagnoses. The condition must be remembered in the differential diagnosis of patients with methemoglobinemia if it is accompanied by neurological manifestations. Families must be provided with genetic counseling for this untreatable condition.

Informed Consent: The patient's guardian provided informed consent.

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CASE REPORT / OLGU SUNUMU
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OCCURRENCE OF THROMBOTIC MICROANGIOPATHY IN A PATIENT WITH GRANULOMATOSIS WITH POLYANGIITIS AFTER REMISSION INDUCTION THERAPY: A RARE PRESENTATION

GRANÜLOMATÖZ POLİANJİT TANILI BİR HASTADA REMİSYON İNDÜKSİYON TEDAVİSİ SONRASI TROMBOTİK MİKROANJİYOPATİ GELİŞMESİ: NADİR BİR PREZENTASYON

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ABSTRACT

In the literature thrombotic microangiopathy (TMA) associated with ANCA-associated vasculitis (AAV) has only been reported in isolated case reports. Here, we report a patient with granulomatosis with polyangiitis (GPA), who presented with TMA after initiation of remission induction therapy. A 36-year-old male patient presented with dyspnea and decreased urine output. Laboratory results demonstrated elevated creatinine, low albumin, low hemoglobin, normal leukocyte and platelet count, normal LDH, and elevated acute phase reactants. Urinalysis revealed proteinuria (1275 mg/day) and an active urine sediment. Serum complement levels were normal and proteinase 3 ANCA titer was> 200 IU/ml. Urinary ultrasound revealed normal kidney sizes and normal parenchymal thicknesses with increased renal parenchymal echogenicity. A kidney biopsy revealed pauci-immune crescentic glomerulonephritis. The diagnosis was GPA and an induction treatment of pulse steroid, intravenous cyclophosphamide, and plasma exchange was initiated. After two doses of cyclophosphamide, rituximab treatment was initiated. Fifteen days after the second dose of rituximab, thrombotic microangiopathy (TMA) was considered in the patient who had no increase in hemoglobin value (despite initiation of erythropoetin)

ÖZET

Literatürde ANCA ilişkili vaskülit (AİV) ile ilişkili trombotik mikroanjiyopati (TMA) sadece olgu sunumlarında bildirilmiştir. Burada remisyon indüksiyonu tedavisi sonrasında TMA tablosuyla başvuran granülomatöz polianjit (GPA) tanılı bir hastayı sunmayı amaçladık. Otuz altı yaşında erkek hasta nefes darlığı ve idrar çıkışında azalma şikayetleriyle başvurdu. Hastanın laboratuvar tetkiklerinde kreatinin ve akut faz reaktanı yüksekliği, albümin ve hemoglobin düşüklüğü, normal lökosit ve trombosit sayısı ve normal LDH düzeyi saptandı. İdrar tahlilinde 1275 mg/gün proteinüri ve aktif idrar sedimenti mevcuttu. Serum kompleman seviyeleri normaldi ancak proteinaz 3 ANCA titresi > 200 IU/ml olarak saptandı. Üriner ultrasonografide normal böbrek boyutları ve normal renal parankim kalınlığı ile artmış renal parankimal ekojenitesi tespit edildi. Böbrek biyopsisinde immün birikimden fakir kresentik glomerülonefrit saptandı. Hastaya GPA tanısı kondu ve yüksek doz steroid, intravenöz siklofosfamid ve plazma değişiminden oluşan güçlü bir indüksiyon tedavisi başlandı. İki doz siklofosfamid sonrası rituksimab tedavisi verildi Eritropoetin başlanmasına rağmen hemoglobin değerinde artış olmayan ve trombosit sayısında azalma olan hastada ikinci rituksimab dozundan 15 gün sonra trombotik mikroanjiyopati (TMA)

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and decreased platelet count. Peripheral blood smear revealed 5-9 schistocytes in each area. A corrected reticulocyte count was elevated, and haptoglobin was low. ADAMTS13 activity was normal. Plasma exchange was not reinitiated. The kidney biopsy was re-evaluated, but no histopathological changes consistent with TMA were found. The patient was under follow-up for TMA by checking his hematological parameters once a week. Two months later, at the third month of rituximab treatment, an increase in hemoglobin and platelet values was observed. Reticulocyte percent and haptoglobin were within normal limits. His follow-up as an outpatient is continuing. In most of the reported cases of TMA associated with ANCA-associated vasculitis, TMA appeared in the course of active vasculitis. Our case is noteworthy due to the fact that TMA developed after the active phase of GPA, even after the initiation of potent remission induction therapy.

