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Aims & Scope

European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December. The journal publishes content in English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, short communication, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.eurjther.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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Instructions to Authors

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

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1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2 Drafting the work or revising it critically for important intellectual content; AND

3 Final approval of the version to be published; AND

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

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.

European Journal of Therapeutics requires corresponding authors to submit a signed and scanned version of the Copyright Agreement and Acknowledgement of Authorship Form (available for download through www.eurjther.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

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Manuscript Types

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

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Review Articles: 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. These authors may even be invited by the journal. 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 Review Articles.

Short Communication: This type of manuscript present significant findings from tangential investigations that are offshoots from larger studies or from early results that will have to be confirmed through further study. An unstructured main text should be prepared for each short communication. Please check Table 1 for the limitations for Short Note.

Technical Notes: This type of manuscripts should present a new experimental, computational method, test, procedure, or comparison of methods. The method described may either be completely new, or may offer a better version of an existing method. The technical note article must describe a demonstrable advance on what is currently available. Please check Table 1 for the limitations for Technical Notes.

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.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Short Communication	1500	200	20	5	1 or total of 5 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in May 2023 - https://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.eurjther.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

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Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:
- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Add the 16-digit ORCID of the author(s)
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 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 (https://www.nlm.nih.gov/mesh/MBrowser.html).

Main Points: All submissions except letters to the editor should be accompanied by 3 to 5 "main points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Main Text

Place the title, abstract, and keywords on the first page of the main text.
Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Limitations, drawbacks, and shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.
Then place the references and figure legends in the main text, respectively.
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.
Define abbreviations at first mention in the text and in each table and figure.
If a brand name is cited, supply the manufacturer's name and address (city and state/country).
DO NOT EMBED IMAGES or TABLES in the main text.

Text Formatting

Manuscripts should be submitted in Word.
Use a normal, plain font (e.g., 12-point Times Roman, 1.5 line spacing and justified) for text.
Do not use field functions.
Use the automatic page numbering function to number the pages.
Do not use field functions.
Do not indent at the beginning of a line.
Save your file in docx format (Word 2013 or higher).

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Tables

All tables are to be numbered using Arabic numerals.
Tables should always be cited in the text in consecutive numerical order.

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Each table must be uploaded as separate files (e.g. table 1, table 2, and table 3).

Figures and Figure Legends

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. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm).

Figures must be saved at a resolution of at least 600 dpi.
Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system (e.g. figure 1, figure 2 and figure 3).
The files should not be embedded in a Word document or the main document.
Figures should not be embedded in the manuscript text file.
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.

References

You can download the file named "EndNote style of the Eur J Ther" on the journal web page.

In references, the names of all authors should be written. Usage of "et al" should not be preferred.
If available, please always include DOIs as full DOI links in your reference list.
(e.g. "https://doi.org/.....").
While citing publications, preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 15% in the journal. If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. 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: Yurci A, Gungor ND, Gurbuz T (2021) High Endometrial Thickness Does not Affect IVF/ICSI Outcomes. Eur J Ther. 27(1):94-98. https://doi.org/10.5152/eurjther.2021.20102

Epub Ahead of Print Articles: Doruk M, Mustafaoglu R, Gül H (2023) The Impact of Using Technological Devices on Mental and Physical Health in Adolescents. Eur J Ther. https://doi.org/10.58600/eurjther.20232902-592.y

Book Section: Anderson DM (2012) Dorland's illustrated medical dictionary, 32nd edn. Saunders Elsevier, Philadelphia

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

Book Chapter: Gray H (1858) Anatomy Descriptive and Surgical 1st edn. In: John W, Parker and Son (eds), London, pp 150-155

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

Online Document: Bergman RA, Afifi AK, Miyauchi R (2007) Persistent congenital arterial anastomoses. Available from http://www.anatomyatlases.org/AnatomicVariants/Cardiovascular/Images0200/0232.shtml Accessed 22 Jan 2022

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

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 Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Reference citations in the text should be numbered in square brackets.

Some examples:

Parent et al. [3] reported that .....
..... on medical radiation [21, 22].
..... sleep quality among adolescents [15, 18-21, 22, 25-30].
..... anxiety, depression, and a decrease in proprioception [5, 16-18].

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Authors are required to propose at least five reviewers when submitting their manuscripts.
It should be noted that there should be no conflict of interest between these proposed reviewers and the authors, and that these recommendations should comply with international ethical standards.
Recommended reviewers should have competence in the subject of the article.
The proposed reviewers must not have collaborated with the authors of the article in the last three years and must not be working in the same institution.

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.

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Editorial: From the Incoming Editors of the European Journal of Therapeutics (Eur J Ther)

Ayşe Balat[1,2], Şevki Hakan Eren[3], Mehmet Sait Menzilcioğlu[4], İlhan Bahşi[5]

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Dear Colleagues,

We are delighted to share the new issue (June 2023, Volume 29, Issue 2) of the European Journal of Therapeutics (Eur J Ther). Furthermore, we are honored to be appointed as the New Editor-in-Chief and New Deputies Editor-in-Chief of Eur J Ther, the international publication of the Gaziantep University Faculty of Medicine published since 1990.

First, we would like to thank the previous Editor-in-Chief, Prof. M. Murat Sucu, and his team for their hard work during their tenure. They significantly increased its contribution to the field and international reputation by further developing the journal.

In addition, we would like to express our gratitude to all the editors, authors, referees, and technical team who have contributed to the journal since 1990, when our journal first started being published.

Unfortunately, due to the change of publishing house, there were some technical problems and interruptions on the web page of Eur J Ther in the first few months of 2023. So, we regret to inform you that there are delays in the evaluation stages of some manuscripts sent to the journal. However, we would like to let you know that from now on, your valuable works submitted to Eur J Ther will be evaluated as quickly as possible. In addition, we would like to announce that all articles accepted for publication in our journal, which is considered an essential innovation, will be published on the web page of our journal as Early View / Accepted Articles in a short time. This innovation will expedite the citation process for your publications.

As the New Editor-in-Chief and New Deputies Editor-in-Chief, we aim to increase the quality and visibility of Eur J Ther and to improve its indexes.

We want to remind you that the journal's target audience is researchers, physicians, and health professionals interested in or working in all medical and dental disciplines. Therefore, we request you submit your valuable research to Eur J Ther to contribute to the development and content of the journal.

Sincerely yours,

Editor-in-Chief
Ayşe Balat, MD

Deputies Editor-in-Chief
Şevki Hakan Eren, MD
Mehmet Sait Menzilcioğlu, MD
İlhan Bahşi, MD, PhD

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Eur J Ther. 2023. https://doi.org/10.58600/eurjther.20232902-edit2.y

News from the European Journal of Therapeutics: A new issue and a new editorial board

Ayşe Balat[1, 2], Şevki Hakan Eren[3], Mehmet Sait Menzilcioğlu[4], İlhan Bahşi[5], İlkay Doğan[6], Ahmet Acıduman[7], Bilal Çiğ[8], Tsvetoslav Georgiev[9, 10], Davut Sinan Kaplan[11], Mehmet Karadağ[12], Murat Karaoğlan[13], Waqar M. Naqvi[14], Ali Nasimi[15], Victor Nedzvetsky[16], Raphael Olszewski[17, 18], Janusz Ostrowski[19], Ayşe Aysima Özçelik[20], Maria Piagkou[21], Halima Resić[22], Aldo Rogelis Aquiles Rodrigues[23], Domenico Santoro[24], Onur Taydaş[25], Gregory Tsoucalas[26], Hamit Yıldız[27], Betül Yılmaz Furtun[28], Matthew J. Zdilla[29], Joseph Schmidt[30]

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Dear Colleagues,

In the previous editorial paper published by Balat et al. [1] as an Early View Article a few months ago, it was reported that there were changes in the Editorial Team of the *European Journal of Therapeutics (Eur J Ther)*. During these few months, while the preparations for the new issue (June 2023, volume 29, Issue 2) continued, the editorial board also was revised. We would like to inform you that the Editorial Board has been strengthened by academics who are competent in their fields from many countries of the world and will continue to be strengthened in the future.

As it is known, *Eur J Ther* started broadcasting in 1990 as a *Journal of the Faculty of Medicine University of Gaziantep (In Turkish: Gaziantep Üniversitesi Tıp Fakültesi Dergisi)*. In the first paper titled "While Starting" (In Turkish: Başlarken) of the first issue, Prof. Sabri Güngör, who was the first Editor-in-Chief, stated that the aim of the journal is to have an influential place in the field of science [2]. Over the past three decades, the journal has continued to advance. At the present time, it is inevitable to reorganize the editorial board of the journal and enrich it with leading international editors in order to move the journal to better places.

This editorial will explain essential developments in the journal in the last few months, and the new Editorial Board Members of the *Eur J Ther* will be introduced.

Changes are inevitable, and we are delighted to announce that this issue marks several significant improvements. Specifically, we bolstered our editorial team with esteemed international academics and expanded our pool of referees. Consequently, the evaluation period for the submitted articles was significantly reduced.

In the last two months, the journal metrics are as follows:

Acceptance rate: %29
Average time until the final decision: 24.4 days
Average time to publish as Accepted/Early View Article, after acceptance: 4.8 days.

Thanks to these improvements, as you will notice, there are 25 articles in this issue. In this way, this issue has been the issue in which most articles have been published so far. In addition, applications were made to DOAJ (Directory of Open Access Journals) and BASE (Bielefeld Academic Search Engine), among the most essential open-access databases in the world, in May 2023.

Moreover, cited references to the previous and/or alternative names of the journal *(Gaziantep Medical Journal, Gaziantep Med J, Gaziantep Tıp Dergisi and Gaziantep Üniversitesi Tıp Fakültesi Dergisi)* in Web of Science that were not reflected in the journal metrics were identified and reported to the Web of Science. Some of these correction requests have been finalized and corrected, and thus the total number of citations and the H-index of the journal increased [3]. After all these data are updated, it will be seen that the citation values of the *Eur J Ther* will increase even more. We will also update the guidelines for the authors and reviewers with respect to the ICMJE [4] and EQUATOR Network [5], which will enhance the quality of research in the medical fraternity.

Additionally, the use of DOI for articles published in the journal started in 2011 (2011, volume 17, Issue 2). In order to facilitate the recognition and access of the articles, DOIs have also been defined for all articles published in previous issues.

Editors

Ayşe Balat, MD, became the new Editor-in-Chief of *Eur J Ther* for the second time, the first between 2007-2010. She is a Professor in Pediatrics and a specialist in Pediatric Nephrology and Rheumatology. She has been working as Vice President of Gaziantep University since October 2020. She was the Dean of Gaziantep University Medical Faculty (2007-2010), President of the Mediterranean Kidney Society (MKS) between 2015 to 2018, and Secretary beginning in 2018. She is also President of the International Association for the History of Nephrology (IAHN) since 2022.

In Gaziantep, she first established Pediatric Nephrology and Pediatric Rheumatology Units, and the first peritoneal dialysis was performed by her.

She has several studies published in international and national peer-reviewed scientific journals (H-index: 26, i10-index: 59 and approximately 2500 citations). She was the Guest Editor of the International Journal of Nephrology in 2012 (special issue titled "Devil's Triangle in Kidney Diseases: Oxidative Stress, Mediators, and Inflammation"). She is a member of many national and international associations related to her field, including membership in the Turkish Pediatric Nephrology Association board in the past. She has several scientific presentation awards at national and international congresses. She has been joined as an "invited speaker" at 20 International Meetings.

As of 2007, she organizes World Kidney Day activities within the scope of the "Survival is not Enough" program (in the first rank among European pediatric nephrologists as an organizer of those activities).

Recently, she was elected as a "lifelong member of the Academy of Medicine and Surgical Sciences" of the University of Naples, which is one of the four important academies in Naples.

Şevki Hakan Eren, MD, is the new Deputy Editor-in-Chief of the *Eur J Ther*. Dr Eren graduated from the Medical School, University of Gaziantep, Turkey and completed Emergency training at Cumhuriyet University. He has been working as a Professor at Gaziantep University, Department of Emergency Medicine, Gaziantep, Turkey. He is interested in traumatology, and toxicology.

Mehmet Sait Menzilcioğlu, MD, is the new Deputy Editor-in-Chief of the *Eur J Ther*. Dr. Menzilcioğlu graduated from the Medical School, University of Gaziantep, Turkey and completed Radiology training at the same University. He has been working as an Associate Professor at Gaziantep University, Department of Radiology, Gaziantep, Turkey. He is interested in neuroradiology, ultrasonography, doppler Ultrasonography, Computerized Tomography, Magnetic Resonance Imaging, interventional radiology, and obstetric sonography.

İlhan Bahşi, MD, PhD, is the new Deputy Editor-in-Chief of the *Eur J Ther*. Dr Bahşi is also on the Editorial Board of the *Journal of Craniofacial Surgery*, *Frontiers in Neuroanatomy*, and *Mersin University School of Medicine Lokman Hekim Journal of History of Medicine and Folk Medicine*. In addition, he has published more than 80 articles (H-index: 12 and i10-index: 15) and has been a referee for more than 600 academic papers in many internationally indexed journals. Dr Bahşi, who has been working in the Department of Anatomy at the Gaziantep University Faculty of Medicine since 2012, completed his doctorate education in 2017 and obtained the title of PhD. Besides anatomy, he is particularly interested in the history of medicine, medical ethics, and education.

İlkay Doğan, PhD, is the new Editorial Board member of the *Eur J Ther* for Statistics and Methodology. He is in the Department of Biostatistics at the Gaziantep University Faculty of Medicine. His professional focus lies in research about Structural Equation Modeling, Multivariate Analysis. With a wealth of experience spanning over 15 years across multiple disciplines, including veterinary, nursing, sport and medicine, Dr Doğan has held various notable articles. He is a member of the Turkish Biostatistics Association.

Ahmet Acıduman, MD, PhD, graduated from Ege University Faculty of Medicine in 1987 and later specialized in Neurosurgery in 1997. Dr Acıduman further expanded his academic credentials by completing a PhD in the History of Medicine and Ethics in 2005. Currently, he is a Professor in the Department of History of Medicine and Ethics at Ankara University Faculty of Medicine. With a notable record of over 200 academic publications, Dr Acıduman's contributions to the field continue.

Bilal Çiğ, PhD, is a new Editorial board member of the *Eur J Ther*. Associate Prof Bilal Çiğ is a Postdoctoral researcher at King's College London Wolfson Card. He has been investigating the roles of ion channels in neurological diseases using the patch clamp technique for nearly 15 years. For the past few years, he has focused on the interactions of TRPA1 and Kir 4.1 channels in demyelination. He has 40 SCI-E and international publications, with about 1300 citations.

Tsvetoslav Georgiev, MD, PhD, holds an esteemed position as an associate professor at the First Department of Internal Medicine in Varna, Bulgaria, while also working as a clinician at the University Hospital St. Marina. He has successfully defended his doctoral dissertation in 2018 at the Medical University in Sofia. Having obtained a specialization in rheumatology that same year, Dr Georgiev has extensive expertise in this intricate field of medicine. He further expanded his knowledge and skills by attending comprehensive courses on imaging diagnostics and musculoskeletal ultrasound in rheumatology held in various locations. Dr Georgiev has been involved in formulating the Bulgarian consensus on osteoarthritis and EULAR recommendations for the non-pharmacological core management of osteoarthritis. Notably, Dr Georgiev has received recognition for his outstanding contributions as a reviewer, earning awards in 2019 and 2021 from the Korean Academy of Medical Sciences.

Davut Sinan Kaplan, PhD, is a new Editorial Board Member of the *Eur J Ther*. Dr Kaplan is an Associate Professor in the Department of Physiology at Gaziantep University Faculty of Medicine. He is also the Graduate School of Health Sciences' Director. He has taken involved in a wide variety of research with animal models. His research generally focuses on Endocrinology, Metabolism, Physical Activity, and Breast Milk. He has mentored a large group of master's and PhD students. He has served for many years as a member of the local animal experiments ethics committee.

Mehmet Karadağ, MD, is a new Editorial Board Member of the *Eur J Ther* for Psychiatry. Dr. Karadag is an Associate Professor of Child and Adolescent Psychiatry. He is in the Department of Child and Adolescent Psychiatry at the Gaziantep University School of Medicine. He has

experience on Posttraumatic Stress, Attention Deficit Hyperactivity, Autism Spectrum, Anxiety, Depressive Disorders and EMDR Therapy. He is also EMDRIA accredited EMDR Consultant.

Murat Karaoglan, MD, is a new Editorial Board Member of the *Eur J Ther* for Endocrinology. Dr. Karaoglan is an Associate Professor of Pediatric Endocrinology. He is in the Department of Pediatric Endocrinology at the Gaziantep University School of Medicine. He has experience on growth disorder, diabetology and disorder of sexual development.

Waqar M. Naqvi, PhD, is a faculty in the Department of Physiotherapy at the College of Health Sciences, Gulf Medical University, Ajman, UAE. His professional focus lies in the development of the research ecosystem within healthcare education, with a particular interest in AI, AR, VR, Sensors, and innovation in health sciences. With a wealth of experience spanning over 14 years across multiple countries, including India, Canada, Cameroon, Hong Kong, and Saudi Arabia, Dr Naqvi has held various notable positions. These include his roles as the Associate Director of Research at the NKP Salve Institute of Medical Sciences, Acting Dean and Vice Dean of the Physiotherapy College, Convener for the International Admission Office, International Accreditation and Quality Assurance Wing, Staff Selection Committee, and Coordinator for a Staff-Student Exchange Program.
In recognition of his outstanding contributions, Dr Naqvi was honored with the Distinguished Service Award and Young Achiever Award from the Indian Association of Physiotherapy. Dr Naqvi is widely recognized for his expertise in conducting seminars and workshops on research, publications, and intellectual property rights.
Specializing as a research trainer in the fields of medicine, dentistry, physiotherapy, and health sciences, Dr Naqvi's unwavering commitment to research excellence and his genuine passion for mentoring aspiring researchers are instrumental in shaping the future of healthcare. He firmly believes in the power of evidence-based practice and actively advocates for its implementation.

Ali Nasimi is a neuroscientist in the field of central regulation of the cardiovascular system.