Keywords: Granulomatosis with polyangiitis, remission induction, thrombotic microangiopathy

düşünüldü. Periferik yaymada her alanda 5-9 şistosit görüldü. Düzeltilmiş retikülosit sayısı yüksek, haptoglobin düzeyi düşük, ADAMTS13 aktivitesi normaldi. TMA tablosu için plazmafereze tekrar başlanmadı. Böbrek biyopsisi tekrar değerlendirildi ancak TMA ile uyumlu histopatolojik değişiklik bulunamadı. Hasta TMA açısından haftalık olarak hematolojik parametrelerle takip edildi. İki ay sonra rituksimab tedavisinin üçüncü ayında hemoglobin ve trombosit değerleri arttı, retikülosit yüzdesi ile haptoglobin normal olarak saptandı. Hastanın poliklinik takibi devam etmektedir. Olgumuz, GPA'nın aktif fazından sonra, hatta güçlü remisyon indüksiyon tedavisi başlandıktan sonra TMA tablosunun gelişmesi nedeniyle dikkat çekicidir.

Anahtar Kelimeler: Granülomatöz polianjit, remisyon indüksiyonu, trombotik mikroanjiyopati

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is an anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) that most often affects the upper and lower respiratory tracts, and kidneys (1). Thrombotic microangiopathies (TMA) are a heterogeneous group of diseases characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage, often involving the kidneys (2). In the literature TMA associated with AAV has only been described in isolated case reports (3). Here, we aimed to describe the development of TMA in a 36-year-old patient with GPA after initiation of remission induction therapy and review the treatment options.

CASE PRESENTATION

A 36-year-old male patient presented to the emergency department with dyspnea and decreased urine output. Past medical history was unremarkable except for recent bilateral hearing loss. He did not regularly use any medications. His body temperature was 36.6 °C, blood pressure was 111/72 mmHg, pulse rate was 72/min, respiratory rate was 20/min, and blood oxygen saturation was 97% by pulse oximetry. Fine crackles were heard in the bases of both lungs on auscultation. Laboratory results were as follows: Urea: 97 mg/dl, creatinine: 8.32 mg/dl, eGFR: 7 ml/min/m^2, albumin: 24.2 g/L, total protein: 52 g/L, hemoglobin: 83 g/dl, mean corpuscular volume: 84 fl, platelet: 228000/µl, LDH: 236 U/L, CRP: 137.7 (0-5) mg/L, sedimentation: 39 mm/hour, microprotein in spot urine: 1275 mg/day, and urine microscopy showed 234 erythrocytes and 27 leukocytes. Initial peripheral blood smear revealed normochromic normocytic erythrocytes, a sufficient number of platelets, and no schistocytes. Proteinase3 (PR3) ANCA titer was> 200 IU/ml, myeloperoxidase (MPO) ANCA and anti-glomerular basement membrane antibodies were negative. Complement 3 was 0.95 g/L (0.9-1.8) and complement 4 was 0.15 (0.1-0.4). He was hospitalized with acute kidney injury. Urinary ultrasound revealed normal kidney sizes and normal parenchyma thicknesses with increased renal parenchymal echogenicity. A kidney biopsy revealed pauci-immune crescentic glomerulonephritis. Paranasal sinus computed tomography (CT) revealed bilaterally increased soft tissue density and decreased aeration in mastoid cells, in the mastoid antrum, and in both middle ear cavities. Thorax CT revealed bilateral pleural effusion, atelectatic changes in the lung areas neighboring the effusion, and two subpleural nodules in the right lung (one 11mm and the other 15 mm in diameter). He was also evaluated by the ear-nose-throat department for the etiology of his recent hearing loss, which turned out to be a sensorineural hearing loss. The patient was diagnosed with GPA. A potent induction treatment of pulse methylprednisolone (1000 mg/day for three days), intravenous cyclophosphamide was initiated and plasma exchange with fresh frozen plasma was performed for a total of eight cycles. During this period, the anuric patient underwent intermittent hemodialysis three times a week. After two doses of cyclophosphamide, which were administrated in doses of 750 mg/day within an interval of two weeks, the control PR3-ANCA titer was >200 IU/ml. Three weeks after the second cyclophosphamide infusion, rituximab treatment was initiated as 2x1000 mg intravenous infusion within an interval of two weeks. Two months after the initiation of induction treatment and 15 days after the second dose of rituximab, thrombotic microangiopathy (TMA) was considered a preliminary diagnosis in the patient who had no increase in hemoglobin value (despite initiation of erythropoetin) and decreased platelet count (116000/uL). Peripheral blood smear revealed a slightly decreased number of platelets, normochromic normocytic erythrocytes, and 5-9 schistocytes in each area. Corrected reticulocyte count was elevated (5.28%), haptoglobin was low, and red cell distribution width was slightly elevated. The ADAMTS13 activity was within normal range. Other potential causes

of TMA such as systemic lupus erythematosus, antiphospholipid syndrome, malignant hypertension, and infective endocarditis were also excluded. A kidney biopsy specimen was re-evaluated, but no histopathological changes consistent with TMA were found. Re-biopsy was not performed because the patient was still anuric and the dialysis treatment was continued. The patient was under follow-up for TMA by checking his hematological parameters once a week. Since alternative causes of TMA were excluded and the patient had already received a potent immunosuppressive regimen (Three days of 1000 mg methylprednisolone pulses, eight cycles of plasmapheresis, two doses of 750 mg cyclophosphamide, and two doses of 1000 mg rituximab), no additional treatment was given for TMA. Prednisolone dose was maintained at 15 mg/day. Plasma exchange was not reinitiated. Two months later, at the third month of rituximab treatment, an increase in hemoglobin and platelet values was observed. Hemoglobin was 16.7 g/dl, platelet was $158x10^3$/uL, reticulocyte percent and haptoglobin were within normal limits. Meanwhile, the patient who had a fever during hemodialysis was hospitalized due to a catheter infection. Stenotrophomonas maltophilia growth was observed in the blood culture, the catheter was changed. PR3-ANCA titers persisted at >200 IU/ml. Due to the persistence of PR3-ANCA titers and the concomitant infection, intravenous immunoglobulin (IVIG) treatment was initiated at a dose of 2 g/kg/month, after rheumatology consultation. There was no finding in favor of infective endocarditis in the transthoracic echocardiography. Antibiotherapy was completed and acute phase reactants regressed. The patient's prednisolone dose was gradually tapered to 5 mg/day. The patient's hearing loss has completely recovered, and control CT images revealed normal mastoid cells, mastoid antrum, and middle ear as well as bilaterally normal lung parenchyma without any nodules or pleural effusion. He continued 3/7 hemodialysis program and his follow-up as an outpatient is continuing. His final PR3-ANCA titer is 53 IU/ml.

DISCUSSION

Thrombotic microangiopathies may rarely be observed in the course of AAV. Activation of the alternative pathway of complement and associated endothelial damage may trigger TMA in patients with AAV (4). The presence of histopathological signs of TMA in kidney biopsies of patients with AAV has been associated with poor renal prognosis in one study and increased all-cause mortality in another study (3, 5). The kidney biopsy of our patient did not demonstrate any signs of TMA.

A French nationwide retrospective case-control study and literature review of TMA in patients with AAV stated that TMA mainly occurred in patients with MPA, although cases with GPA have also been reported (6-8). In most of the reported cases, TMA appeared in the course of active vasculitis (6). Our case is noteworthy due to the fact that TMA was not present at the initial presentation of GPA, but it occurred after initiation of potent induction treatment, namely three doses of pulse methylprednisolone, 8 cycles of plasmapheresis, two doses of cyclophosphamide and two doses of rituximab. However, the treatment was not changed, considering that the therapeutic effect of rituximab would appear late. In addition, when the literature was evaluated, no additional treatment recommendations were found (9). Two months later, at the third month of rituximab treatment, the hematological findings of TMA completely disappeared.

In conclusion, TMA in a patient with AAV may also develop after the active phase of the disease, even after the initiation of potent remission induction therapy. However, it seems reasonable to wait for a while before changing therapy for TMA, especially in patients on remission induction therapy containing rituximab.

Informed Consent: Written informed consent for publication was obtained from the patient.

Peer Review: Externally peer-reviewed.

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DIAGNOSIS AND ENDOVASCULAR TREATMENT OF AN ARTERIOVENOUS FISTULA IN THE BREAST

MEMEDE ARTERİYOVENÖZ FİSTÜL OLGUSUNUN TANI VE ENDOVASKÜLER TEDAVİSİ

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ABSTRACT

Arteriovenous fistulas (AVF) are abnormal connections between the arteries and veins in the absence of normal capillaries. The etiology of AVFs includes surgical planning for hemodialysis, congenital/syndrome related conditions, malignancy and trauma, and iatrogenic complications. Breast AVFs are rare, and most of those reported in the literature are biopsy-related acquired cases. A 91-year-old female patient was diagnosed with AVF in the right breast via radiological imaging findings and underwent endovascular treatment. The AVF could not be associated with any acquired etiology. Doppler ultrasonography and MDCTA-MRA are guides for the diagnosis of AVF. Digital angiography is both the gold standard in diagnosis and can be used for endovascular treatment in suitable cases.