Victor Nedzvetsky, PhD, DrSc is a full professor of Physiology, Biochemistry and Lab Diagnostics, where coordinates courses on Neurochemistry, Molecular and Cell Biology. Additionally, he is a vice-director of "The Biosafety Center" research and development company (Ukraine). He obtained PhD in biochemistry at Dnipropetrovsk University, Ukraine (1990). After postdoctoral training, he received a degree of Doctor Science at Kyiv National University (2006). Since 2015 he was involved as an invited professor of Bingol University, Turkey as a supervisor of PhD projects on genetic and molecular biology. He has participated in both the education and research work of the Dept. Art and Science of Bingol University from 2015 to 2021. His current research interests are focused on intestinal barrier function, brain blood barrier, astrocytes, cognitive deficits, bioactive compounds as anticancer agents, nanomaterials, and neuroprotection. He is the author of over 230 research publications and ten patents. He is a member of the editorial board of the journal "Regulatory Mechanisms of Biosystems".

Raphael Olszewski, DDS, MD, PhD, DrSc is a full professor of oral surgery and dentomaxillofacial radiology at the Université Catholique de Louvain (UCLouvain), Brussels, Belgium. Professor Olszewski is an oral surgeon and member of the Department of Oral and Maxillofacial Surgery at Cliniques Universitaires Saint Luc, UCLouvan, Brussels, Belgium. Prof Olszewski is the Editor-in-Chief of NEMESIS: Negative effects in medical sciences: oral and maxillofacial surgery.

Janusz Ostrowski, MD, PhD. Internal medicine, nephrology, and public health specialist. Former Head of the Department of Internal Medicine and Nephrology at the Provincial Hospital in Wloclawek, Poland. Director for Peritoneal Dialysis in Diaverum Company Poland. Secretary of the Historical Section of the Polish Society of Nephrology. Former President of the International Association for the History of Nephrology. Professor, Vice Dean of the School of Public Health and Head of the Department of the History of Medicine in the Centre of Postgraduate Medical Education in Warsaw, Poland.

Ayşe Aysima Özçelik, MD, is a new Editorial Board member of *Eur J Ther* for Neurology. She is the head of the pediatric neurology department and works at Gaziantep University Faculty of Medicine. She is the regional manager for the treatment of spinal muscular atrophy disease. She is an experienced physician in the treatment and follow-up of genetic neurological disorders, epilepsy, and neuromuscular diseases.

Maria Piagkou, DDS, MD, MSc, PhD is a new Editorial Board member of *Eur J Ther* for Neurology. She is an associate professor at the Department of Anatomy, School of Medicine, Faculty of Health Sciences, National and Kapodistrian University of Athens. She is a Deputy Vice-President of the Hellenic Association of Public Health in Greece and a President of the printed material handling committee of the National Organization for Medicines. She has twenty-one years of teaching activity in the field of anatomy, focused on head and neck, oral

and maxillofacial area, as well as on skull base anatomy and anatomical variants. Her main areas of interest are head and neck anatomy and surgery, skull base anatomy, oral surgery, maxillofacial and dental trauma, rehabilitation, intraoral fixation after condylar fractures, and teeth replantation. She is an associate editor in 2 journals of Anatomy and acts as Editorial Board Member in six other journals. She authored six chapters in neuroanatomy and oral and maxillofacial surgery and thoracic surgery books, two monographs, and edited the translation of 9 books. She is a reviewer in 30 international scientific journals. She authored 156 publications in PubMed, 91 abstracts in 26 international congresses, and 318 abstracts in Greek scientific meetings. She is General Secretary of the Sports Medicine Association of Greece and treasurer of the Hellenic Association of Anatomy.

Halima Resić, MD, PhD is a Professor of Internal Medicine – Nephrology in Sarajevo. Professor Resić studied medicine at the University of Belgrade where she also undertook a clinical fellowship in nephrology. She finished her postgraduate studies also at the University of Belgrade in 1987. Professor Resić worked at the Clinical Centre of Belgrade from 1972 to 1992. In 1993, she worked at the Marmara University of Istanbul. Also, in the period from 1994 to 1996, she took part in projects for refugees in Munich with the support of the Ministry of Health of the city of Munich. From 1996 till 2019, professor Resić worked at the Clinical Center University of Sarajevo, where she was head of the Clinic of Hemodialysis. In 2001, she obtained her PhD degree in Nephrology. She became a professor at the Medical Faculty of the University of Sarajevo in 2013.
Professor Resić published about 180 professional and scientific papers in relevant journals. She has been a president of organizations of a few national congress and nephrology schools, and also an active participant of ERA congress and WCN congress. She has also been invited lecturer in over 60 different international and national congresses.
Professor Resić was President of the BANTAO Society (2017-2019), and President of the Mediterranean Kidney Society. She has been President of the Society of Nephrology, Dialysis and Kidney Transplantation in Bosnia and Herzegovina (2010-2020) and also, she is President of Donor's network of Bosnia and Herzegovina. She is a member of ERA EDTA and ISN, and also a member of the Committee of SRC by ISN. She is a member of the Council of EAPE (European Association of Professor Emerita). She is also vice president of IANUBIH (International Academy of Science and Arts in Bosnia and Herzegovina) and a member of the board of South Eastern Europe by ISN.
In her carrier, she obtains many international awards for her work in the field of Nephrology.

Aldo Rogelis Aquiles Rodrigues is a new Editorial Board member of *Eur J Ther* for Neurology. Currently, he is an associate professor in physiology at the Federal University of Triângulo Mineiro, MG, Brazil since 2006. Before that, he worked as a research associate at the Department of Neurophysiology, Madison, USA from 2002 to 2005. He has experience in auditory neurons electrophysiology, enteric neurons, and ion channels in general.

Domenico Santoro is a Full Professor of Nephrology, Director of the Division of Nephrology and Coordinator of the Nephrology Fellowship Program University of Messina, AOU G. Martino – Messina. He is s a clinical expert in glomerular disorders with a scientific formation at the section of renal Pathology of the CSMC UCLA Los Angeles. He collaborated in genetic studies in glomerular disease. He coordinates as principal investigators several studies in glomerular disease both in clinical/therapeutical as well genetic aspects. He is the Associate Editor of the *Journal of Nephrology* and MBC Nephrology. Author of more than 270 scientific publications indexed on Scopus, H-index in Scopus: 38; H-index in Google Scholar: 46.

Onur Taydaş, MD, is a new Editorial Board Member of the *Eur J Ther* for Radiology. Dr Taydas is an Associate Professor in the Department of Radiology at the Sakarya University School of Medicine. He has a Turkish Society of Radiology Proficiency Certificate, a European Diploma in Radiology, and a Turkish Interventional Radiology Diploma. He has experience in neuroradiology, musculoskeletal radiology, and interventional radiology.

Gregory Tsoucalas (or Tsoukalas), born in 1974 and originated from the Island of Skopelos in the center of the Aegean Sea, he had studied Medicine in the University of Saint Kliment Ohridski in Sofia Bulgaria. He had then continued his studies in Lyon France and Athens Greece. He had been a Nuclear Medicine-Oncology-End stage physician in Saint Savvas Anticancer Hospital of Athens. He had after that moved to the city of Volos where he had been a physician in the Saint George Clinic for Alzheimer and Related Dementia Syndromes-End stage. He had finally moved to the General Clinic Anassa of Volos in the Internal Pathology Department. He currently holds the position of the Assistant professor of the History of Medicine, and head of the Department of History of Medicine and Medical Deontology, Medical School, University of Crete, Heraklion, Greece. Specialized in Nuclear Medicine, MSc in Palliative Medicine and PhD in the History of Medicine from National and Kapodistrian University of Athens, History of Medicine Diploma from Claude Bernard Lyon 1 University, post-doc in Anatomy from Democritus University of Thrace, Anthropology Course Diploma from Leiden University. He holds diplomas in Mastology and Clinical Nutrition for the related European Societies. He is the General Secretary of the Hellenic Branch of the

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Balkan Medical Union. Interested in the fields of History of Medicine, Deontology, Bioethics, Anatomy and Humanities, he is the writer of more than 200 articles in the PubMed database and more than 200 in other bases. He loves books and had published 10, while he had participated with chapters in various publications. Member of the International Society of the History of Medicine he had presented more than 130 speeches and 50 lectures in international level. Member of DELTOS (Hellenic Society) he had presented more than 400 speeches in local level. He enjoys more than 2500 citations, H-index: 17, and i10-index: 41.

Hamit Yıldız, MD, PhD, is the new editorial Board member for Internal Medicine. Dr Yildiz is an internal medicine specialist and practices in Gaziantep University Hospital. He is Board Certified in Internal Medicine. He completed his internship at Gaziantep University in Gaziantep and also graduated with a PhD in molecular biology. He has more than ten years of experience as a specialist who focuses on patients with diabetes, hypertension and thyroid diseases. His special interest is recombinant DNA technologies and the development of biotechnological drugs.

Betül Yılmaz Furtun, MD, FASE, FAAP, is a new Editorial Board Member for the *Eur J Ther*. She is an Associate Professor of Pediatrics at the Texas Children's Hospital, Baylor College of Medicine and Associate Medical Director of the Fetal Cardiology/Fetal Cardiac Intervention Program at Texas Children's Hospital. Dr Yilmaz Furtun is also a Course Director of Fetal Cardiology Education/Curriculum Development for advanced and categorical cardiology fellows and an Associate Director of the Fetal Care Center Steering Committee for fetal cardiology at Texas Children's Hospital. Dr Yilmaz Furtun is a pediatric cardiologist with expertise in advanced imaging modalities including fetal echocardiography, transthoracic and transesophageal echocardiography. Dr Yilmaz Furtun completed her pediatrics training at Washington University in St. Louis, pediatric cardiology training at Columbia University Medical Center, New York Presbyterian Hospital, and fetal cardiology/advanced imaging training at Cincinnati Children's Hospital. Dr Yilmaz Furtun actively participates in fetal and pediatric echocardiography laboratory protocol development and fetal and echocardiography lab and Fetal Care Center quality and improvement initiatives. Dr Yilmaz Furtun has been a member of the American Society of Echocardiography, the International Society of Ultrasound in Obstetrics and Gynecology, the Fetal Heart Society as well as American College of Cardiology. Dr Yilmaz Furtun's clinical and research focus relates to cardiac imaging by echocardiography and fetal echocardiography. She utilizes her experience in these areas to study how we can use non-invasive imaging modalities for investigating normal and abnormal cardiac function in patients with congenital heart disease and in fetuses with cardiac compromise. Her primary research interests focus on fetal cardiovascular assessment and cardiac dysfunction in patients with congenital heart disease, in fetuses with congenital abnormalities, and in multiple gestation pregnancies complicated by twin-twin transfusion syndrome.

Matthew Zdilla, DC, is a new Editorial Board Member for the *Eur J Ther*. Dr Zdilla was educated at the University of Pittsburgh and Northeast College of Health Sciences. He serves as an Associate Professor at the West Virginia University School of Medicine in the United States of America. He is an award-winning, internationally recognized clinical anatomist who has published scores of high-impact research papers regarding human diversity and the impact of anatomical variation on clinical procedures. In addition to his experience as an accomplished researcher, Zdilla brings his experience as an *ad hoc* reviewer for nearly 40 journals to the *European Journal of Therapeutics*.

Joseph Schmidt, MFA has taught academic writing for the University of Louisville and various campuses of The City University of New York (CUNY). An accomplished poet, he has contributed content to, and edited a number of small literary journals. At Gaziantep University, he has lent his editorial and native English language talents to some of his Turkish colleagues in the sciences. He teaches in the university's School of Foreign Languages (YDO).

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REFERENCES

[1] Balat A, Eren ŞH, Menzilcioğlu MS, Bahşi İ (2023) Editorial: From the Incoming Editors of the European Journal of Therapeutics (Eur J Ther). Eur J Ther. 29(2):e1-e1 https://doi.org/10.58600/eurjther.20232902-edit1.y

[2] Güngör S (1990) Başlarken. Eur J Ther 1(1):3-3. https://doi.org/10.58600/eurjther.19900101-1225

[3] Web of Science Advanced Search. https://www.webofscience.com/wos/woscc/summary/322e907e-3993-4bac-b4c7-7164b521bf73-906d2f10/relevance/1 Accessed Date: 09 June 2023

[4] International Committee of Medical Journal Editors (ICMJE). https://www.icmje.org/ Accessed Date: 13 June 2023

[5] EQUATOR Network - Enhancing the QUAlity and Transparency Of health Research. https://www.equator-network.org/ Accessed Date: 13 June 2023

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Original Research

Serum Nuclear Factor Erythroid-2 Related Factor-2 (NRF2) as an Indicator of Oxidative Stress is Related to Coronary in-Stent Restenosis

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ABSTRACT

Objective: In the treatment of coronary artery disease, stent implantation has become the standard treatment, but development of in-stent restenosis (ISR) limits the benefit of this treatment modality.

Methods: Based on the connection between oxidative stress and thiol/disulphate and NRF2, it was intended to measure NRF2 and thiol/disulphate levels.

Results: Coronary angiography images of 76 stable angina pectoris patients were evaluated. Of the 51 patients with a history drug eluting stent implantation, we determined 25 patients with ISR (Group 1) and 26 patients without ISR (Group 2). Twenty-five patients with normal coronary arteries were included in the study as control group (Group 3). NRF2 level was found to be significantly higher in patients who did not develop ISR (p=0.01). Total thiol was significantly higher in group 3 (738.76 micromole/L) compared to group 1 (626.11 micromole/L) and group 2 (630.27 micromole/L) (p=0.014). Native thiol was also significantly higher in group 3 (570.53 micromole/L) compared to group 1 (483.91 micromole/L) and group 2 (501 micromole/L)(p=0.006).

Conclusion: We think that total and native thiol levels might be useful as an indicator of oxidative stress in early diagnosis of coronary artery disease, and the NRF2 level can be used in predicting patients who might develop coronary ISR.

Keywords: NRF2, Thiol/Disulfate, Neointimal Hyperplasia, In-Stent Restenosis

INTRODUCTION

The severity of remodeling and intimal proliferation in the damaged artery wall with elastic recoil and fibrotic contractions after angioplasty play a role in the pathophysiology of coronary in-stent restenosis (ISR). Neointimal hyperplasia after remodeling and intimal proliferation is a natural response of the endothelium for vascular healing after stent implantation. Some of the previous studies suggested that inflammation and proliferation together with oxidative stress also might play a role in the mechanism of ISR mechanism [1,2].

The disorder in the balance between the production of reactive oxygen species (ROS), free radicals and antioxidant defense mechanisms is called oxidative stress [3-5]. This situation arises as a result of the insufficiency of reactive oxygen species such as superoxide radical, hydrogen peroxide, hydroxyl radical and antioxidant agents that detoxify them.

After oxidative stress, the body's immune system, especially the cytokine cascade, is activated. Serum nuclear factor erythroid-2 related factor-2 (NRF2) is a central regulator of antioxidant response element-associated gene expression and immune response. NRF2 enhances the expression of many antioxidant enzymes [6-8].

Thiols are antioxidant compounds with a sulfhydryl group attached to a carbon atom that prevent any oxidative stress in the body. Free oxygen radicals created during any oxidative stress situation are neutralized via binding by thiols. With oxidative stress, this balance shifts in favor of disulfide and thiols are reduced. As a result of the reaction, free disulfide bonds are created. Thiol groups are accepted as antioxidants and disulfide bonds as oxidants. Thus, dynamic thiol/disulfide balance is provided in the body [9-12].

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In this study, considering that the most common cause of coronary ISR is neointimal hyperplasia, we planned to measure serum nuclear factor erythroid-2 related factor 2 (NRF2), thiol and disuphate levels as potential antioxidants, which might play a role in inflammation. This study was planned with the anticipation that these molecules might potentially help in the early diagnosis and therefore possible early treatment of patients who would develop coronary ISR.

METHODS

In this single-center cross-sectional study, patients who presented to our cardiology clinic with the complaint of stable angina pectoris (CCS II-IV) between January 2020 and December 2020 despite optimal anti-ischemic medications and also had a single drug eluting coronary stent implanted at least 12 months ago were included. Out of 484 patients whose coronary angiography images were investigated, 76 patients were included in the study after evaluation for exclusion criteria. The 76 patients included in the study were divided into 3 groups: patients with 50-100% restenosis in the implanted stent (Group 1, patients with ISR, n=25); patients without ISR (less than 50% stenosis) (Group 2, patients without ISR, n=26) and patients with similar age and atherosclerotic risk profile who have normal coronary arteries on coronary arteriography were included in the study as control group (Group 3, control group, n=25)..Hospital records, epicrisis and coronary angiography images of the patients were examined, and patients who had a single type of stent implanted (everolimus-eluting Promus stent, Boston Scientific, USA) were included in the study.

Patients who had pregnancy, active infection, cancer, rheumatologic and autoimmune diseases were excluded from the study. Patients presenting with acute coronary syndrome, having high troponin values, having more than one coronary stent or drug eluting stents containing different types of antiproliferative drugs, and patients who have implanted bare metal stents were excluded from the study. If the patient was a woman during the menstrual period, she is also excluded from the study. The patients were informed with our written consent form approved by the ethics committee of the institution, and patient consent was obtained.

Two-dimensional coronary angiographies of the patients were evaluated by performing selective left and right coronary arteriography using the Judkins technique. Angiography procedures were performed and evaluated by interventional cardiologists who have coronary angiography and percutaneous coronary intervention experience (>250 cases/year). Coronary arteries were visualized using cranial, caudal, and antero-posterior angulation in right and left anterior oblique positions [13,14].

Stenosis degrees were determined by angiographic images and calibration techniques for the vessels. The stenosis of the detected lesion was measured with the Quantitative Coronary Angiography (QCA) software (Siemens, Erlangen, Germany) with reference to the healthy segment in the proximal and distal part of the lesion (Figure 1). For optimal evaluation of the previously implanted stent, operators paid attention to take images from at least two orthogonal planes. Measurements were taken as the diameter of the artery in such a way that it cuts the vessel cross sectionally through the lumen and the stenosis severity was calculated over the vessel luminal diameter. ISR was defined as greater than 50% diameter of narrowing in the stent or within 5 mm of stent proximal or distal margins. In a study, it was determined that quantitative methods are better than visual calculation in detecting in stent restenosis [15]. Both intra and interobserver variability for in stent restenosis was less than%1. It's If there is diffuse neointimal hyperplasia along the stent, the healthy segment distal to the stent was taken as reference [16-18].

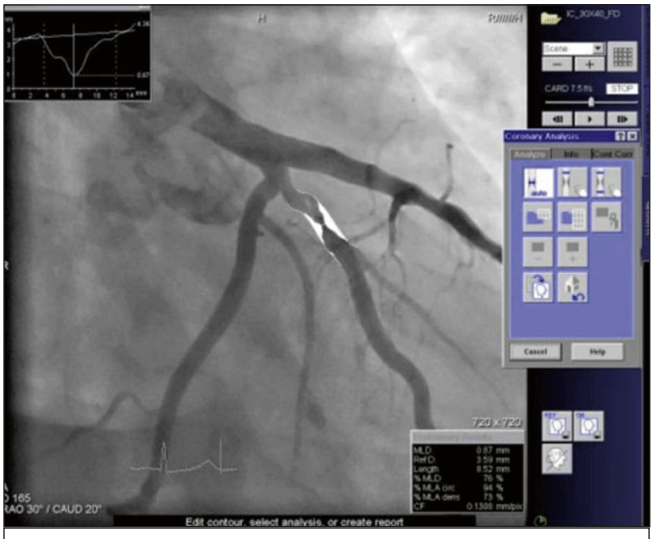

Figure 1. Example of Quantitative Coronary Angiography (QCA) analysis for measurement of coronary in-stent restenosis

Venous blood samples were taken immediately after the angiography procedure from the patients and serum was obtained by centrifugation at 5000 rpm for 10 minutes. It was kept at -80°C until the day of calculation. When the samples were completed, they were taken out of the freezer and kept at room temperature until they melted, and the measurements were made with the same kit. NRF-2, Total Thiol, Native Thiol, Disulfide levels, Total Thiol/Disulfide, Native Thiol/Disulfide and Native Thiol/Total Thiol ratios were measured in the blood samples.

Serum nuclear factor erythroid-2 related factor 2 (NRF2) measurement was made with the human NRF2 ELISA kit coded REF: CK-bio-12691 LOT: 202008 (Shanghai Coon Koon Biotech Co. Ltd). Total thiol measurement was made with the Rel Assay Diagnostics brand kit with the code REF: RL0178 LOT: AS2001T. Native thiol measurement was performed with the Rel Assay Diagnostics brand kit with the code REF: RL0185 LOT: AS2001N. After measuring native and total thiol, disulfide content, disulfide/total thiol ratio (SS/SH + SS), native thiol/total thiol ratio (SH/SH + SS), disulfide/native thiol ratios (SS/SH) were calculated.

Statistical Analysis

The compatibility of numerical variables to normal distribution was tested by Shaphiro Wilk test. For the comparison of variables

in three groups, ANOVA and LSD tests were used in normal distribution, and Kruskal Wallis and Dunn multiple comparison tests were used in other parameters. Mann-Whitney-U test was used to compare variables that were not normally distributed in two groups. Relationships between categorical variables were tested with Chi-square and Bonferroni tests. SPSS 25.0 (IBM, USA) program was used for the analyzes. p value of <0.05 was accepted significant.

RESULTS

The demographic characteristics of all patients included in the study are shown in Table 1. As can be appreciated, age, gender characteristics, atherosclerotic risk factors and statin drug use are similar. Coronary artery stents of the patients were selected as the everolimus eluting (Promus, Boston Scientific, USA) drug type. In Table 1, it has been demonstrated that there is no statistically significant difference regarding stent diameter or length between groups 1 and 2 (p>0.05).

Total thiol was significantly higher in group 3 (738.76 micromole/L) compared to group 1 (626.11 micromole/L) and group 2 (630.27 micromole/L)(p=0.01). Native thiol was significantly higher in group 3 (570.53 micromole/L) compared to group 1 (483.91 micromole/L) and group 2 (501 micromole/L)(p= 0.006). There was no significant difference between the groups in terms of Native thiol/Total thiol ratio (p = 0.428)(Table 2).

For disulfide, no significant difference was found between group 1 (71.1 micromole/L), group 2 (64.64 micromole/L) and group 3 (84.11 micromole/L)(p=0.10). Also, there was no significant difference in Native thiol/Disulfide ratio in all three groups (p=0.42). Additionally, there was no significant difference between the three groups in the ratio of Total thiol/Disulfide (p=0.428)(Table. 2).

Total thiol levels were significantly higher in the control group than in group 1 and group 2 (p=0.009 and p=0.013, respectively). No difference was found between group 1 and group 2 in terms of total thiol (p=0.92). Native thiol levels were significantly higher in the control group than group 1 and group 2 (p=0.003 and p=0.015, respectively). No difference was also found between group 1 and group 2 in terms of native thiol (p=0.54)(Table 3). Thiol levels were found to be higher in patients with normal coronary arteries (group 3), as expected.

NRF2 levels were found as 105.97 pg/mL in group 1, 131.53 pg/mL in group 2 and 116.54 pg/ mL in group 3, and a statistically significant difference was also observed (p=0.029)(Table 4). When the groups are compared with each other in terms of NRF2 levels there was a significant difference between the group 1 and 2 (p=0.01)(Table 5).

In our study, the low level of NRF2 in group 1 patients who developed ISR suggests that NRF2 did not prevent neointimal hyperplasia and remodeling sufficiently, but NRF2 was significantly higher in group 2, that NRF2 protects coronary vessels from ISR and neointimal hyperplasia.

Table 1. Comparison of the demographic characteristics of all three groups and the sizes of implanted stents for Groups 1 and 2

	Group 1 (ISR +)	**Group 2 (ISR -)**	**Group 3 (Control)**	**p**
	n=25	**n=26**	**n=25**	
Age (year)	62.8±7.6	64.5±9.9	62.5±9.7	0.42
Gender (M/F)	18/7	18/8	16/9	0.82
Diabetes mellitus n(%)	10 (40)	8 (30)	9 (36)	0.78
Hypertension n(%)	16 (64)	15 (57)	10 (40)	0.12
Hyperlipidemia n(%)	20 (80)	20 (76)	14 (56)	0.18
Smoker n(%)	8 (32)	10 (38)	6 (24)	0.53
Family history n(%)	10 (40)	10 (38)	8 (32)	0.82
Stent diameter (mm)	3.15±0.57	3.11±0.59	-	0.84
Stent length (mm)	30.9±5.1	29.3±4.2	-	0.07
Use of statin n(%)	12 (48)	13 (50)	11 (44)	0.11

ISR: in-stent restenosis; M: male; F: female, mm: milimeter

Table 2. Comparison of thiol, disulfide levels and their ratios between study groups

	Group1 (ISR+) n=25	Group2 (ISR-) n=26	Group3 (Control) n=25	p
Total thiol (micromole/L)	626.11±173.47	630.27±111.42	738.76±150.16	0.01
Native thiol (micromole/L)	483.91±105.69	501.00±87.79	570.53±96.49	0.006
Disulfide (micromole/L)	71.10±36.70	64.64±22.85	84.11±33.21	0.10
Native thiol/Disulfide	10.26±10.08	8.57±2.93	8.04±4.11	0.42
Total thiol/Disulfide	12.26±10.08	10.57±2.93	10.04±4.11	0.42
Nativ thiol/Total thiol	0.79±0.07	0.8±0.05	0.78±0.06	0.42

ISR: in-stent restenosis

Table 3. Comparison of Total Thiol and Native Thiol levels between groups of two

Total thiol (micromole/L)	Group1	Group2	0.922
		Group3	0.009
	Group2	Group1	0.922
		Group3	0.013
	Group3	Group1	0.009
		Group2	0.013
Native thiol (micromole/L)	Group1	Group2	0.540
		Group3	0.003
	Group2	Group1	0.540
		Group3	0.015
	Group3	Group1	0.003
		Group2	0.015

Table 4. Comparison of NRF2 value between study groups

	Group 1 (ISR +) n=25			Group 2 (ISR -) n=26			Group 3 (Control) n=25			p
	Median	% 25	% 75	Median	% 25	% 75	Median	% 25	% 75	
NRF2 (pg/mL)	105.97	100.68	133.58	131.53	111.84	140.63	116.54	106.56	128.88	0.029

ISR: in-stent restenosis

Table 5. Multiple comparisons between study groups for NRF2 value

Groups	p
Group 1 - Group 3	0.48
Group 1 - Group 2	0.01
Group 3 - Group 2	0.06

DISCUSSION

Coronary stents used in the percutaneous treatment of coronary artery disease are thin strut metal skeletons that are implanted in the stenotic part of the vessel lumen and apply radial force to the intima layer of the vessel and provide luminal opening. Trauma to the vascular wall causes an increase in neointimal hyperplasia and restenosis that develops within the first 6-12 months [19,20]. Since rapamycin analogues (sirolimus, zotarolimus, everolimus, biolimus A9, novolimus and amphilimus) and paclitaxel, which show anti-inflammatory and antiproliferative properties, these drug eluting coronary stents prevent neointimal hyperplasia. Consequently ISR is less common in these patients. In this way, ISR rates have been reduced to 5-10% [21]. However, ISR development still continues to be an issue for daily clinical practice. Inflammation and neointimal proliferation play a role in the ISR mechanism, and it is thought that oxidative stress might also have possible effects for ISR [22].

It is predicted that oxidative stress could be responsible for the pathogenesis of many diseases, especially cancer, diabetes mellitus, cardiovascular and neurological diseases, atherosclerosis and inflammatory disorders [23,24]. Free oxygen radicals occurring in any oxidative stress situation are neutralized via binding by thiols. Thiol groups are considered to be effective as antioxidants, while disulfide bonds are considered to be effective as oxidants.

Abnormal thiol hemostasis has been associated with a variety of diseases, while exogenous thiol administration increased tolerance to oxidative stresses and, in some cases, the prevention or treatment of diseases in humans [25]. The compounds used include "protiol" compounds such as GSH and its derivatives, thiols such as cysteine and N-acetyl-L-cysteine, dithiols such as lipoic acid, and OTC that are converted intracellularly into free thiols [12]. In our study, we measured thiol and disulfide levels in coronary artery disease patients with and without ISR, and also in cases who have normal coronary arteries. Statins have antioxidant and pleiotropic effects. But in our study all the groups used statins with similar ratio.

NRF2 provides gene regulation by taking part in intracellular signal transduction, thus it is effective in the development of transcription, anabolic metabolism, cell proliferation and extracellular matrix remodeling [26]. As a result, NRF2 manages the resistance and repair of tissue against damage [27]. We expected the NRF2 level to be high in group 2 patients who did not develop restenosis by suppressing the in-stent inflammatory response caused by oxidative stress and keeping remodeling in balance. Thus, NRF2 level was found to be significantly higher in this group compared to other groups in our study.

A study has been conducted to suggest that there might be a relationship between atherosclerosis resistance and NRF2 activation in human endothelial cells [12] Exposure to oxidized LDL in the endothelium causes an increase in NRF2 protein in macrophages and protects cells from oxidative injury. NRF2 deficiency in macrophages leads to increased proatherogenic foam cell formation and aggravation towards atherosclerosis [28]. Considering the protective effect of NRF2, it can be considered that a drug that induces NRF2 is promising for possible protection from atherosclerosis and its clinical results.

In a study conducted by Serruys PW et al, it was observed that everolimus significantly reduced late lumen loss in angiographies at 6 and 12 months in the comparison of cobalt chromium bare metal stent and everolimus-releasing stent in coronary artery patients during 5-year follow-up [29]. In our study, all patients were selected among the patients with new generation everolimus eluting coronary stents, and thus, the effect of possible antiproliferative drug diversity or the use of bare metal stents between the groups was eliminated.

In a study conducted with coronary artery patients, the relationship between total antioxidant status, oxidative stress and coronary artery disease was investigated [30]. 87 patients who were hospitalized for coronary angiography were included in the study group. Plasma total oxidative status (TOD) and total antioxidant capacity (TAC) levels were measured and the oxidative stress index (OSI) was calculated. Plasma total antioxidant capacity levels were found to be high in people with coronary artery disease and the severity of coronary atherosclerosis was found to be associated with TAC. In our study, total and native thiol levels were studied, and antioxidant thiols in group 1 and group 2 with coronary artery disease were significantly lower than in group 3 without coronary artery disease. However, the number of patients in our study was not sufficient to determine a cut-off thiol level to exclude the presence or absence of coronary artery disease.

Recently in a study it's determined that some oxidative and antioxidative markers showed the potential in the prediction of ISR risk.31 Also in our study we found that NRF2 protects coronary vessels from ISR and neointimal hyperplasia

In a study done by Chen QM et al, it was found that high NRF2 levels suppressed the development of inflammation and atherosclerosis in the vascular endothelium. Considering the possible protective effect of NRF2, it was thought that a drug that induces NRF2 level could be promising for myocardial protection [7].

In order to evaluate the importance of thiol/disulfide balance for antioxidant defense mechanisms in protecting against oxidative stress, Kundi et al. investigated the role of thiol/disulfide balance in patients with acute myocardial infarction [32,33]. As a result of the study, it was determined that native thiol and total thiol levels were lower, and disulfide/native thiol and disulfide/total thiol ratios were higher in the acute myocardial infarction group compared to healthy adults. They reported that high disulfide levels and disulfide/total thiol levels are risk indicators for acute myocardial infarction. In our study, unlike this study group, patients with stable angina pectoris predicted to have stable atherosclerotic plaques were selected instead of acute coronary syndrome. In this way, we eliminated the expected inflammatory response in patients with acute coronary syndrome possibly affecting oxidative stress test results.

Study Limitations

The relatively small number of patients is the most important limitation of the study. However, even with this number of patients, statistically significant results were obtained. In addition, making a single measurement from each patient and not checking repetitive values in the time interval might be another limitation of the study.

CONCLUSION

In conclusion, it is thought that thiol/disulphate balance could be used as an indicator of oxidative stress in the early diagnosis of coronary artery disease, and the NRF2 level might allow early diagnosis and treatment of patients who develop coronary ISR. Further studies which could be done with larger number of patients would clarify this situation.

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REFERENCES

1. Ross R et al (1999) Atherosclerosis- an inflammatory disease. N Engl J Med. 340:115-26. https://doi.org/10.1056/NEJM199901143400207
2. Otsuka F, Finn AV, Yazdani SK, Nakano M, Kolodgie FD, Virmani R (2012) The importance of the endothelium in atherothrombosis and coronary stenting. Nat Rev Cardiol. 9:439-53. https://doi.org/10.1038 /nrcardio.2012.64
3. Halliwell B et al (1994) Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet. 344:721-4. https://doi.org/10.1016/s0140-6736(94)92211-x
4. Özcan O, Erdal H, Çakırca G, Yönden Z (2015) Oxidative stress and its impacts on intracellular lipids, proteins and DNA. J Clin Exp Invest. 6:18-25. https://doi.org/10.5799/ahinjs.01.2015.03.0545
5. Harris C, Hansen JM (2012) Oxidative stress, thiols, and redox profiles. Methods Mol Biol. ;889:325-46. https://doi.org/10.1007/978-1-61779-867-2_21
6. Hayes JD, Dinkova-Kostova AT (2014) The NRF2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci. 39:199-218. https://doi.org/10.1016/j.tibs.2014.02.002
7. Chen QM, Maltagliati AJ (2018) NRF2 at the heart of oxidative stress and cardiac protection. Physiol Genomics. 50:77-97. https://doi.org/10.1152/physiolgenomics.00041.2017
8. Ruotsalainen A-K, Inkala M, Partanen ME, Lappalainen JP, Kansanen E, Mäkinen PI et al. (2013) The absence of macrophage NRF2 promotes early atherogenesis. Cardiovascular Research. 98:107-15. https://doi.org/10.1093/cvr/cvt008
9. Altıparmak IH, Erkus ME, Sezden H et al. (2016) The relation of serum thiol levels and thiol/disulphide homeostasis with the severity of coronary artery disease. Kardiol Pol. 74:1346-53. https://doi.org/10.5603/KP.a2016.0085
10. Erel O, Neselioglu S (2014) A novel and automated assay for thiol/disulphide homeostasis Clinical Biochemistry. 47:326-32. https://doi.org/10.1016/j.clinbiochem.2014.09.026
11. Sen CK, Packer L (2000) Thiol homeostasis and supplements in physical exercise. The American Journal of Clinical Nutrition. 72:653-669. https://doi.org/10.1093/ajcn/72.2.653S
12. Deneke SM (2000) Thiol-based antioxidants. Curr Top Cell Regul. 36:151-80. https://doi.org/10.1016/s0070-2137(01)80007-8
13. Sheldon WC (1971) Cine Coronary Arteriography. Surgical Clinics of North America. 51:1015-22. https://doi.org/10.1016/s0039-6109(16)39527-5
14. Judkins MP (1967) Selective coronary arteriography. A percutaneous transfemoral technic. Radiology. 89:815-24. https://doi.org/10.1148/89.5.815
15. Masayuki Yoshimura, Tomoko Nao, Munemasa Okada, Yoshiteru Nakashima, Tatsuhiro Fujimura et al. (2015) New quantitative method to diagnose coronary in-stent restenosis by 64-multislice computed tomography. J Cardiol. 65(1):57-62. https://doi.org/10.1016/j.jjcc.2014.03.013
16. Ong ATL, Aoki J, McFadden EP, Serruys PW (2004) Classification and Current Treatment Options of In-Stent Restenosis. Herz. 29:187-94. https://doi.org/10.1007/s00059-004-2574-4
17. Nayak AK, Kawamura A, Nesto RW, Davis G, Jarbeau J, Pyne CT et al. (2006) Myocardial Infarction as a Presentation of Clinical In-Stent Restenosis. Circ J. 70:1026-9. https://doi.org/10.1253/circj.70.1026
18. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF et al. (1999) Angiographic Patterns of In-Stent Restenosis: Classification and Implications for Long-Term Outcome. Circulation. 100:1872-8. https://doi.org/10.1161/01.cir.100.18.1872

19. Rensing BJ, Hermans WRM, Beatt KJ, Laarman GJ, Suryapranata H, van den Brand M et al. (1990) Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. The American Journal of Cardiol. 66:1039-44. https://doi.org/10.1016/0002-9149(90)90501-q

20. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L (1987) Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 316:701-6. https://doi.org/10.1056/NEJM198703193161201

21. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong C. Et al. (1996) Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 94:35-43. https://doi.org/10.1161/01.cir.94.1.35

22. Stolker JM, Kennedy KF, Lindsey JB, Marso SP, Pencina MJ, Cutlip DE, vd. Predicting Restenosis of Drug-Eluting Stents Placed in Real-World Clinical Practice: Derivation and Validation of a Risk Model From the EVENT Registry. Circ Cardiovasc Interv. 2010;3:327-34. https://doi.org/10.1161/CIRCINTERVENTIONS.110.946939