Keywords: Breast, arteriovenous fistula, Doppler ultrasound, magnetic resonance angiography, digital angiography, endovascular treatment

ÖZET

Arteriyovenöz fistüller (AVF), arterler ve venler arasında normal kapiller vasküler sistemin olmadığı anormal bağlantılardır. AVF'lerin etiyolojisinde hemodiyaliz için cerrahi planlama, konjenital/sendrom ilişkili durumlar, malignite ve travma ve iatrojenik komplikasyonlar bulunmaktadır. Meme AVF'leri nadirdir ve literatürde bildirilenlerin çoğu biyopsi ile ilişkili edinsel vakalardır. Doksan bir yaşında kadın hastaya radyolojik görüntüleme bulguları ile sağ memede AVF tanısı konuldu ve endovasküler tedavi uygulandı. Olgumuzun anamnezinde AVF etyolojisi bulunamamıştır. Doppler ultrasonografi ve MDCTA-MRA AVF tanısında yol göstericidir. Dijital anjiyografi altın standarttır ve uygun olgularda endovasküler tedavi olanağı sağlamaktadır.

Anahtar Kelimeler: Meme, arteriyovenöz fistül, Doppler ultrason, manyetik rezonans anjiyografi, dijital anjiyografi, endovasküler tedavi

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INTRODUCTION

Arteriovenous fistulas (AVF) are abnormal connections between an artery and a vein in the absence of capillaries. The blood flow in AVFs creates a hyperdynamic shunt from the artery to the vein. The etiology of AVFs includes surgical planning of hemodialysis, congenital/syndrome-related conditions, pathological processes such as malignancy or trauma, or iatrogenic complications (1). Radiological findings include the presence of a low-resistance arterial feeder and arterialized high-flow velocity vein using Doppler ultrasonography (USG). Multidetector computed tomographic angiography (MDCTA) and magnetic resonance angiography (MRA) show early filling of the draining vein at the early arterial phase, and digital angiography shows arterial feeders and draining veins.

CASE PRESENTATION

A 91-year-old female patient was admitted with complaints of bruising, stiffness, and pain in the right breast. The patient presented with essential hypertension, congestive heart failure, and chronic obstructive pulmonary disease. The patient was taking an antihypertensive and a daily 100 mg/day acetylsalicylic acid treatment. Physical examination indicated the presence of extensive ecchymosis of the skin in the right breast with a warm-pulsatile palpable lesion in the outer quadrant. The hemogram, biochemistry, and coagulation examination results and expected normal ranges were as following: WBC: 8.56x10^3 cells/µl (4.1-11.2), Hb: 11.2 g/dL (11.7-15.5), Platelets: 167x10^3/µl (160-390), Neu: 5.24x10^3/µl (1.3-7); Glucose: 112 mg/dL (70-100), Creatinine: 0.69 mg/dL (0.7-1.4), CRP: 13.06 mg/L (0-5), INR: 0.82 (0.85-1.2), PT time:10 s (10-15), Prothrombin activity: 136.6% (70-130), and APTT: 25.1 s (21-36).

Mammography images indicated the presence of a tortuous dilated vascular structure in the upper outer quadrant of the right breast as a tubular opacity with atherosclerotic calcification on its wall. A 3-cm opacity covered by parenchyma was observed adjacent to the dilated vascular structure, which was more evident on the mediolateral oblique view (MLO) mammogram. In addition, diffuse thickening and increased trabeculation were observed in the right breast skin (Figure 1). USG examination indicated the presence of extensive dilated superficial vascular collaterals, cutaneous-subcutaneous fatty tissue edema, and increased echo signal along the upper and outer quadrants of the right breast. A hypo-isoechoic lesion 17x18x38 mm in size was observed at the 9 o'clock position in the right breast. The location was consistent with the opacity observed in the mammogram. Doppler examination indicated the presence of a low-resistance arterial feeder and arterialized high-flow velocity vein adjacent to the hypoechoic lesion with turbulent flow in its lumen, suggesting the presence of a partially thrombosed pseudoaneurysm-associated AVF (Figure 2).

To further investigate the origin of the vascular pathology, the time-resolved 3D MRA technique with IV contrast for the right axilla and breast, along with arterial and venous phase MRA, was first applied to the patient. This was followed by the acquisition of conventional MR images by placing the breast coil in the prone position. MRA images showed the presence of focal aneurysmatic dilations from the proximal segment of the right thoracic lateral artery originating from the axillary artery and multiple collaterals in the outer quadrant of the right breast compatible with the presence of an AVF in the retro-mammillary area (Figure 3). In addition, venous return starting in the early arterial phase was observed.