23. Berlett BS, Stadtman ER (1997) Protein oxidation in aging, disease, and oxidative stress. J Biol Chem. 272:20313-6. https://doi.org/10.1074/jbc.272.33.20313

24. Gupta RK, Patel AK, Shah N, Choudhary AK, Jha UK, Yadav UC et al. (2014) Oxidative Stress and Antioxidants in Disease and Cancer: A Review. Asian Pacific Journal of Cancer Prevention. 15:4405-9. https://doi.org/10.7314/apjcp.2014.15.11.4405

25. Turell L, Botti H, Carballal S, Radi R, Alvarez B (2009) Sulfenic acid-a key intermediate in albumin thiol oxidation. J Chromatogr B Analyt Technol Biomed Life Sci. ;877:3384-92. https://doi.org/10.1016/j.jchromb.2009.03.035

26. Chan K, Han X-D, Kan YW (2001) An important function of NRF2 in combating oxidative stress: Detoxification of acetaminophen. Proceedings of the National Academy of Sciences. 98:4611-6. https://doi.org/10.1073/pnas.081082098

27. Li R, Jia Z, Zhu H (2019) Regulation of Nrf2 Signaling. React Oxyg Species. Apex. 8:312-22.

28. Dai G, Vaughn S, Zhang Y, Wang ET, Garcia-Cardena G, Gimbrone MA (2007) Biomechanical forces in atherosclerosis-resistant vascular regions regulate endothelial redox balance via phosphoinositol 3-kinase/Akt-dependent activation of NRF2. Circ Res. 101:723-33. https://doi.org/10.1161/CIRCRESAHA.107.152942

29. Serruys PW, Ong ATL, Piek JJ, Neumann F-J, van der Giessen WJ, Wiemer M (2005) A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. EuroIntervention. 1:58-65. PMID: 19758878

30. Aydın M, Selcuki Y, Nazlı Y, Yalçın KS, Canbal M, Demirçelik B et al (2012) Relationship between total antioxidant capacity and the severity of coronary artery disease. J Clin Exp Invest. 3:22-28. https://doi.org/10.5799/ahinjs.01.2012.01.0105

31. Ganjali S, Mansouri A, Abbasifard M, Moallem SA, Tayarani-Najaran Z, Sahebkar A (2022) Association between Oxidative Burden and Restenosis:A Case-Control Study Oxid Med Cell Longev. 68:832. https://doi.org/10.1155/2022/3577761

32. Kundi H, Ates I, Kiziltunc E, Cetin M, Cicekcioglu H, Neselioglu S et al. (2015) A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med. 33:1567-71. https://doi.org/10.1016/j.ajem.2015.06.016

33. Kundi H (2017) Association of novel inflammatory and oxidative stress biomarkers with in-stent restenosis. Angiology. 68:832. https://doi.org/10.1177/0003319717700747

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Original Research

Neutrophil–Lymphocyte Ratio, Monocyte–Lymphocyte Ratio and Platelet–Lymphocyte Ratio in Manic Episode Patients with Bipolar Disorder

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ABSTRACT

Objective: Inflammation is one of several etiopathological mechanisms contributing to bipolar disorder. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) are relatively cheap hematological parameters recommended to measure the level of inflammation. In this study, the NLR, MLR, and PLR values of the same patients during manic and euthymic periods were compared to a healthy control group.

Methods: This retrospective study was conducted on inpatients with bipolar disorder manic episodes at the Karamanoglu Mehmetbey University Faculty of Medicine psychiatry clinic. Ninety-nine patients with manic episodes of bipolar disorder and age and gender-matched 101 volunteers without prior psychiatric illness were included in the study. Neutrophil, lymphocyte, monocyte, and platelet counts during the disease period were recorded, and NLR, MLR, and PLR values were calculated from these values. Similar hematological parameters of the same patients in the euthymic period after discharge were compared.

Results: Of the patients, 52 (52.6%) were male and 47 (47.4%) were female. The mean age of the patients was 35.3±13.09 years. Patients with manic episodes were shown to have significantly higher neutrophil, platelet, NLR, MLR, and PLR levels than the control group ($p<0.001$). Monocyte count was significantly lower in manic episode patients compared to controls ($p<0.001$). Neutrophil and monocyte counts were significantly lower during the euthymic period compared to the control group, while NLR, MLR, and PLR levels were higher ($p<0.001$).

Conclusions: The fact that NLR, MLR, and PLR are higher in BD patients compared to the healthy control group in both manic and euthymic periods indicates that they can be used as trait biomarkers. For biomarker studies, prospective studies with large samples are needed.

Keywords: Bipolar disorder; inflammation; biomarkers; neutrophil-lymphocyte ratio

INTRODUCTION

Bipolar disorder (BD) is a multifactorial chronic disease marked by mood swings between manic/hypomanic episodes and depressive periods. Bipolar disorder has a 4.4 percent lifetime prevalence, has a negative economic and social effect, and is one of the top causes of disease-related disability globally [1]. If untreated, it can lead to suicide [2]. Despite the current medications, the disease's progress is frequently unrelenting and a group of patients is resistant to treatment [3]. Inadequate therapy may be due to a lack of understanding of the physiopathology of BD. There is no specific laboratory finding or biomarker for diagnosis, and detailed clinical evaluation is the keystone of diagnosis [4]. Biomarkers are essential in understanding the pathophysiology of a disease, identifying new treatment targets, and monitoring the response to therapy [5]. The discovery of pathophysiological biomarkers in BD may be crucial in developing novel molecular treatments [6]. Inflammation is one of many etiopathological mechanisms of bipolar disorder that have recently been highlighted [7]. Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) have all been proposed as inflammatory markers [8]. NLR, MLR, and PLR biomarkers are widely available, cheap, and widely used.

The aim of this study was to investigate how NLR, MLR, and PLR alter during bipolar manic and euthymic episodes.

To achieve this, firstly, NLR, MLR, and PLR values in mania and euthymia in Patients with BD were compared to healthy controls

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and secondly, changes in NLR, MLR, and PLR values in BD patients were assessed from the manic to the subsequent euthymic period.

METHODS

This retrospective survey was carried out on bipolar disorder inpatients. (DSM-V) manic episodes at the Karamanoglu Mehmetbey University Faculty of Medicine psychiatry clinic between January 1, 2016, and January 1, 2022. All data were collected from patient files in the hospital's electronic medical record database; patients with full blood counts within the first 24 hours of admission were included. Those who have any local and systemic inflammatory disease, use anti-inflammatory therapy and have acute and chronic illnesses that may cause abnormal inflammatory parameters were left out of the research. Those under the influence of drugs and pregnant women were also withdrawn from participating in the research.

After obtaining the necessary permissions, the data were scanned retrospectively from the hospital archive. A total of 162 BD patients' records were accessed. The study excluded 21 diabetes patients, 15 hypertension patients, 13 people with various rheumatological disorders, 6 pregnant women, and 8 adults over the age of 65.

The study comprised 99 participants with bipolar illness and manic episodes. Patients' sociodemographic characteristics and clinical features were collected. Whole blood count was performed on the first day of hospitalization. Blood samples were collected on EDTA tubes. Neutrophil, monocyte, thrombocyte, and lymphocyte numbers values, were measured on an automatic whole blood analyzer. The NLR, MLR, and PLR were calculated.

The numbers of neutrophils, monocytes, platelets, and lymphocytes at the first hospitalization were recorded and used to calculate NLR, MLR and PLR values. Neutrophil, monocyte, thrombocyte, and lymphocyte counts, NLR, MLR, and PLR values were retaken while the same patients were in the euthymic period after they were discharged. Euthymic period blood values were taken between two months and twelve months after remission.

The control group consisted of people who donated to the hospital blood bank. Examinations were made to show that those who want to donate blood do not have any chronic diseases, infectious diseases, or drug use. Written consent was obtained for future studies like this study. Blood values of age- and gender-matched 101 volunteers without prior psychiatric illness were recorded retrospectively.

Main points

- In our study, NLR, MLR and PLR were found to be high in BD manic patients.
- The persistence of NLR, MLR, and PLR elevations in the euthymic period of patients indicates that it may be a trait marker.
- Our findings show that inflammation persists even when patients recover.

Exclusion criteria for all participants were;
(i) those with autoimmune disease
(ii) severe systemic diseases like hematological, endocrinological, neurological, renal, hepatic disease, cardiovascular diseases, lung disease, and infectious diseases
(iii) all other acute and chronic diseases
(iv) use of any drug including anti-inflammatory and anticoagulant drugs
(v) alcohol and substance use disorders
(vi) neurodevelopmental disorders
(vii) traumatic injury
(viii) pregnancy
(ix) body mass index (BMI) greater than 30 kg/m^2.

This study was carried out in accordance with the updated version of the Helsinki Declaration.

Karamanoglu Mehmetbey University Faculty of Medicine Clinical Research Ethics Committee approved the study 104096.

Statistical Analysis

The data were analyzed using the IBM SPSS 26 packet data software, with 95% confidence limits (p=0.05). Descriptive statistics of continuous measurements are given as mean, standard deviation, min-max, and median values. The Kolmogorov-Smirnov test and the skewness-kurtosis criterion were used to determine the normality test of continuous measurements. The t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables were used to compare the two groups. The Wilcoxon test was used to compare before and after measures, such as the patients' euthymic and manic episodes.

RESULTS

Table 1 shows demographic statistics. The research included 200 individuals, including 101 healthy controls and 99 bipolar disorder patients. The groups did not differ in terms of age or gender. The mean disease duration in the bipolar disorder group was 12.44 years. 54% of the patients had psychotic symptoms. Six patients suffered from their first manic episode (Table 1).

Neutrophil, platelet count, NLR (Figure 1), MLR (Figure 2), and PLR (Figure 3) values were found to be significantly higher in patients with manic episodes compared to the control group. Monocyte count was significantly lower in manic episode patients compared to controls.

In the euthymic period, neutrophil and monocyte counts were significantly lower, and NLR, MLR, and PLR were higher than in the control group. There was no significant difference in platelet count between the euthymic and control groups. When compared to the manic stage, there was a significant rise in lymphocyte count during the remission period (Table 2).

Table 1. Sociodemographic data of the groups

		Bipolar-Manic Disorder (n:99)		Control Group (n:101)		p Value
Age, mean ± SD		35.3±13.09		34.8±11.7		0.190
Gender	Female	47	47.4%	41	40.6%	0.327
	Male	52	52.6%	60	59.4%	
Psychotic symptom	Yes	54(55%)				
	No	45(45%)				
First episode	Yes	6(6%)				
	No	93(%93)				
Duration of disease		12.44± 8.3				
Treatment						
Valproate		31(31%)				
Lithium		53(53%)				
Valproate+Lithium		7(7%)				
Other mood stabilizer		3(3%)				
Antipsychotic		83(83%)				

Table 2. Blood counts and NLR, MLR, and PLR values of the groups

Variables	Bipolar-manic (n:99) Median (min-max)	Bipolar-euthymic (n:99) Median (min-max)	Control (101) Median (min-max)	p(1)	p(2)	p(3)
Neutrophil	5.03(1.89-13.3)	4.25(2.19-7.88)	4.82(2.4-16.6)	p<0.001	0.004	0.688
Lymphocyte	2.25(0.7-5.2)	2.31(1.26-4.31)	2.56(1.2-4.8)	0.224	0.256	p<0.001
Monocyte	0.54(0.3-1.06)	0.45(0.18-0.99)	0.57(0.06-1.06)	p<0.001	p<0.001	0.542
Platelet	259(138-548)	244(100-420)	247(143-450)	0.043	0.32	0.514
NLR	2.23(0.87-7.63)	2.2(0.91-7.57)	1.7(0.8-5.3)	p<0.001	p<0.001	0.686
MLR	0.24(0.11-0.96)	0.25(0.03-0.56)	0.19(0.1-0.6)	p<0.001	p<0.001	0.483
PLR	118.75(36.4-314.7)	118.05(27.6-302.9)	105.6(51.86-265.9)	0.001	0.008	0.606

NLR; Neutrophil-to-lymphocyte ratio, MLR; monocyte-to-lymphocyte ratio, PLR; platelet-to-lymphocyte ratio
Data are expressed as median(min-max).
P1: The bipolar-manic episode and the control group comparison.
P2: Bipolar remission phase and control group comparison.
P3: Bipolar manic and remission periods are comparison.

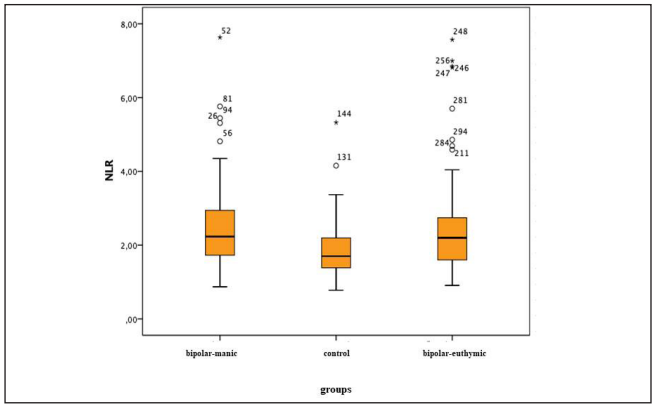

Figure 1. NLR distribution of groups

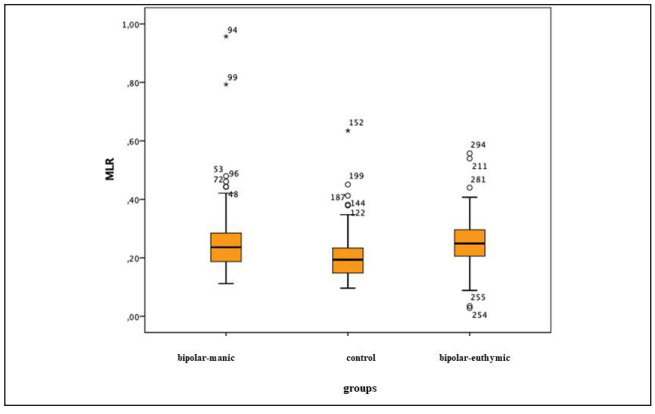

Figure 2. MLR distribution of groups

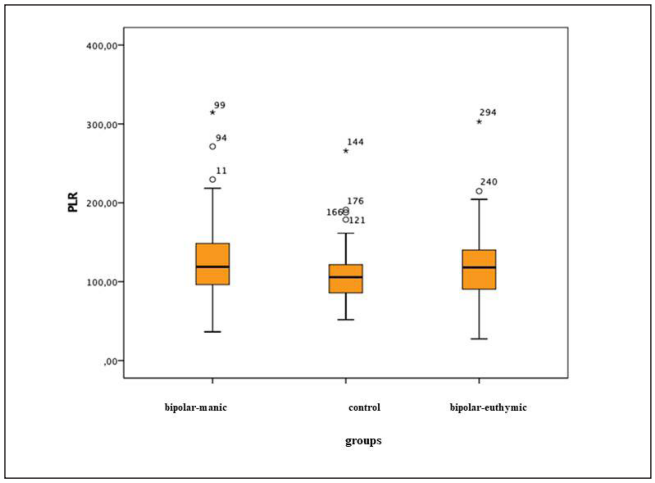

Figure 3. PLR distribution of groups

DISCUSSION

This study aimed to examine how certain inflammatory markers, such as NLR, MLR, and PLR, change in bipolar disorder patients over time. Thus, the blood parameters of bipolar disorder patients were compared within the disease periods and with healthy controls. NLR, MLR, and PLR values were significantly higher in manic episode BD patients compared to healthy controls. Previous studies also found an increased NLR through manic episode BD patients [8,9]. However, the findings of PLR and MLR are inconsistent. There are some studies showed an increase in all NLR, MLR, and PLR parameters [10], while some others showed an increase in only NLR [11], with MLR [12,13], or with PLR [14]. It's known that NLR has a predictive value in many non-psychiatric disorders treatment responses and prognoses [15,16]. A meta-analysis concluded that NLR predicted acute ischemic stroke, chronic obstructive respiratory disease, acute coronary syndrome mortality, and morbidity [17,18,19]. High NLR has been linked to a bad prognosis in terms of mortality and morbidity in several disorders.. Considering these findings of NLR regarding non-psychiatric conditions, this field of study of psychiatric illnesses is also promising [20]. Indeed, a prospective study in which BD patients were followed for 18 months reported that NLR has predictive significance in people suffering from manic episodes [21]. NLR, MLR, and PLR values were higher in the euthymic period of BD patients, as in the manic episode, compared to the healthy control group. Few studies compare manic and euthymic episodes of the same patients with a healthy control group, and the results are variable. In a study that found NLR, MLR, and PLR were significantly higher in manic episode BD patients compared to healthy controls, only MLR was higher in these patients' euthymic periods. The authors interpreted NLR as PLR as a state marker and MLR as a trait marker [22]. In another study, BD patients were found to have higher NLR and MLR than healthy controls, regardless of the disease periods [23].

This is one of the rare studies that evaluate inflammatory parameters in bipolar disorder patients between mania and remission, and it was discovered that NLR, MLR, and PLR did not alter between manic attack and remission phases. One of the previous studies showed that while NLR increases in mania, MLR and PLR did not change [14]. Another study found that NLR, PLR and MLR, which were elevated during the manic period, decreased during the euthymic period after treatment [18].

Inflammatory parameters (NLR, MLR, PLR) were higher in the BD group in both mania and remission periods than in healthy controls. However, there was no difference in the attack and remission phases of the same patients, indicating that these parameters may be trait markers. Our findings support that inflammation persists even during the remission period in bipolar disorder[24]. Subthreshold symptoms and loss of psychosocial functionality can be seen in the euthymic period of bipolar disorder, and it may be related to the ongoing inflammatory process [25]. This finding suggests that anti-inflammatory drugs could be used as a therapy option. A small-sample randomized controlled trial reports that N-acetyl cysteine (NAC), an anti-inflammatory agent, is effective in treating mania and hypomania [26]. In yet another randomized controlled study, Celecoxib, a Non-Steroidal Anti-Inflammatory Drug (NSAID), was shown to be effective in treating manic attacks [27].

The effect of anti-inflammatory therapy on treating manic episodes is still unclear [28]. To identify novel therapy targets, the inflammatory processes that may play a role in the etiology should be fully understood. Examining inflammatory markers in different periods of the BD may give some clues to understanding these inflammatory processes. In addition, a possible inflammatory marker can guide determining treatment targets, monitoring treatment response and prognosis, and diagnosing when clinical data are insufficient.

Limitations

This research has certain limitations. This was, first and primarily, a retrospective research. Secondly, psychiatric medications and smoking may influence inflammatory parameters, and the purpose of this research was not to rule out this possibility. Third, patients did not participate in the study on depressive episodes. Prospective studies that include depressive episodes in the same patients are required. On the other hand, one of our study's strengths was that we evaluated the same patient group on different episodes.

CONCLUSION

BD markers have been studied as trait markers and state markers. Trait markers remain stable even during relapse and remission in BD and differ from healthy controls. State markers, on the other hand, differ between the disease's attack and remission periods. Our study showed NLR, MLR, and PLR values in manic and euthymic episodes of BD patients were significantly higher than in healthy controls. These findings suggest that inflammation persists even when patients recover, and Inflammation is crucial in the pathophysiology of BD. The fact that NLR, MLR, and PLR are high in both the disease and the euthymic period suggests they can be used as trait biomarkers. There are preliminary studies in BD patients examining different periods of the same patients. More studies are needed to determine whether NLR, MLR, and PLR markers are trait or state markers.

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Ethics Committee Approval: The study described in this article was conducted within the framework of the Declaration of Helsinki. Karamanoglu Mehmetbey University Faculty of Medicine Clinical Research Ethics Committee approved the study (approval number: 104096).

REFERENCES

1. Kessing LV, González-Pinto A, Fagiolini A, et al. (2021)DSM-5 and ICD-11 criteria for bipolar disorder: Implications for the prevalence of bipolar disorder and validity of the diagnosis -A narrative review from the ECNP bipolar disorders network. Eur Neuropsychopharmacol. 47:54-61. https://doi.org/10.1016/j.euroneuro.2021.01.097

2. Miller JN, Black DW (2020) Bipolar Disorder and Suicide: a Review. Curr Psychiatry Rep. 22(2):6. https://doi.org/10.1007/s11920-020-1130-0

3. Fountoulakis KN, Yatham LN, Grunze H, et al. (2020) The CINP Guidelines on the Definition and Evidence-Based Interventions for Treatment-Resistant Bipolar Disorder. Int J Neuropsychopharmacol. 23(4):230-256. https://doi.org/10.1093/ijnp/pyz064

4. Vieta E, Berk M, Schulze TG, et al. (2018) Bipolar disorders. Nat Rev Dis Primers. 4:18008. https://doi.org/10.1038/nrdp.2018.8

5. Akbayram S, Gokcen C, Karadag M (2020) Increased of platelet indices in patients with attention deficit/hyperactivity disorder. Psychiatry Behav. Sci. 10:86-89. https://doi.org/10.5455/PBS.20190912052825

6. Quintero M, Stanisic D, Cruz G, Pontes JGM, Costa TBBC, Tasic L (2019) Metabolomic Biomarkers in Mental Disorders: Bipolar Disorder and Schizophrenia. Adv Exp Med Biol. 1118:271-293. https://doi.org/10.1007/978-3-030-05542-4_14

7. Fries GR, Walss-Bass C, Bauer ME, Teixeira AL (2019) Revisiting inflammation in bipolar disorder. Pharmacol Biochem Behav. 177:12-19. https://doi.org/10.1016/j.pbb.2018.12.006

8. Marazziti D, Torrigiani S, Carbone MG, et al. (2022) Neutrophil/Lymphocyte, Platelet/Lymphocyte, and Monocyte/Lymphocyte Ratios in Mood Disorders. Curr Med Chem. 29(36):5758-5781. https://doi.org/10.2174/0929867328666210922160116

9. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M (2018) Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 84(Pt A):229-236. https://doi.org/10.1016/j.pnpbp.2018.03.012

10. Özdin S, Sarisoy G, Böke Ö (2017) A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients - a retrospective file review. Nord J Psychiatry. 71(7):509-512. https://doi.org/10.1080/08039488.2017.1340517

11. Kulacaoglu F, Yıldırım YE, Aslan M, İzci F (V) Neutrophil to lymphocyte and monocyte to high-density lipoprotein ratios are promising inflammatory indicators of bipolar disorder. Nord J Psychiatry. 77(1):77-82. https://doi.org/10.1080/08039488.2022.2116106

12. Inanli I, Aydin M, Çaliskan AM, Eren I (2019) Neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and mean platelet volume as systemic inflammatory markers in different states of bipolar disorder. Nord J Psychiatry. 73(6):372-379. https://doi.org/10.1080/08039488.2019.1640789

13. Wei Y, Feng J, Ma J, Chen D, Chen J (2022) Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in patients with affective disorders. J Affect Disord. 309:221-228. https://doi.org/10.1016/j.jad.2022.04.092

14. Bulut NS, Yorguner N, Çarkaxhiu Bulut G (2021) The severity of inflammation in major neuropsychiatric disorders: comparison of neutrophil-lymphocyte and platelet-lymphocyte ratios between schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and obsessive compulsive disorder. Nord J Psychiatry. 75(8):624-632. https://doi.org/10.1080/08039488.2021.1919201

15. Yang S, Li S (2022) Development of prognostic predictive model with neutrophil-lymphocyte ratio (NLR) in patients with gastric signet ring carcinoma. Medicine (Baltimore). 101(1):e28043. https://doi.org/10.1097/MD.0000000000028043

16. Ge YL, Zhang HF, Zhang Q, et al. (2019) Neutrophil-to-Lymphocyte Ratio in Adult Community-Acquired Pneumonia Patients Correlates with Unfavorable Clinical Outcomes. Clin Lab. 65(5). https://doi.org/10.7754/Clin.Lab.2018.181042

17. Wang L, Song Q, Wang C, et al. (2019) Neutrophil to lymphocyte ratio predicts poor outcomes after acute

ischemic stroke: A cohort study and systematic review. J Neurol Sci. 406:116445. https://doi.org/10.1016/j.jns.2019.116445

18. Ye Z, Ai X, Liao Z, You C, Cheng Y (2019) The prognostic values of neutrophil to lymphocyte ratio for outcomes in chronic obstructive pulmonary disease [published correction appears in Medicine (Baltimore). Medicine (Baltimore). 98(28):e16371. https://doi.org/10.1097/MD.0000000000016371

19. Dong CH, Wang ZM, Chen SY (2018) Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: A systematic review and meta-analysis. Clin Biochem. 52:131-136. https://doi.org/10.1016/j.clinbiochem.2017.11.008

20. Zulfic Z, Weickert CS, Weickert TW, Liu D, Myles N, Galletly C (2020) Neutrophil-lymphocyte ratio - a simple, accessible measure of inflammation, morbidity and prognosis in psychiatric disorders?. Australas Psychiatry. 28(4):454-458. https://doi.org/10.1177/1039856220908172

21. Melo MCA, Garcia RF, de Araújo CFC, Abreu RLC, de Bruin PFC, de Bruin VMS (2019) Clinical significance of neutrophil-lymphocyte and platelet-lymphocyte ratios in bipolar patients: An 18-month prospective study. Psychiatry Res. 271:8-14. https://doi.org/10.1016/j.psychres.2018.10.077

22. Özdin S, Usta MB (2021) A comparison of inflammatory markers in manic and euthymic states of bipolar disorder. Nord J Psychiatry. 75(2):124-129. https://doi.org/10.1080/08039488.2020.1807048

23. Dadouli K, Janho MB, Hatziefthimiou A, et al. (2022) Neutrophil-to-Lymphocyte, Monocyte-to-Lymphocyte, Platelet-to-Lymphocyte Ratio and Systemic Immune-Inflammatory Index in Different States of Bipolar Disorder. Brain Sci. 12(8):1034. https://doi.org/10.3390/brainsci12081034

24. Gan Z, Wu X, Liao Y, et al. (2019) The association between low-grade inflammation and the clinical features of bipolar disorder in Han Chinese population. Psychoneuroendocrinology. 101:286-294. https://doi.org/10.1016/j.psyneuen.2018.12.239

25. Dargél AA, Roussel F, Volant S, et al. (2018) Emotional hyper-reactivity and cardiometabolic risk in remitted bipolar patients: a machine learning approach. Acta Psychiatr Scand. 138(4):348-359. https://doi.org/10.1111/acps.12901

26. Magalhães PV, Dean OM, Bush AI, et al. (2013) A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. Aust N Z J Psychiatry. 47(6):564-568. https://doi.org/10.1177/0004867413481631

27. Arabzadeh S, Ameli N, Zeinoddini A, et al. (2015) Celecoxib adjunctive therapy for acute bipolar mania: a randomized, double-blind, placebo-controlled trial. Bipolar Disord. 17(6):606-614. https://doi.org/10.1111/bdi.12324

28. Rosenblat JD, McIntyre RS (2017) Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications. Brain Sci. 7(11):144. https://doi.org/10.3390/brainsci7110144

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Original Research

Anti-phospholipase A2 Receptor Antibody Measurement in Patients with Idiopathic Membranous Nephropathy Diagnosed by Renal Biopsy

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ABSTRACT

Objective: Our study is a cross-sectional study that aims to evaluate the presence and levels of anti-phospholipase A2 receptor (PLA2R) antibodies in healthy volunteers and idiopathic membranous nephropathy (IMN) patients and to assess the relationship between these levels and clinical parameters.

Methods: Serum anti-PLA2R antibody levels, complete blood count, urea, creatinine (Kre), total protein, albumin, low-density lipoprotein (LDL)-cholesterol, triglycerides (TG), high-density lipoprotein (HDL)-cholesterol, total cholesterol, C-reactive protein (crp), sedimentation, proteinuria were measured from 71 IMN patients and 48 healthy volunteers.

Results: Of the values compared between the two groups, the urea, creatinine, and modified diet renal disease (MDRD) were similar, total protein, albumin, LDL-cholesterol, TG, total cholesterol, HDL-cholesterol, and complete urinalysis protein values were statistically significantly high in the patient group, as expected in nephrotic syndrome ($p<0.01$). The anti-PLA2Rantibody levels measured using enzyme-linked immunosorbent assay (ELISA) in patient and control groups were found to be negative. The anti-PLA2R level was found to be 0.104 (0.093-0.129) ng/ml in the IMN group, while it was 0.141 (0.117-0.177) ng/ml in the control group (P=0,001). Although the P value was significant, the anti-PLA2R antibody level was found to be high in the control group and was outside the reference range of the kit.

Conclusion: There is a need to conduct more sensitive studies with a higher number of patients in order to distinguish between primary and secondary nature and to investigate the presence of anti-PLA2R in IMNpatients, which constitute the majority of nephrotic syndromes in adults. Antibody titer levels were observed to be low and it was revealed that the measurement range of the antibody kit used in the study should be more sensitive.

Keywords: anti-phospholipase A2 receptor (anti-PLA2R) antibody, idiopathicmembranous nephropathy (IMN), proteinuria

INTRODUCTION

Membranous nephropathy is the most common cause of nephrotic syndrome in adults [1]. There are primary or idiopathic and secondary forms. Secondary membranous nephropathy may develop due to systemic autoimmune diseases, chronic hepatitis B, non-steroidal anti-inflammatory drugs, and malignant tumors [2]. Idiopathic membranous nephropathy (IMN) is an antibody-associated autoimmune glomerular disease characterized by subepithelial immune deposition. The target antigen for IMN disease has been investigated in a wide range clinically and experimentally. Of these, podocyte antigenic targets defined as megalin in Heyman's nephritis have been shown to be responsible for in situ subepithelial immune complexes [3]. However, this antigen was not detected in human kidney podocytes. In 2002, neutral endopeptidase was found to be the antigen responsible for alloimmune antenatal membranous nephropathy [4]. In 2009, M-type phospholipase A2 (PLA2R) receptor, a membrane glycoprotein located on podocytes, was found to be the target

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antigen in IMN patients [5]. Circulating antibodies against this antigen combine with PLA2R antigen on podocytes in the glomeruli, causing in situ immune complex formation and secondary complement activation. As a result of these, proteinuria begins and kidney damage occurs [6]. In some studies, serum anti-PLA2R antibody levels were found to be associated with diagnosis, prognosis and treatment response in patients with IMN. While the antibody was positive in IMN patients, low titer was positive or negative in patients with secondary membranous nephropathy, low titer positivity and low disease activity were correlated in IMN patients. Antibody negativity was also detected in patients who developed membranous nephropathy due to causes such as malignancy and heavy metals [7-9].

We aimed to evaluate the role of anti-PLA2R antibody level in the diagnosis and treatment of IMN patients diagnosed with follow-up biopsy in our nephrology clinic and secondary causes excluded.

METHODS

Our study included 71 IMN patients followed up in our nephrology clinic between January 2015-November 2017 and 48 healthy control groups. Healthy volunteers group consists of healthy individuals between the ages of 18-65 who have no previous history of disease, especially renal disease and drug use. Ethics committee approval for our study was obtained by Gaziantep University Clinical Research Ethics Committee with the date of 22.05.2017 and decision number 2017/200. Anti-nuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibody (p-anca), anti-neutrophil cytoplasmic antibody (c-anca), anti-double stranded deoxy ribonucleic acid (ds dna), complement 3 and 4, hepatitis B, C and human immunodeficiency virus (HIV) in terms of excluding secondary mebranous nephropathy of patients whose renal biopsies are compatible with membranous nephropathy that tests were performed and found to be negative. The study was divided into two groups as patient and control group. In addition to anti-PLA2R antibody levels, complete blood count, 24-hour urine micro total proteinuria (MTP) level, total protein, creatinine, blood urea nitrogen (BUN), albumin, LDL-cholesterol, TG, total cholesterol, HDL-cholesterol, crp, sedimentation, urea, creatinine, MDRD levels were examined. All patients who received or did not receive immunosuppressive therapy were included, but those who had undergone a change in immunosuppressive therapy within the last 1 month were excluded. All parameters except anti-PLA2R antibody levels were obtained from the hospital registration system. Patients between the ages of 18-65, glomerular filtration rate (GFR) >60 ml/min, no more than 10% change in GFR values in the last 3 months, using angiotensin receptor inhibitors/blockers were included in the study.

Main points

- Idiopathic membranous nephropathy is a common cause of proteinuria in adults
- The primary-secondary distinction of membranous nephropathy is of vital importance in terms of treatment and prognosis
- Renal biopsy couldn't make this distinction
- Numerous studies have been conducted on the anti-PLA2R antibody in terms of a marker that can make this distinction

Routine biochemical parameters are determined on a Roche/Hitachi Modular (Tokyo, Japan) analyzer system using solutions, controls and calibrators from the same manufacturer (Roche Diagnostics, Mannheim, Germany). Complete blood count parameters are measured in Beckman Coulter (CA, USA) complete blood count device using solutions, controls and calibrators from the same manufacturer. Creatinine is studied according to the compensated Jaffe method. The creatinine method was standardized by isotope dilution-mass spectrometry (ID MS). Albumin is measured colorimetrically by the bromocresol green method. Cholesterol is measured enzymatic colorimetrically by the cholesterol oxidase method. HDL; It is measured enzymatic colorimetrically using a polyethylene glycol modified enzyme. LDL; selective detergent, cholesterol esterase/cholesterol oxidase and homogenous enzymatic colorimetric method. From the 24-hour urine MTP of the participants; the amount of protein was evaluated in the Backmancoulter Unicel DxC800 device at University Medical Faculty Central Laboratory. GFR was calculated with the 4-parameter MDRD Formula [10].

GFR = 186 X ([Scr] -1.154) X ([Age] -0.203) X (0.742 if female) X (1.21 if black)

The level of anti-PLA2R antibody (mybiousource, USA) in serum samples was measured using the ELISA method. This kit measures human anti-PLA2R antibody level by quantitative double sandwich enzyme immunassay method in 6 hours. Antigen and solid phase carriers were connected to form the immobilized antibodies. Uncombined antigens, foreign substances were washed off. Immobilized antigens for contact rectification participated in the test. After a while, it was expected that the antibodies and antigens in the carriers would combine with antibody complexes. Uncombined antigens and foreign substances were washed off again. Antigens were added to combine with antibodies on immune complexes. The uncombined antigens were thoroughly washed. The amount of enzyme on the transporter has now been positively assessed by the amount of the tested substance in the samples. Anti-PLA2R antibody standards (20.0; 10.0; 5.0; 2.5; 1.25; 0.625; 0.312 ng/ml) and the samples were sandwiched between immobilized antibody and PLA2R antibody-specific antibody. All non-binding materials were removed by washing again and the peroxidase enzyme substrate was added. The reaction was stopped by leaving it in the dark to form a color and adding an acid solution. The color intensity was read spectrophotometrically at 450 nm with an ELISA reader (Biotek Instruments, USA). The anti-PLA2R antibody level of the patients and controls was calculated using a standard graph.

Statistical Analysis

The suitability of the numerical data to the normal distribution was tested with the Shapiro Wilk test. The independent samples t-test and Mann–Whitney U-test were used to compare two

independent groups of variables. Relationships between non-normally distributed numerical variables were tested with the Spearman correlation coefficient. The diagnostic test effectiveness for numerical variables was revealed with the help of the ROC curve. SPSS 22.0 package program was used in the analyses. P<0.05 was considered significant.

RESULTS

In our study, the data were evaluated between the patient group and the healthy group. There was no statistically significant difference between the two groups in terms of demographic and laboratory findings, age, gender, urea, creatinine, GFR, HDL-cholesterol, hemoglobin, sodium, potassium, aspartate aminotransferase, alanine aminotransferase values. While total protein and albumin values were found to be lower in the patient group, total cholesterol, TG, LDL-cholesterol, 24-hour urine protein, and MTP values were found to be statistically significantly higher than the control group. While protein positivity was observed in the IMN group in the complete urine test, it was found to be negative in the healthy group. In addition, white blood cell countand neutrophil count, which are among the parameters of the complete blood count, were found to be statistically high in the patient group, while there was no difference in hemoglobin, platelet, mean corpuscular volume (MCV) (Table 1).