At the interventional radiology unit, the patient underwent a modified Allen test, after which a 4F vascular sheath was placed by sonography-assisted radial artery

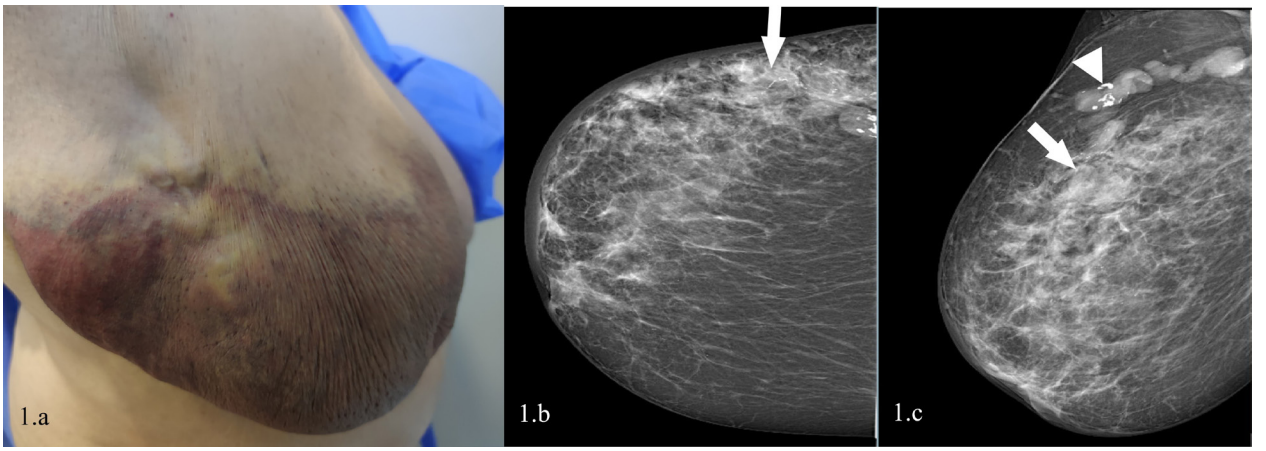

Figure 1: (a) Extensive ecchymosis of the skin in the right breast, (b) CC and (c) MLO mammography images indicating the presence of tortuous dilated vascular structure (black arrowhead), opacity (pseudoaneurysm location) covered by parenchyma adjacent to the dilated vascular structure (black arrow).

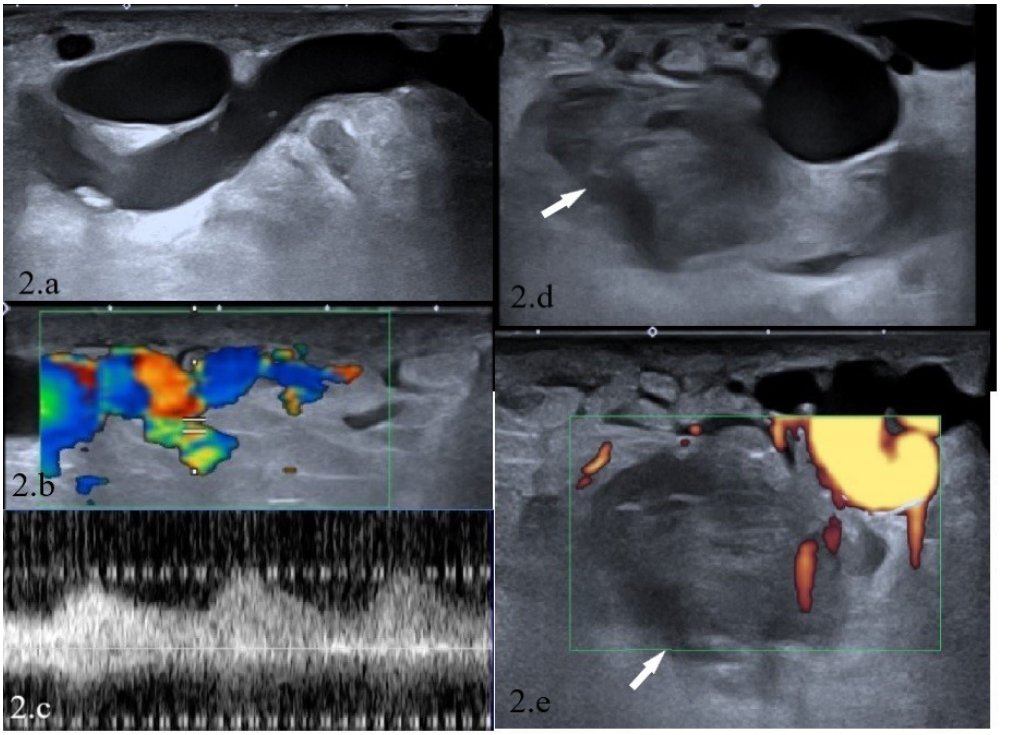

Figure 2: (a, b) Extensive dilated superficial vascular collaterals, cutaneous-subcutaneous fatty tissue edema, and echo increase; (c, d, e) hypo-isoechoic lesion (white arrow), Doppler examination indicating the presence of a low resistance arterial feeder, and arterialized high-flow velocity vein adjacent to the hypoechoic lesion with turbulent flow in its lumen, suggesting the presence of a partially thrombosed pseudoaneurysm-associated AVF.