Table 1. Demographic characteristics and laboratory values of the IMN and control groups

	IMN(n=71)	Control (48)	P
Age†	38±13	36±11	P=0.867
Gender, female/male (n)	41/30	27/21	P=0.745
Anti-PLA2R ab(ng/ml)#	0.104 (0.093-0.129)	0.141(0.117-0.177)	P=0.001*
Ure(mg/dl)#	24(18-42)	22.5(19-25.5)	P=0.789
Cre(mg/dl)#	0.75(0.60-1.10)	0.69(0.62-6.84)	P=0.216
MDRD(ml/min/1.73 m2)#	109(75-123)	117.5(101.5-130.5)	P=0.674
Total Protein(g/dl)#	7(6.5-7.5)	7.6(7.4-7.8)	P=0.001*
Albumin(g/dl)#	4.1(3.8-4.3)	4.55(4.3-4.8)	P=0.001*
LDL(mg/dl)#	129(110-170)	97(75-117)	P=0.001*
TG(mg/dl)#	195(119-277)	71.5(57-111)	P=0.001*
Total cholesterol(mg/dl)#	221(178-270)	165(65.5-178.5)	P=0.005
HDL-C(mg/dl)#	48.5(42.5-64.5)	49(35-66)	P=0.512
Leucosyte(mcl)#	9430(7590-11810)	4420(3265-5280)	P=0.001*
Neutrophil(mcl)#	5630(4180-7370)	4420(3265-5280)	P=0.001*
HGB(g/dl)#	14.1(12.4-15.5)	14(13.35-15.1)	P=0.697
Urine-protein#	1(0-3)	0(0-0)	P=0.001*
Urine-erithyrocyte#	0(0-1)	0(0-0)	P=0.001*
MTP(mg/day)#	462(155-1105)	96(74-115)	P=0.001*

* p<0.05; †Mean±.standart deviasion,# Median(minimum-maximum), **MDRD**: Modification of Diet in Renal Disease,
Cre: creatinin, **TG:** triglyceride, **HGB**: hemoglobin, **LDL-C**: Low density lipoprotein-cholesterol,
HDL-C : high density lipoprotein-cholesterol, **MTP:** micro total protein

Table 2. Correlation analysis results between the numerical variables

		Anti-PLA2R ab
Anti-PLA2R ab	**r**	1.000
	p	
Age	**r**	0.118
	p	0.325
MDRD	**r**	0.084
	p	0.487
Albumin	**r**	-0.044
	p	0.715
Proteinuria	**r**	-0.166
	p	0.292

r: Spearman rank correlation coefficient.

The anti-PLA2R level was found to be 0.104 (0.093-0.129) ng/ml in the IMN group, while it was 0.141 (0.117-0.177) ng/ml in the control group (P=0.001). Although the P value was significant, the anti-PLA2R antibody level was found to be high in the control group and was outside the reference range of the kit. Also, the correlation analysis is shown in Table 2.

Although the test was below the reference values and the determined values, and the control features of the finger test to the range of curve (ROC) extension seem to have high values, the highest antibody titer was 0.308 ng/ml when all the obtained values were examined, and the smallest value to which the test was both sensitive was 0.5. A clear evaluation cannot be made if it does not match the ng/ml value and is not between 1.56-100 ng/ml values, which is the reference range of the test. For these reasons, it has been accepted that these ROC movements were taken in such a way that they could not give clear accurate data.

DISCUSSION

The patient group in our study consists mainly of women and individuals under the age of 40. In the data of a study, IMN and anti-PLA2R antibody positivity were found to be more common in men aged 40-70 years [11]. The fact that our patients were under the age of 40 and the female gender was higher may have caused meaningless results. Although this is not the only factor in negative test results, it was found to be significant in terms of playing an active role.

The sensitivity of the ELISA kit used in anti-PLA2R antibody measurement is important in detecting the disease. In a study conducted by Dou et al., the low threshold value for the diagnosis of anti-PLA2R antibody levels increased the probability of detecting the disease (12). The high threshold value of the test we used in our study led to the thought that the test was effective in producing meaningless results.

Although a small number of patients were studied in a research, low levels of anti-PLA2R antibodies can show spontaneous remission in patients with a diagnosis of IMN. When these patients are followed without treatment, a complete cure can be achieved proteinuria level < 8 g/day and no clinical findings), and it showed that low antibody titer could be a biomarker that could be used to predict this condition [13]. The protein level in the 24-hour urine of the patients in the IMN group was 462 mg/day; low proteinuria may have played a role in negative anti-PLA2R antibody results.

Contrary to the studies in the literature, there was no statistically significant difference in our study when we compared the patients diagnosed with IMN and the control group in terms of anti-PLA2R levels. Anti-PLA2R antibody level was associated with disease activity. It has been found in some studies that during the active periods of the disease, high proteinuria levels and increased periods were correlated with antibody titers [14]. In our study, it was found to be negative in both the patient groups that we accepted in remission and the patient groups in which the disease progressed actively.

Although the total protein and albumin measurements in the IMN group were significantly lower than the healthy group, these values were consistent with the values in the normal healthy population. In a study by Hofstra et al., low anti-PLA2R antibody level was found to be associated with high serum albumin level and low proteinuria [15]. Anti-PLA2R antibody negativity in our patients was evaluated to be associated with high total protein and albumin levels.

When we look at the positivity rate of anti-PLA2R antibody levels in patients with IMN diagnosis and the studies comparing these antibody titers with values such as proteinuria and serum albumin values, we saw that the test measures as RU/ml and our measurements are ng/ml. However, when we looked at the literature, we could not find a formula for this antibody in terms of converting from ng/ml to RU/ml. With the kit we studied, antibody levels were found to be negative in both the patient group and the control group, below the reference range; it has emerged that antibody kits sensitive to smaller antigen levels are needed for the detection of the antibody level. For example, in a study conducted by Qin et al., anti-PLA2R antibodies were found to be positive at a rate of 69% at the time of first diagnosis in patients diagnosed with IMN, and the prevalence of autoantibodies was found to be lower in patients who went into remission after treatment (15.8%) compared to patients at the time of initial diagnosis. This study also shows that factors such as the time of first diagnosis and the state of being in remission after treatment affect the test positivity rate [16]. Although all of our patient group was outside the reference range of the test, 50 of our patients (which corresponds to 70% of our patient group) had a MTP level below 1 g/day. This shows that if most of our patients are accepted in the remission stage, it can be shown among the possible reasons for the test to be negative.

Nanogram/milliliter was given as the unit of measurement for the kit we used in our study. When we look at the kits used to measure this antibody detection, we see that some of them give the unit of measurement as microgram/milliliter. This shows that the sensitivity of the test has increased even more. In addition, the test measures with the double sandwich technique, and in this case, it can be interpreted that the test is better in terms of technique and precision. 71 patients diagnosed with IMN in our study were diagnosed with kidney biopsy, and at the same time, all patients were diagnosed by considering the negativity of autoimmune markers and hepatitis markers in order to exclude secondary causes. Although some studies say that the antibody level may be negative if the disease is in remission, when we look at the patients with IMN, we see that the antibody titers of the patients who are not in remission are also outside the reference range. The values read were also evaluated by different biochemists, and the same values were sent to the company and similar results were obtained.

Even if we consider 70% of the patients in our study to be in remission in terms of proteinuria level, even the other 30% of the patients can be evaluated in terms of the possibility of being negative when proteinuria regresses. In a study, it was observed that the level of anti-PLA2R antibody could regress with immunosuppressive treatment, or the antibody level may decrease and become negative after the proteinuria level

decreases over time. At the same time, if it is taken into account that the antibody becomes negative or its level decreases some time before proteinuria decreases, it may occur that it is possible for the antibody to be negative even in patients we accept as active [17]. Antibody levels were measured in all IMN patients, regardless of whether our patients were in remission or in the active period. In another study, remission of the disease was found to be associated with low or negative antibody levels [18]. For this reason, it was thought that the low proteinuria level of our patients in remission or close to remission may play an active role in the negative antibody level.

We determined our group consisting of healthy volunteers as the comparison group for anti-PLA2R antibody and aimed to determine the positivity rate and antibody levels in these individuals. However, as mentioned in the material and method section above, antibody positivity and antibody levels were measured in serum samples from the collected blood in accordance with the technique. As a result of the measurements, very low values were measured in nanogram/ml in all patient groups, but the determined values were outside the reference range of the test and a significant antibody titer could not be reached. Since the values found were below the reference range and optic density (od) values, the correct values could not be accepted for comparison and evaluation of these detected antibody levels. The PLA2R antibody values of the samples we used for the patient and control groups could not be read because they were outside the measurement ranges of the kit used. It has been reported in studies that anti-PLA2R antibody measurements made with the ELISA method may differ depending on whether the disease is in remission or under treatment at the time of diagnosis. It has been reported in studies that anti-PLA2R antibody measurements made with the ELISA method may differ depending on whether the disease is in remission or under treatment at the time of diagnosis [19,20]. For this reason, it has come to the fore that different titration values can be used for anti-PLA2R antibody kits. It has been emphasized that algorithms will also be needed in this regard [21].

In addition, some studies have suggested the use of specific measurement kits for immunoglobulin G subtypes and antigen epitopes to increase the probability of detecting IMN patients [22,23]. The negative results of the kits we used in our patients suggested that the use of more sensitive kits may be beneficial.

Anti-PLA2R antibody values obtained in our study were below the reference range of the test, it was accepted that this ROC curve could not give clear accurate data and was considered meaningless. For this reason, the low threshold value for the test is also important in terms of increasing the probability of detecting the disease. In a study, the low threshold value supported that the measurement kit used in the diagnosis of the disease increased the sensitivity [24].

Our study is among the first studies in our country to evaluate anti-PLA2R antibody in IMN patients. Anti-PLA2R antibody has been widely researched all over the world since it was detected in 2009, and many countries provide their own population study data. Many countries have conducted population-based studies. This study is one of the population-based studies in our country in which patients with a diagnosis of IMN are evaluated in terms of this antibody positivity. In addition, we also considered which measurement kit could contribute to the use of anti-PLA2R antibodies in our study.

Limitations

This study had some limitations. We did not evaluate the immunosuppressive treatments received by the patients, and mixed the patients with continuing or negative proteinuria into a mixed evaluation, and not checking the antibody level in a group consisting of other nephropathies, including secondary membranous nephropathy in the comparison group, and not checking the antibody level with a kit containing a different measurement method from the same samples. It was considered to be checked with a kit with a lower anti-PLA2R measurement sensitivity, but could not be done due to the cost factor.

CONCLUSION

There is a need for patients with a diagnosis of IMN to have the test for the determination of anti-PLA2R antibody level and to measure the measurement with which unit. In our institutions, ng/ml unit has been determined for the determination of anti-PLA2R antibody, but the level of the indicator of the values found has not been increased.

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Ethics Committee Approval: The study described in this article was conducted within the framework of the Declaration of Helsinki. Gaziantep University Faculty of Medicine Clinical Research Ethics Committee approved the study (approval number: 2017-200, approval date: May 22, 2017).

REFERENCES

1. Ponticelli, Claudio, and Richard J Glassock (2014) Glomerular diseases: membranous nephropathy-a modern view. Clin J Am Soc Nephrol. 9(3):609-616. https://doi.org/10.2215/CJN.04160413

2. Beck L, Bomback AS, Choi MJ, Holzman LB, Langford C, Mariani LH, et al (2013) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis. Am. J. Kidney Dis. 62(3):403-441. https://doi.org/10.1053/j.ajkd.2013.06.002

3. Heymann W, Hackel DB, Harwood S, Wilson SG, Hunter JL (1959) Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspensions. Proc Soc Exp Biol Med. 100(4):660–664. https://doi.org/10.3181/00379727-100-24736

4. Debiec H, Guigonis V, Mougenot B, Decobert F, Haymann JP, Bensman A et al (2002) Antenatal membranous glomerulonephritis due to anti–neutral endopeptidase antibodies. N Engl J Med. 346(26); 2053-2060. https://doi.org/10.1056/NEJMoa012895

5. Beck Jr, Laurence H, Bonegio RG, Lambeau G, Beck DM, Powell DW et al (2009) M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 361(1);11-21. https://doi.org/10.1056/NEJMoa0810457

6. Glassock RJ (2012) The pathogenesis of membranous nephropathy: evolution and revolution. Curr. Opin. Nephrol. Hypertens. 21(3);235-242. https://doi.org/10.1097/MNH.0b013e3283522ea8

7. Dai H, Zhang H, He Y (2015) Diagnostic accuracy of PLA2R autoantibodies and glomerular staining for the differentiation of idiopathic and secondary membranous nephropathy: an updated meta-analysis. Sci Rep. 5(1);8803. https://doi.org/10.1038/srep08803

8. Svobodova B, Honsova E, Ronco P, Tesar V, Debiec H (2013) Kidney biopsy is a sensitive tool for retrospective diagnosis of PLA2R-related membranous nephropathy. Nephrol. Dial. Transplant. 28(7);1839-1844. https://doi.org/10.1093/ndt/gfs439

9. Oh YJ, Yang SH, Kim DK, Kang SW, Kim YS (2013) Autoantibodies against phospholipase A2 receptor in Korean patients with membranous nephropathy. PLoS One. 8(4);e62151. https://doi.org/10.1371/journal.pone.0062151

10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D at al. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann. Intern. Med. 130(6);461-470. https://doi.org/10.7326/0003-4819-130-6-199903160-00002

11. Hoxha E, Thiele I, Zahner G, Panzer U, Harendza S, Stahl RA (2014) Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J. Am. Soc. Nephrol. 25(6);1357-1366. https://doi.org/10.1681/ASN.2013040430

12. Dou Y, Zhang L, Liu D, Wang C, Quan S, Ma S et al (2016) The accuracy of the anti-phospholipase A2 receptor antibody in the diagnosis of idiopathic membranous nephropathy: a comparison of different cutoff values as measured by the ELISA method. Int Urol Nephrol. 48;845-849. https://doi.org/10.1007/s11255-016-1263-6

13. Timmermans SA, Damoiseaux JG, Heerings-Rewinkel PT, Ayalon R, Beck Jr, Laurence H et al (2014) Evaluation of anti-PLA2R1 as measured by a novel ELISA in patients with idiopathic membranous nephropathy: a cohort study. Am. J. Clin. Pathol. 142(1);29-34. https://doi.org/10.1309/AJCP8QMOY5GLRSFP

14. Akiyama SI, Akiyama M, Imai E, Ozaki T, Matsuo S, Maruyama S (2015) Prevalence of anti-phospholipase A2 receptor antibodies in Japanese patients with membranous nephropathy. Clin. Exp. Nephrol. 19;653-660. https://doi.org/10.1007/s10157-014-1054-2

15. Hofstra JM, Debiec H, Short CD, Pellé T, Kleta R, Mathieson PW et al (2012) Antiphospholipase A2 receptor antibody titer and subclass in idiopathic membranous nephropathy. J. Am. Soc. Nephrol. 23(10);1735-1743. https://doi.org/10.1681/ASN.2012030242

16. Qin W, Beck LH, Zeng C, Chen Z, Li S, Zuo K et al (2011) Anti-phospholipase A2 receptor antibody in membranous nephropathy. J. Am. Soc. Nephrol. 22(6);1137-1143. https://doi.org/10.1681/ASN.2010090967

17. Hoxha E, Harendza S, Pinnschmidt H, Panzer U, Stahl RA (2014) PLA2R antibody levels and clinical outcome in patients with membranous nephropathy and non-nephrotic range proteinuria under treatment with inhibitors of the renin-angiotensin system. PLoS One. 9(10);e110681. https://doi.org/10.1371/journal.pone.0110681

18. Ruggenent P, Debiec H, Ruggiero B, Chianca A, Pellé T, Gaspari F et al (2015) Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. J. Am. Soc. Nephrol. 26(10);2545-255. https://doi.org/10.1681/ASN.2014070640

19. Van de Logt AE, Dahan K, Rousseau A, Van Der Molen R, Debiec H, Ronco P et al (2018) Immunological remission in PLA2R-antibody–associated membranous nephropathy: cyclophosphamide versus rituximab. Kidney Int. 98(4);1016-1017. https://doi.org/10.1016/j.kint.2017.12.019

20. Bobart SA, De Vriese AS, Pawar AS, Zand L, Sethi S, Giesen C et al (2019) Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. Kidney Int. 95(2);429-438. https://doi.org/10.1016/j.kint.2018.10.021

21. Chen P, Mao M, Wang C, Zhang X, Zhao X, Gao Y et al (2023) Preliminary study on the efficacy of rituximab in the treatment of idiopathic membranous nephropathy: A single-centre experience. Front Endocrinol (Lausanne). 15(14):1044782. https://doi.org/10.3389/fendo.2023.1044782

22. Van de Logt AE, Fresquet M, Wetzels JF and Brenchley P (2019) The anti-PLA2R antibody in membranous nephropathy: what we know and what remains a decade after its discovery. Kidney Int. 96(6);1292-1302. https://doi.org/10.1016/j.kint.2019.07.014

23. Zhao Y, Cai M, Jiang Z, Dong B, Yan Y, Wang Y et al (2022) Association of serum mannose-binding lectin, anti-phospholipase A2 receptor antibody and renal outcomes in idiopathic membranous nephropathy and atypical membranous nephropathy: a single center retrospective cohort study. Ren. Fail. 44(1);428-433. https://doi.org/10.1080/0886022X.2022.2048016

24. Li C, Li P, Guo W, Chen L, Li J, Wang R et al. (2022) The optimal anti-phospholipase A2 receptor cutoff for the diagnosis of idiopathic membranous nephropathy: a single-center retrospective study. Korean J Intern Med. 37(1);154. https://doi.org/10.3904/kjim.2020.366

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Original Research

Real-Life Data of Neoadjuvant Chemotherapy in Breast Cancer: Aegean Region Experience

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ABSTRACT

Objective: The use of neoadjuvant chemotherapy (NACT) in breast cancer is increasing. However the management of locally advanced breast cancer differs due to the approach of the center to which the patient applied and the approach of the following physician. From this point of view, we aimed to evaluate the real life data of our region.

Methods: The study included 106 patients treated with NACT in the medical oncology clinic of two different university hospitals. Association between clinicopathological features and pathological complete response (pCR) were analyzed.

Results: The pCR rate was higher in patients with negative hormone receptors and this difference was statistically significant (p:0.000). The rate of obtaining pCR increased as the NACT duration increased, and this increase was statistically significant. The mean NACT duration applied to the patients with pCR was 5.48 ± 0.22 months, and the mean NACT duration for those who could not obtain pCR was 5.01 ± 0.1 months (p:0.041). The recurrence rate of patients with pCR was 11.1%, while the recurrence rate of patients who could not obtain pCR was 31.6% (p:0.04).