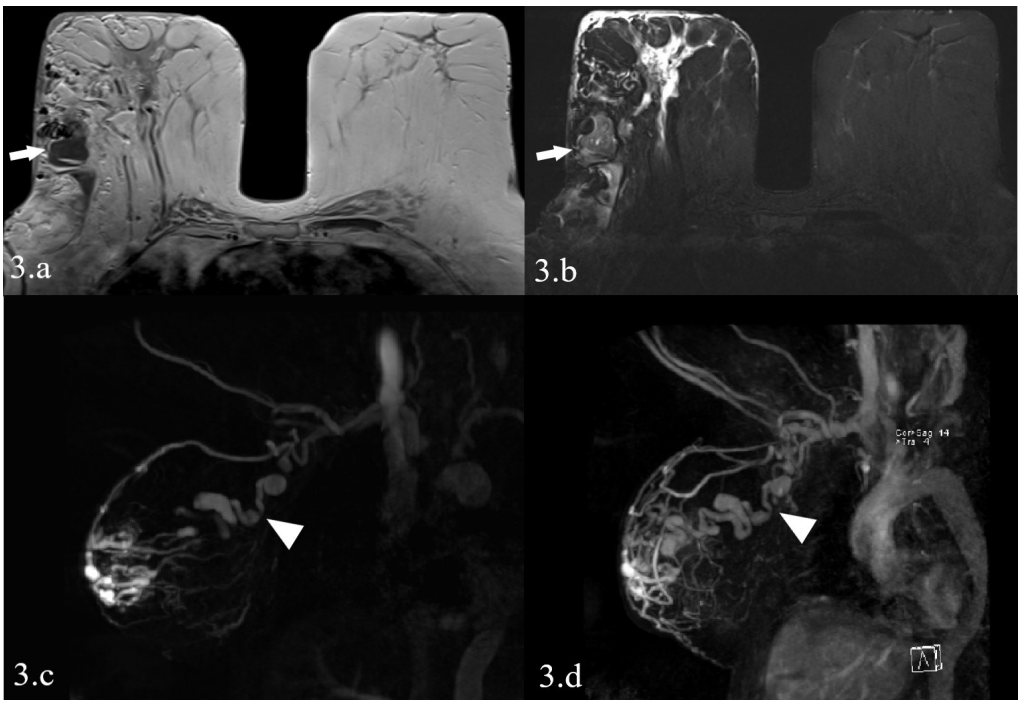

Figure 3: (a, b) Partially thrombosed pseudoaneurysm with intermediate signal intensity in T1W and T2W images (white arrow); (c, d) Focal aneurysmatic dilations from the proximal segment of the right thoracic lateral artery originating from the axillary artery, and multiple collaterals in the outer quadrant of the right breast (white arrowhead).

access from the right wrist. The right subclavian artery was then catheterized with a 0.035-inch guidewire and a 4F diagnostic vertebral catheter. Digital subtraction angiography (DSA) was carried out by administering the contrast material via a pump. The DSA images indicated that the lateral thoracic branch of the right axillary artery was prominently hypertrophic and tortuous in appearance. The images obtained by selective catheterization of the right lateral thoracic artery indicated a multisegmental aneurysmatic expansion along the lateral thoracic artery followed by early filling of multiple venous drainage veins (Figure 4).

The fistula was reached by passing the aneurysmatic segments with a 2.4F Progreat Micro Catheter System (Terumo, Tokyo). Next, a 10% Histoacryl® (B/Braun, Tuttlingen, Germany) lipiodol mixture was given as a slow injection through the microcatheter, primarily to eliminate any flow in the fistula. Once the fistula flow was eliminated, the microcatheter was withdrawn, and the pathological segments of the afferent artery were embolized with a glue/lipiodol mixture, including all aneurysmatic segments. The selective internal mammary artery images taken at the end of the procedure confirmed that the pathological vascularization had been eliminated (Figure 5). The endovascular treatment procedure was terminated successfully, and the patient was discharged after a one-day hospital stay and prescribed co-amoxiclav, paracetamol, proton pump inhibitor (pantoprazole), and nonsteroidal anti-inflammatory (lornoxicam) drugs. The patient was scheduled for a follow-up examination 7 days later.

A follow-up examination of the patient indicated that the ecchymosis in the breast had largely regressed and become limited to the outer quadrant; the patient's complaints had also been alleviated. A control ultrasonography indicated that the pseudoaneurysm in the right breast outer quadrant had been completely thrombosed. A dirty acoustic shadowing was observed in the lumen due to the embolization of the injected contrast material with other collateral vascular structures; moreover, no flow was observed in the Doppler examination (Figure 6). In addition, the skin edema and inflammatory echo increase in fatty tissue had also been resolved.

DISCUSSION

Congenital AVFs are associated with deviations in the development and differentiation of arteries and veins during the embryological period (2). Acquired AVFs are encountered more frequently than congenital causes. Acquired AVFs usually have a dominant arterial feeder and a dominant draining vein, while congenital AVFs

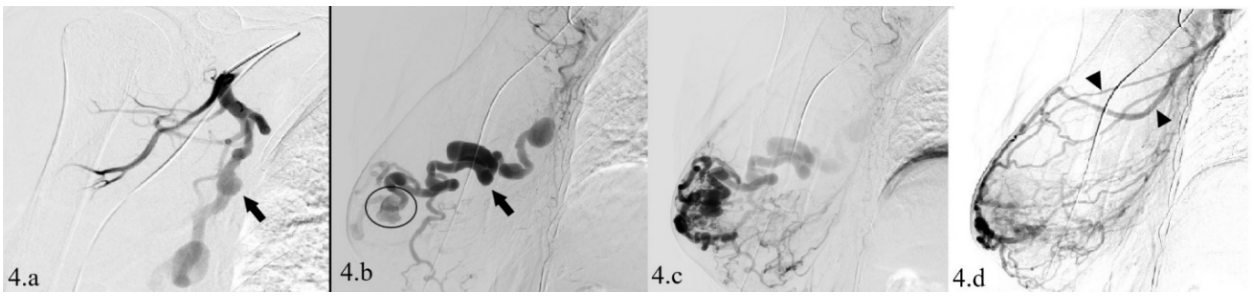

Figure 4: Digital subtraction angiography, right breast, AVF. (a, b) Aneurysmatic dilated lateral thoracic artery with a tortuous course in the early arterial phase (black arrow) and fistula location (marked with a black circle); (c) retromamillary venous drainage veins; (d) mixed venous drainage into the lateral thoracic vein and internal mammary vein (black arrowhead).

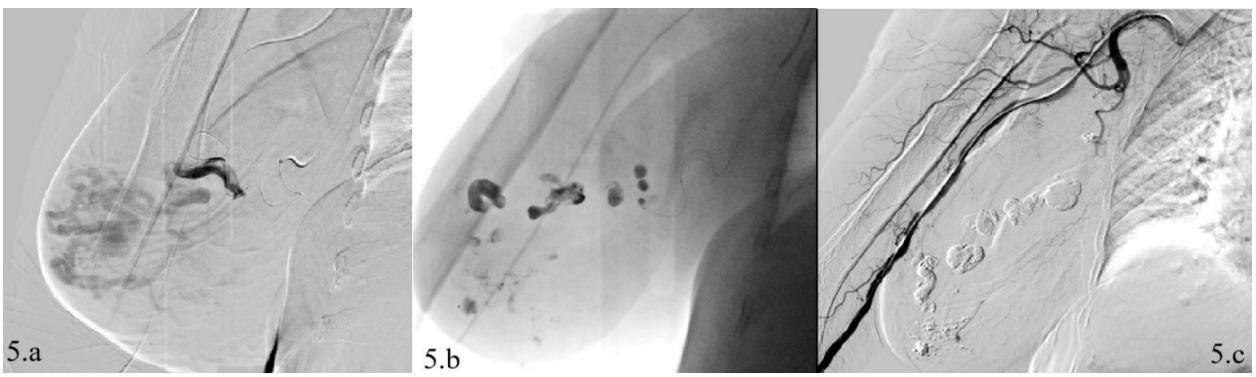

Figure 5: (a, b) Stagnation by embolizing injection; (c) No reflow was observed in the fistula-related collaterals of the right breast in the post-embolization angiography images taken via selective internal mammarian artery catheterization.