Conclusion: Pathological response to chemotherapy is an important factor in determining prognosis. There appears to be a need for new biomarkers that allow the prediction of pCR and long-term outcomes.

Keywords: breast neoplasms, developing countries, neoadjuvant therapy, pathologic response

INTRODUCTION

Breast cancer is the most common cancer in women worldwide and is the leading cause of cancer-related death in women [1]. 80-85 % of the patients have local disease, 15% have locally advanced disease, and 5% have clinically evident metastatic disease [2]. Since locally advanced breast cancer is a highly heterogeneous group, disease management and treatment responses also vary. At this point, neoadjuvant therapies are increasingly becoming the standard treatment option due to their advantages. These advantages include increasing the rate of breast-conserving surgery, reducing the morbidity of surgery, providing in vivo information about the response, and giving an idea about the prognosis. Pathological complete response (pCR) is defined as no residual invasive disease on pathological evaluation of the surgical breast specimen. It has been shown that patients with a pCR have better clinical outcomes than those who do not [3]. Obtaining a pCR is related to many factors such as hormone receptor status, human epidermal growth factor receptor 2 (HER2) positivity and the chemotherapy regimen used [4].

In our country as in the rest of the world breast cancer is the most common cancer in women, and its incidence is increasing with the aging population and western-like lifestyle changes. Despite all the developments of screening and diagnostic techniques, unfortunately, due to the individual and social characteristics of our country, most of the breast cancers are diagnosed at locally advanced stages [5]. The management of breast cancer at this stage also differs due to the approach of the center to which the patient applied and the approach of the following physician.

Since most of the randomized controlled studies on NACT in the literature included young and well-performing patients, this suggests that there may be unrepresented patient groups from real life. In our study, in which we retrospectively analyzed

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patients from medical oncology clinics of two different tertiary care centers in the Aegean region, we aimed to evaluate the effect of patient characteristics on clinical responses after neoadjuvant therapy.

METHODS

106 patients who were treated in the medical oncology clinic of two different university hospitals between 2012 - 2018 were included in our study. All patients had a biopsy-confirmed diagnosis of breast cancer and all had received NACT. Clinical and demographic data were obtained retrospectively from patient files.

Tumor histology was defined according to the World Health Organization criteria, and grading was performed according to the recent TNM Classification of Malignant Tumours (TNM) classification [6]. The expression of estrogen receptor (ER),progesterone receptor (PR), HER2 and Ki-67 was assessed using formalin-fixed paraffin-embedded tumor tissue according to international standards. pCR was defined as no residual invasive tumor on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled lymph nodes.

For the evaluation of the data obtained in the study SPSS v21.0 (Statistical Package for the Social Sciences) statistics program was used. Differences between the two groups were analyzed with the Pearson chi-square or Fisher's exact test. Categorical variables were divided into 2 groups. Predictive factors associated with pCR were analyzed by logistic regression testing. $p<0.05$ was considered statistically significant.

Ethics committee approval was obtained from the health sciences ethics committee with the decision dated 20.01.2021 and numbered 20.478.486.

RESULTS

The clinical and pathological characteristics of the 106 patients included in the study are shown in Table 1.

Majority of patients (85.8 %) had stage 3 disease. The number of patients aged 40 and under was 25 (23%), and 81 (76%) patients were over 40 years of age. The pCR was found to be 20% (5/25) in the younger group and 27.2% (22/81) in the group over 40 years of age , and this difference was statistically significant (p=0.06).

Main Points:

- Pathological response to NACT is an important factor in determining prognosis.
- The pattern of response to NACT is used to tailor systemic and locoregional treatment, therefore it is important to adapt current data to real life.
- Predicting response to NACT is essential for clinical decision making.

Table 1. Clinical and pathological characteristics of the patients

No of patients	106
Median age (range)	49 (26–75)
Histologic Type [No. (%)]	
IDC	101 (95.3)
ILC	3
Other	2
Stage [No. (%)]	
2	4 (3.8)
3	91 (89.6)
4	11 (10.4)
Preoperative T stage [No. (%)]	
1	19 (17.9)
2	64 (60.4)
3	23 (21.7)
Type Of Surgery [No. (%)]	
MRM	87 (82.1)
BCS+SLNB	7 (6.6)
MRM+SLNB	4 (3,8)
BCS+AD	8 (7.5)
Pathologic Response [No. (%)]	
Residual disease	79 (74.5)
Complete response	27 (25.5)
Chemotherapy Regimen	
Antracycline based	90 (85.8)
Other	15 (14.2)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, MRM: Modified radical mastectomy, BSC: Breast-conserving surgery, SLNB: Sentinel lymph node biopsy

Immunohistochemical profiles of tumor tissues are shown in table 2. Hormone receptor-negative patients comprised 34% of the entire study population. It was observed that the pCR rate was higher in patients with negative hormone receptors and this difference was statistically significant (p=0.000)

The median radiological tumor diameter was 4.01±2.2 and the median pathological tumor diameter was 2.09±3.91. The median number of lymph nodes removed after NACT was 19.5±10.5 and the median number of lymph nodes with metastasis was 3.9±6.2. Median NACT duration was 5.1±1.01 months. The rate of patients with complete primary tumor response after NACT was 27.4% and the rate of patients with residual disease was 72.6%. There were 45 (42.5%) patients with axillary complete response and 61 (57.5%) patients with axillary residual disease. The rate of patients with pCR was 25.5%. No statistically significant correlation was observed between the stage of diagnosis and obtaining a pCR (p=0.062)

According to the NACT regimen used, it was observed that 85.8% received a combination of anthracycline and taxane. 28.3% (30) of the patients were HER2 positive. Trastuzumab was administered

to all HER2 positive patients in the neoadjuvant treatment protocol. pCR was 50% (15/30) in HER2 positive group.

It was observed that 28 (26%) patients developed recurrence during the follow-up, and 23 (21.7%) of them had systemic and 5 (4.7%) local recurrences. The recurrence rate of patients with pCR was 11.1%, while the recurrence rate of patients who could not obtain pCR was 31.6% (p=0.04).

The mean NACT duration applied to the patients with pCR was 5.48 ± 0.22 months, and the mean NACT duration for those who could not obtain pCR was 5.01 ± 0.1 months (p=0.041).

No correlation was observed between T stage, Ki 67 ratio, chemotherapy regimen and the pCR rate (p>0.05).

Table 2. Immunohistochemical profiles of tumor tissues

	Negative [No. (%)]	Positive [No. (%)]
ER	36 (34.0)	70 (66.0)
PR	64 (60.4)	42 (39.6)
HER2	76 (71.7)	30 (28.3)

ER: Estrogen receptors PR: Progesterone receptors
HER2: Human epidermal growth factor receptor 2

Table 3. Association between clinicopathological features and pCR

	pCR	Residual disease	P value
Stage			
2	3 (2.8)	1 (0.9)	
3	22 (20.8)	69 (65.1)	0.062
4	2 (1.9)	9 (8.5)	
Chemotherapy Regimen [No. (%)]			
Antracycline based	67 (70.5)	23 (15.2)	0.820
Other	4 (3.8)	11 (10.5)	
Hormon receptor status [No. (%)]			
Negative	19 (52.8)	17 (47.2)	**0.000**
Positive	8 (0.3)	62 (20.6)	
Ki67 Percentage [No. (%)]			
≤20	1 (1.6)	19 (29.7)	
21–50	7 (10.9)	17 (26.6)	0,057
>51	7 (10.9)	13 (20.3)	

pCR: Pathological complete response

DISCUSSION

The incidence of locally advanced breast cancer, which is 5-10% in developed countries, rises to over 50% in developing countries [7]. In a Turkish epidemiological study involving approximately 2500 patients, stage III breast cancer rate was determined as 20% [8]. In this patient group, a significant survival advantage was achieved with multidisciplinary treatment approaches, especially with the addition of NACT to the treatment [9].

Although it has been shown that breast-conserving surgery rates increase with NACT, only 7% of patients in our study group had breast-conserving surgery [10]. The advantages demonstrated by large randomized controlled trials do not appear to be reflected in the real-life population. It is seen that there is a large group of patients who did not undergo breast conserving surgery despite receiving NACT due to reasons such as high local recurrence rates, the surgeon's guidance and patient preference.

The pathological response is an important prognostic factor in determining the prognosis. Rastogi et al. demonstrated that individuals who achieved a pCR continue to have superior disease free survival (DFS) and overall survival (OS) outcomes compared with patients who did not achieve a pCR (DFS HR: 0.47, P<0.0001; OS HR: 0.32, P<0.0001)[11]. The recurrence rate of our patients with pCR was 11.1%, while the recurrence rate of patients who could not obtain pCR was 31.6% and this difference was statistically significant (p=0.04).

The addition of taxanes to anthracycline based chemotherapy regimen has shown to be superior in terms of clinical response, pathologic response, DFS and OS to the anthracycline-based regimen alone [12]. In our study, all patients received taxane, and most of them received it in combination with anthracycline. There was no statistically significant difference between anthracycline-containing regimens and taxane-only regimens in terms of pCR rates. On the other hand addition of pertuzumab to docetaxel and trastuzumab in the phase III CLEOPATRA trial resulted in a significant improvement in OS in first-line, metastatic, HER2 positive breast cancer [13]. However, since the study design was retrospective, pertuzumab was not licensed in our country in those years, so pCR rates in HER2 positive disease remained lower than in the literature.

In most Western countries, the mortality rate of breast cancer has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection [14]. In the univariate analysis performed by Öztürk et al., young age (≤40), tumor size, axilla positivity, chemotherapy regimen, pathological stage, and local recurrence were found to be important factors affecting survival [15]. In our study, pCR was found to be 20% (5/25) in the group aged 40 years and younger, and 27.2% (22/81) in the group over 40 years of age, and this difference was statistically significant (p=0.06). In the study of Spring et al., it was suggested that the achievement of pCR with NACT may be a robust marker for survival in young women with breast cancer, and the high mortality rate of 22.9% in their study population belonged mostly to patients who did not achieve pCR. They highlighted the need for better treatments for young women with breast cancer [16].

In our study, NACT duration and hormone receptor negativity were determined as factors affecting pCR. When the relationship between NACT duration and pCR was examined, it was observed that the rate of obtaining complete response increased as the

NACT duration increased, and this increase was statistically significant. The mean NACT duration applied to the patients with pCR was 5.48 ± 0.22 months, and the mean NACT duration for those who could not obtain pCR was 5.01 ± 0.1 months (p=0.041). Although the association between NACT time and pCR was demonstrated, it was not recorded whether the treatment protocols were given with a dose-intensive scheme, which is the shortcoming of the study.

Tumors that are hormone negative tend to have a higher pathologic response rate to chemotherapy than hormone positive tumors [17]. In our study group pCR was obtained in 19 of 36 hormone negative patients. On the other hand, pCR was observed in only 8 of 70 hormone positive patients. This difference was statistically significant and consistent with the literature.

Park et al. suggested in their study that negative ER status is associated with local recurrence and distant metastasis [18]. Although it is known that hormone positive tumors have less NACT response than negative tumors, in the light of the findings of Park et al. the idea of preferring more intense schemes in receptor negative patients comes to the fore in determining the treatment regimen when planning NACT.

There are some limitations of our study. First, we cannot exclude a possible selection bias as only two of the breast cancer units in the Aegean region participated. Second, we cannot say that all breast cancer patients are represented, as there is no national clinical cancer registry to which our study sample can be compared.

As a result pathological response to NACT appears to be due to the complex and unclear interplay of systemic therapy and tumor biology. Future analyses of randomized trials with targeted therapies will provide better guidance on the implementation of individualized treatments.

CONCLUSION

In conclusion, NACT should be a standard treatment in locally advanced breast cancer. Pathological response to chemotherapy is an important factor in determining prognosis. There appears to be a need for new biomarkers that allow the prediction of pCR and long-term outcomes.

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REFERENCES

1. Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. (2018) Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016 a systematic analysis for the global burden of disease study global burden o. JAMA Oncol. 4(11):1553–68. https://doi.org/10.1001/jamaoncol.2018.2706

2. Simos D, Clemons M, Ginsburg OM, Jacobs C. (2014) Definition and consequences of locally advanced breast cancer. Curr Opin Support Palliat Care. 8(1):33–8. https://doi.org/10.1097/SPC.0000000000000020

3. Cortazar P, Geyer CE. (2015) Pathological Complete Response in Neoadjuvant Treatment of Breast Cancer. Ann Surg Oncol. 22(5):1441–6. https://doi.org/10.1245/s10434-015-4404-8

4. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E; ESMO Guidelines Committee. (2019) Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 30(8):1194–220. https://doi.org/10.1093/annonc/mdz173

5. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. Türkiye Kanser İstatistikleri 2016 [Internet]. Ankara. 2019. Available from: https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Trkiye_Kanser_statistikleri_2016.pdf

6. Sawaki M, Shien T, Iwata H. (2019) TNM classification of malignant tumors (Breast Cancer Study Group). Jpn J Clin Oncol. 49(3):228–31. https://doi.org/10.1093/jjco/hyy182

7. Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E, Harford J. (2008) Guideline implementation for breast healthcare in low-income and middle-income countries: Overview of the breast health global initiative Global Summit 2007. Cancer. 113(8 SUPPL.):2221–43. https://doi.org/10.1002/cncr.23844

8. Güler N, Karabulut B, Koçdor MA, Kaya H, Esen G, Özaslan C, et al. (2011) 2010 İSTANBUL MEME KANSER İ KONSENSUS TOPLANTISI CONSENSUS MEETING. 68–89.

9. Klein J, Tran W, Watkins E, Vesprini D, Wright FC, Look Hong NJ, Ghandi S, Kiss A, Czarnota GJ. (2019) Locally advanced breast cancer treated with neoadjuvant chemotherapy and adjuvant radiotherapy: A retrospective cohort analysis. BMC Cancer. 19(1):1–11. https://doi.org/10.1186/s12885-019-5499-2

10. Killelea BK, Yang VQ, Mougalian S, Horowitz NR, Pusztai L, Chagpar AB, Lannin DR. (2015) Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: Results from the national cancer database. J Am Coll Surg [Internet]. 220(6):1063–9. http://dx.doi.org/10.1016/j.jamcollsurg.2015.02.011

11. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, Margolese RG, Hoehn JL, Vogel VG, Dakhil SR, Tamkus D, King KM, Pajon ER, Wright MJ, Robert J, Paik S, Mamounas EP, Wolmark N. (2008) Preoperative chemotherapy: Updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 26(5):778–85. https://doi.org/10.1200/JCO.2007.15.0235

12. Trudeau M, Sinclair SE, Clemons M. (2005) Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: A systematic review. Cancer Treat Rev. 31(4):283–302. https://doi.org/10.1016/j.ctrv.2005.03.007

13. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, Ciruelos E, Schneeweiss A, Loi S, Monturus E, Clark E, Knott A, Restuccia E, Benyunes MC, Cortés J; CLEOPATRA study group (2013) Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol [Internet]. 14(6):461–71. http://dx.doi.org/10.1016/S1470-2045(13)70130-X

14. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP; CONCORD Working Group. (2015) Global surveillance of cancer survival 1995-2009: Analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet [Internet]. 385(9972):977–1010. http://dx.doi.org/10.1016/S0140-6736(14)62038-9

15. Öztürk A, Bozdoğan A, Selamoğlu D, Müslümanoğlu M, İğci A, Özmen V. (2012) Lokal İleri Meme Kanserli Olgularda Neoadjuvan Kemoterapi Sonrasi Hastaliksiz Ve Genel Sağkalimi Etkileyen Faktörler Uzun Dönem Sonuçlarimiz. J Breast Health. 8(3):138–45.

16. Spring L, Greenup R, Niemierko A, Schapira L, Haddad S, Jimenez R, Coopey S, Taghian A, Hughes KS, Isakoff SJ, Ellisen LW, Smith BL, Specht M, Beverly M, Bardia A. (2017) Pathologic complete response after neoadjuvant chemotherapy and long-term outcomes among young women with breast cancer. JNCCN J Natl Compr Cancer Netw. 15(10):1216–23. https://doi.org/10.6004/jnccn.2017.0158

17. Ring AE, Smith IE, Ashley S, Fulford LG, Lakhani SR. (2004) Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. Br J Cancer. 91(12):2012–7. https://doi.org/10.1038/sj.bjc.6602235

18. Park YR, Lee J, Jung JH, Kim WW, Park CS, Lee RK, Chae YS, Lee SJ, Park JY, Park HY. (2020) Absence of estrogen receptor is associated with worse oncologic outcome in patients who were received neoadjuvant chemotherapy for breast cancer. Asian J Surg [Internet]. 43(3):467–75. https://doi.org/10.1016/j.asjsur.2019.05.010

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Original Research

Does Inferior Oblique Muscle Overaction Affect Ocular Vestibular Evoked Myogenic Potentials?

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ABSTRACT

Objectives: Inferior oblique muscle overaction (IOOA) is a common ocular motility disorder. Ocular Vestibular Evoked Myogenic Potentials (oVEMP) are tests that evaluate the reflex pathway between the utricular macula and the inferior oblique muscle to detect vestibular diseases. Our study is of great importance as it is the first study in the literature to evaluate the effect of inferior oblique muscle overaction on oVEMP parameters.

Methods: Thirty-five patients with unilateral inferior oblique muscle overaction (IOOA group) and 18 healthy volunteers without any neurological or vestibulocochlear disease were included in this study. All patients and healthy volunteers were evaluated with oVEMP.

Results: No statistically significant difference was found between the n1 latency, p1 latency, n1-p1 latency measurement values of the participants included in the study ($p>0.05$). A statistically significant difference was found between the n1-p1 amplitude measurement values of the participants in patient groups (non-squint eyes, squint eyes) and control groups (p-value was 0.038).