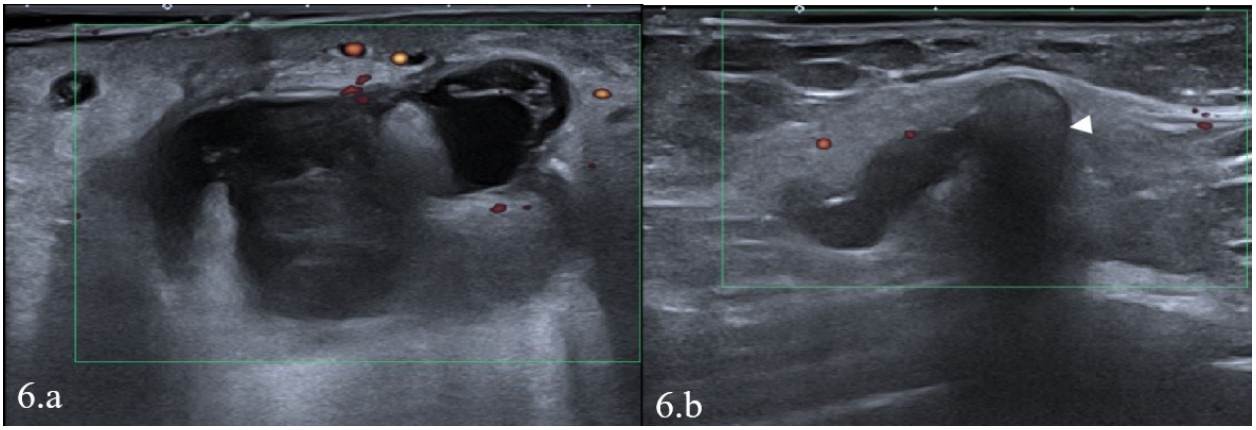

Figure 6: Control ultrasonography 1 week post-intervention. The pseudoaneurysm was completely thrombosed. A dirty acoustic shadowing was observed in the lumen due to the embolization of the injected contrast material with other collateral vascular structures; moreover, no flow was observed in the Doppler examination.

have multiple arterial feeders and draining veins forming a complex connection (2). Digital angiography in the current case showed the presence of the lateral thoracic artery as the major single arterial feeder, while the lateral thoracic and internal mammary veins were observed as the major draining veins.

Published data on the etiology of AVF in the breast suggest that, apart from congenital causes, AVFs can result from malignant masses, Tru-cut/fine needle aspiration biopsies, trauma, surgical interventions, and superior vena cava thrombosis/stenosis-related causes (2-6). A detailed anamnesis to understand the etiology of AVF in the current case suggested that the patient had no previous history of intervention, such as vascular intervention or tissue biopsy of the breast. To the best of our knowledge, no reported cases of spontaneous breast AVF are found in the literature; thus, we were unable to identify an explanatory etiology in the current case. The presence of a history of unremembered trauma is a feasible speculation.

The presence of a ying-yang sign (back-and-forth flow pattern) in the pseudo aneurysm lumen, a low resistance arterial feeder, and arterialized high-flow velocity vein in the Doppler USG are indicative of the presence of a pseudoaneurysm-associated arteriovenous fistula (PA-AVF) (3). MRA and/or MDCTA contribute to the detection of early filling of the draining vein in the early arterial phase and clarifies the anatomy of the arterial feeder and venous drainage. In addition to these techniques, digital angiography is considered the gold standard for determining the relationship between AVF-related arterial and venous structures and also provides the opportunity to map percutaneous endovascular embolization treatments.

The absence of any capillary vascular system able to provide passage in AVFs can lead to complications such as venous hypertension, pseudoaneurysm, hematoma, and symptoms of heart failure due to high-velocity blood flow from the artery to the vein (2). Options for the treatment of AVF-associated pseudoaneurysms include ultrasound-guided compression, thrombin injection, alcohol injection, endovascular treatment, and surgical ligation treatment (3, 6, 7). The lesion size of PA-AVF is important in determining the treatment approach: Pseudoaneurysms <2 cm can be followed by thrombin injection and observation, while endovascular or surgical intervention is generally preferred for lesions >2 cm (3).

One published case report presented an AVF that was closed on angiography but required surgical ligation and excision in the follow-up (6). In the current case, the AVF was closed during embolization. More importantly, the follow-up ultrasonography carried out a week later showed that the pseudoaneurysm had been completely thrombosed, with no flow observed in the associated arterial and venous collaterals.

CONCLUSION

AVFs of the breast are rare, and most of the cases reported in the literature are biopsy-related acquired cases. In the case reported in the current study, no associated etiology could be identified. Doppler USG, MDCTA, and MRA can guide the diagnosis of AVF. Digital angiography is the gold standard in diagnosis and can also be used for endovascular treatment in appropriate cases.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author Contributions: Conception/Design of Study-R.G.C., M.S.Ç., R.Y., S.E., B.U.; Drafting Manuscript-R.G.C., M.S.Ç., R.Y., S.E., B.A.; Critical Revision of

Manuscript- M.S.Ç., B.A.; Final Approval and Accountability- R.G.C., M.S.Ç., R.Y., S.E., B.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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ERRATUM / DÜZELTME
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ERRATUM TO: ASSESSMENT OF THE RANSON SCORE IN ACUTE PANCREATITIS: ITS VALUE IN AN EMERGENCY SETTING UPON ADMISSION

Naci ŞENKAL, Latif KARAHAN, Ali Emre BARDAK, Hilal KONYAOĞLU, Ebru TEBERİK KAMA, İsmail İNCİ, Leman Damla ERCAN, Alpay MEDETALİBEYOĞLU, Tufan TÜKEK

In the article by Şenkal et al., titled 'Assessment of the Ranson Score in Acute Pancreatitis: Its Value in an Emergency Setting Upon Admission,' published in the July 2023 issue of the Journal of İstanbul Faculty of Medicine, by mistake, sources 16 and 17 were not added to the reference list. After evaluating the situation with the editor and technical office, these two references below have been added to the last page of the PDF file.

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