Conclusion: In IOOA patients, vestibulo-ocular reflex pathway may be affected, vestibular symptoms may develop thus o-VEMP responses may be affected. A careful anamnesis should be taken in IOOA patients, and it should be kept in mind that n1-p1 amplitudes and asymmetries may be significantly higher when o-VEMP is performed

Keywords: o-VEMP, Strabismus, Inferior oblique muscle overaction, Balance, Vertigo

INTRODUCTION

Inferior oblique muscle overaction (IOOA) is a common ocular motility disorder manifested by elevation of the affected eye during adduction and usually seen together with horizontal strabismus [1,2]. IOOA is divided into two types as primary and secondary in terms of aetiology [3]. In the primary type, the aetiology is unknown and it is not accompanied by other extraocular muscle paralysis. The secondary type occurs as a result of superior oblique muscle paralysis of the same eye or superior lateral rectus muscle paralysis of the opposite eye [4]. Clinically, in the primary type, excessive elevation of the eye in adduction and slight elevation in the opposite gaze is accompanied by a slight head tilt, however, the head-bending test is negative. In the secondary type, in the eye with muscle paralysis, elevation is observed at the adduction state, and hypertrophy is observed at the overaction eye. The Bielschowsky test is positive with abnormal head position [5]. The treatment strategies of primary and secondary types -though differ from each other etiologically and clinically- is the same and these include surgeries such as desinsertion/tenotomy, myotomy/myectomy, regression and denervation-muscle extirpation [6].

Vestibular Evoked Myogenic Potentials (VEMP) are tests that evaluate the reflex pathway between peripheral vestibular organs and the muscles that respond to their stimulation to detect vestibular diseases. Cervical VEMP (c-VEMP) assesses the pathway between the saccular macula and the sternoclaidomastoid muscle, the ocular VEMP (o-VEMP) assesses the pathway between the utricular macula and the inferior oblique muscle [7].

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The input signal for an oVEMP is either sound or vibration, and the output is the response triggered average of EMG from the ocular muscles, generally those just under the eye. While oVEMPs were developed using bone vibration, the most common method of eliciting oVEMPs is with sound, in a way similar to cVEMPs. The best sound frequency is identical to cVEMPs, about 500 Hz. For the bone stimulus, subjects are positioned lying supine and looking upward and undergo repeated applications of the stimulus through a source of vibration, commonly a "mini shaker". The electrodes are placed under the eye to record EMG activity from the inferior oblique muscle. Because the inferior oblique is located under the eyeball, it is activated by looking upward.

In the literature review, no study was found regarding o-VEMP responses in IOOA patients thus we think our study is important as the first study in the literature by evaluating the effect of inferior oblique muscle overfunction on o-VEMP parameters.

METHODS

Research Design

In this study, a descriptive cross-sectional study design was used to investigate the effect of inferior oblique muscle overfunction on o-VEMP responses.

Study Group

This is a single-center study conducted in a tertiary university hospital between January-March 2022 on 35 patients with unilateral inferior oblique muscle overaction (IOOA group) and 18 healthy volunteers without any neurological or vestibulocochlear disease.

Anamnesis of the participants was taken carefully, their medical records were reviewed, and ear, nose and throat, neurological and vestibular examinations were performed. Exclusion criteria for this study were; patients with vestibular cochlear and neurologic disease, who used ototoxic or vestibule-suppressant drugs, who had conductive hearing loss, who had an ocular disease other than IOOA or who had a history of ocular surgery. They were evaluated with o-VEMP tests.

o-VEMP test was performed with Neurosoft brand Neuro-Audio model device. Electrodes were placed in the middle of the forehead, 15-20 mm below the orbits, and on the cheeks, not too far or too close with these electrodes. Electromyographic signals were amplified and filtered between 1 and 1000 Hz. The patients were asked to look up and measurements were made by sending a 500 Hz tone-burst stimulus at a sound intensity of 105 dB nHL. N1 and P1 absolute latencies, N1-P1 interlatency, N1-P1 amplitude and percent of asymmetry of the obtained waves were evaluated.

Main Points:

- Inferior oblique muscle overaction (IOOA) is a common ocular motility disorder manifested by elevation of the affected eye during adduction and is usually seen together with horizontal strabismus.
- Vestibular Evoked Myogenic Potentials (VEMP) are tests that evaluate the reflex pathway between peripheral vestibular organs and the muscles that respond to their stimulation to detect vestibular diseases. The ocular VEMP (o-VEMP) assesses the path between the utricular macula and the inferior oblique muscle.
- In IOOA patients, the vestibular-ocular reflex pathway may be affected, therefore, o-VEMP responses may be complicated.

Statistical Analysis

The analysis of the data was carried out with the SPSS (Statistical Program in Social Sciences) 25 program. The conformity of the data to the normal distribution was tested with the Shapiro Wilk test. The differences between the two groups for the variables providing the assumption of normal distribution were examined with the independent sample t test.

On the other hand, the difference between the two groups was examined with the Mann Whitney u test for the variables that did not provide the assumption. The difference between more than two groups was examined with the Kruskal Wallis test for the variable that does not assume a normal distribution. The gender and right and left ear variables in the patient group presented in Table 1 are categorical variables, and the chi-square ($\chi 2$) analysis was performed to investigate the relationship between the groups. At the same time, the age variable is continuous, and the independent sample t test was used to examine the difference between groups.

Ethical Principles of Research

Ethical approval was obtained from the University Health Sciences Institute Non-Interventional Clinical Research Ethics Committee (decision number: 2021/2754, date: 30.11.2021), and written and verbal informed consent was obtained from the parents of all children participating in the study.

RESULTS

The participants included in the study showed any difference between and within the groups according to demographic variables, and the results are shown in Table 1.

There was no statistically significant difference between the case and control groups according to age and gender ($p>0.05$), and the groups showed a homogeneous distribution. There was no statistically significant difference between the case groups in the study, with a squint in the right eye and a squint in the left eye according to gender ($p>0.05$, Table 1).

It was tested whether the participants included in the study showed a difference between squinted and non-squinted eyes in terms of n1 latency, p1 latency, n1-p1 latency, n1-p1 amplitude measurements in the right-eyed and left-eyed squint groups, and the results are shown in Table 2.

No statistically significant difference was found between the squinted and non-squinted sides according to the n1 latency, p1 latency, and n1-p1 latency measurement values in both the right-eye and the left-eye group ($p>0.05$). A statistically significant difference was found between the squinted and non-squinted

sides in terms of n1-p1 amplitude measurement values in both the right-eye group and the left-eye group of the participants (p values were 0.032, 0.034, respectively). A statistically significant difference was found between the groups (right eye, left eye, and control groups) according to the asymmetry measurements (p-value was 0.042, Table 2).

It was tested whether a difference exists between the groups in terms of the presence of o-VEMP wave between the squint eyes and controls, and the results are shown in Table 3.

There was no statistically significant difference between the groups regarding o-VEMP wave presence between the right and left eyes with or without squint (p>0.05).

It was tested whether there was a difference between the groups (right squint, left squint, and control) according to both right and left n1 latency, p1 latency, n1-p1 latency, n1-p1 amplitude, and asymmetry measurements, and the results are shown in Table 4.

According to the n1 latency, p1 latency, and n1-p1 latency measurement values, no statistically significant difference was found between the eyes without squint, eyes with squint and control groups (p>0.05). A statistically significant difference was found between the n1-p1 amplitude measurement values between the eyes without squint, eyes with squint, and control groups (p-value was 0.038, Table 4).

Table 1. Comparison of Demographic Variables Between Groups

		Group				Total	Test	p
		Case n (%)			Control n (%)			
Gender	Female	20 (57.1)			10 (55.6)	30 (56.6)	0.012[a]	0.912
	Male	15 (42.9)			8 (44.4)	23 (43.4)		
	Total	35 (100.0)			18 (100.0)	53 (100.0)		
		Squint eye					0.010[a]	0.922
		Right n (%)	Left n (%)	Total n (%)				
	Male	9 (56.3)	11 (57.9)	20 (57.1)				
	Female	7 (43.8)	8 (42.1)	15 (42.9)				
	Total	16 (100.0)	19 (100.0)	35 (100.0)				
		Mean ± sd (Min-Max)			Mean ± sd (Min-Max)			
Age		8.77 ± 1.71			9.11 ± 1.68		-0.927[b]	0.354
		(7-13)			(7-14)			

[a] Chi-square Test value ($\chi 2$), [b] independent sample t test

Table 2. Comparison of o-VEMP Parameters According to Squint Eyes

Strabismus Condition	Measurement	Right eye mean ± sd (M) [Min-Max.]	Left eye mean ± sd (M) [Min-Max.]	p
Right Eye Squint	n1 latency	9.63 ± 0.93	9.94 ± 0.77	0.154
		(9.4)	(9.8)	
		[8.4 - 11.8]	[8.6 - 11.9]	
	p1 latency	15.05 ± 1.35	15.26 ± 1.12	0.552
		(14.5)	(15)	
		[13.1 - 17.4]	[13.9 - 17.2]	
	n1-p1 latency	5.48 ± 1	5.32 ± 1.03	0.525
		(5.5)	(5.1)	
		[3.6 - 7.3]	[3.9 - 7.1]	
	n1-p1 amplitude	9.5 ± 5.79	9.02 ± 6.52	0.034*
		(8.8)	(8.9)	
		[1.9 - 20.9]	[1.1 - 23.9]	

Left Eye Squint	n1 latency	9.7 ± 0.96	9.83 ± 0.94	0.594
		(9.7)	(10)	
		[8.4 – 11.7]	[8.3 – 11.7]	
	p1 latency	15.22 ± 1.25	15.48 ± 1.42	0.510
		(15.1)	(15.8)	
		[13 – 17.6]	[12.4 – 18.7]	
	n1-p1 latency	5.46 ± 0.71	5.59 ± 0.91	0.707
		(5.5)	(5.5)	
		[4-7]	[4.1 – 7.2]	
	n1-p1 amplitude	6.5 ± 4.37	8.51 ± 4.67	0.032*
		(5.1)	(8.3)	
		[1.8 – 19.8]	[1.4 – 16.8]	
	Right Eye Squint	Left Eye Squint	Control	
Asymmetry	22.36 ± 11.24	20.97 ± 14.07	13.45 ± 8.64	0.042* Difference
	(21.3)	(23.8)	(14.0)	
	[8.8 – 48.4]	[50.3 – 0]	[0.4 – 28.2]	

[a]; Mann Whitney U Test, [b]; Kruskal Wallis Test, *; p<0.05

Table 3. Comparison of o-VEMP Parameters Between Squint Eyes and Control Groups

o-VEMP Wave Presence		Right Eye Squint n (%)	Left Eye Squint n (%)	Control n (%)	Total	Test	p
Right o-VEMP Wave Presence	Yes	16 (100.0)	17 (89.5)	17 (94.4)	50 (94.3)	0.426	0.514
	No	0 (0.0)	2 (10.5)	1 (5.6)	3 (5.7)		
	Total						
Left o-VEMP Wave Presence	Yes	14 (87.5)	19 (100.0)	18 (100.0)	51 (96.2)	3.431	0.064
	No	2 (12.5)	0 (0.0)	0 0.0	2 (3.8)		
	Total	16 (100.0)	19 (100.0)	18 (100.0)	53 (100.0)		

Test value; Chi-square Test value ($\chi 2$)

Table 4. Comparison of o-VEMP Parameters of Case Group's Squint Eyes, Healthy Eyes, and Control Group

	Squint Eyes	Healty Eyes of Squints	Control	Test	p
Measurement	mean ± sd (M) [Min-Max.]	mean ± sd (M) [Min-Max.]	mean ± sd (M) [Min-Max.]		
n1 latency	9.74 ± 0.93 (9.5) [8.3 – 11.8]	9.81 ± 0.87 (9.8) [8.4 – 11.9]	9.66 ± 0.96 (9.5) [8.2 – 12.1]	0.825	0.662
p1 latency	15.28 ± 1.39 (15.2) [12.4 – 18.7]	15.24 ± 1.17 (15.0) [13 – 17.6]	14.87 ± 1.09 (14.9) [12.4 – 17.4]	2.058	0.357
n1-p1 latency	5.54 ± 0.94 (5.5) [3.6 – 7.3]	5.4 ± 0.86 (5.3) [3.9 – 7.1]	5.17 ± 0.84 (5.3) [3.9 – 7.1]	2.661	0.265
n1-p1 amplitude	8.96 ± 5.16 (8.5) [1.8 – 20.9]	7.64 ± 5.5 (6.7) [1.1 – 23.9]	7.73 ± 4.56 (7.5) [1.4 – 21.6]	3.995	0.038*

Mann Whitney U Test *; p<0.05

DISCUSSION

o-VEMP is an EMG recording of extra-ocular muscle activity resulting from the vestibulo-ocular reflex pathway. Fibers emerging from the utricle macula reach the 8th nerve nucleus and from there to the opposite side 3rd nerve nucleus via the medial longitudinal fasciculus (MLF) in the brain stem. The extraocular muscles, especially the inferior oblique muscle, are stimulated by the 3rd nerve [8]. In this study, it was aimed to investigate how o-VEMP responses are affected in the case of overfunction of the inferior oblique muscle, which is the last stop of the vestibulo-ocular reflex pathway.

There are various studies on vestibular diseases that may affect VEMP responses. VEMP responses were compared especially in benign paroxysmal positional vertigo (BPPV) [9], Meniere's Disease [10], vestibular neurinitis [11], vestibular migraine [12], semicircular canal dehiscence syndrome (SCDS) [14], which are the most common vestibular system diseases. In addition, VEMP responses were also examined in diseases such as sudden hearing loss, inner ear diseases and otosclerosis that may affect the utricle and saccule, and significant differences were found [14,15].

Since VEMP reflects the functions of the peripheral as well as the central autolytic pathways, it can also be used for disorders of the central nervous system. VEMP studies have been reported in central nervous system disorders related to multiple sclerosis (MS) [16], spino-cerebellar degeneration [17], brain stem and cerebellar infarction [18], Parkinson's disease [19]. The difference between c-VEMP results and o-VEMP results is considered an important method for evaluating lesions in the brainstem [8]. There are also other factors that will affect o-VEMP responses such as, older patients have been shown to have a lower o-VEMP amplitude while younger patients are more likely to have higher o-VEMP amplitudes [20]. This appears to be the result of age-related vestibular loss rather than a change in static muscle tension with aging [21]. In this study, careful selection of the age distribution of the patient and control groups was made in order to reduce the effect of the aging factor.

Various studies have been conducted to investigate whether o-VEMP responses were affected in eye-related diseases. Monitoring of EMG responses in patients with eyeball enucleation but with preserved extraocular muscles [22] or in patients with eyes closed [23] for o-VEMP responses, the findings supported the view that these responses are potentials in the extraocular muscles independent of retina but due to vestibular stimulation. The finding of a study by Bayram et al. the fact that there was no significant difference between the o-VEMP responses between the healthy and blind eyes of patients with visual loss and the o-VEMP responses between the control group- also supports this theory [24]. As o-VEMP responses rely on activation of the contralateral inferior oblique muscle, control of muscle contraction is important for reproducible and reliable results [25,26].

Other variables to consider when performing o-VEMP testing include electrode positioning [27] and stimulus repetition rate [28]. In this study, all tests in terms of standardization were performed by an experienced audiologist.

In our literature review, no study was found regarding o-VEMP responses in IOOA patients.

In our study, it was predicted that the overfunction of the inferior oblique muscle may affect the vestibular system, as it causes a change in the vestibulo-ocular reflex arc of the patient and a change in the eye-head position.

The finding of n1, p1 and n1-p1 latencies in IOOA patients are similar with the control group draws attention to that, muscle overfunction has no effect at the time of muscle contraction and reflex formation. However, the significant difference in n1-p1 amplitude and asymmetry rates in IOOA patients compared to the control group shows the effect of muscle overfunction on amplitudes and the effect of asymmetry rates due to amplitudes.

Limitations

Studies with larger sample groups are needed to say that IOOA disease may affect the o-VEMP responses and cause vestibular symptoms. In addition, following the clinical improvement of these patients after surgical treatment, control o-VEMP tests should be performed and compared with previous results. It is also important to monitor the process with quantitative data by evaluating it in combination with all vestibular test batteries in order to objectively reveal whether VEMP effects on these patients and vestibular system symptoms.

CONCLUSION

In IOOA patients, the vestibulo-ocular reflex pathway may be affected, vestibular symptoms may develop, and therefore, o-VEMP responses may be complicated.
A careful anamnesis should be taken in these patients, and it should be kept in mind that n1-p1 amplitudes and asymmetries may be significantly higher when o-VEMP is performed. In addition, it is essential to follow these patients regarding vestibular involvement and vestibular symptoms.

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Author's Contributions: Conception: ID, DUC, CC; Design: ID, MZY, DUC, CC; Supervision: ID, DUC, SA, CC; Fundings: ID, SA; Materials: ID, SA; Data Collection and/or Processing: ID; Analysis and/or Interpretation: ID, DUC, AMT; Literature Review: ID, MZY, DUC, SA, CC, AMT; Writing: ID, MZY; Critical Review: ID, DUC, CC, AMT.

REFERENCES

1- Alajbegovic-Halimic J, Zvizdic D, Sahbegovic-Holcner A, Kulanic-Kuduzovic A (2015) Recession vs Myotomy-Comparative Analysis of Two Surgical Procedures of Weakening Inferior Oblique Muscle Overaction. Med Arch. (Sarajevo, Bosnia Herzegovina) 69:165–8. https://doi.org/10.5455/medarh.2015.69.165-168

2- Sanjari MS, Shahraki K, Nekoozadeh S, Tabatabaee SM, Shahraki K, Aghdam KA (2014) Surgical Treatments in Inferior Oblique Muscle Overaction. J Ophthalmic Vis Res. 9:291–5. https://doi.org/10.4103/2008-322X.143355

3- Chang BL, Yang SW (1988) Inferior oblique overaction. Korean J Ophthalmol. 2:77. https://doi.org/10.3341/kjo.1988.2.2.77

4- Wilson ME, Parks MM (1989) Primary Inferior Oblique Overaction in Congenital Esotropia, Accommodative Esotropia, and Intermittent Exotropia. Ophthalmology. 96:950–7. https://doi.org/10.1016/s0161-6420(89)32774-6

5- Moon K, Lee SY (2006) The effect of graded recession and anteriorization on unilateral superior oblique palsy. Korean J Ophthalmol. 20:188–91. https://doi.org/10.3341/kjo.2006.20.3.188

6- Özsoy E (2020) Surgical management of primary inferior oblique muscle overaction: a subgroup-specific surgical approach. Beyoglu Eye J. 5:38–42. https://doi.org/10.14744/bej.2020.81904

7- Rosengren SM, Welgampola MS, Colebatch JG (2010) Vestibular evoked myogenic potentials: Past, present and future. Clin Neurophysiol. 121:636–51. https://doi.org/10.1016/j.clinph.2009.10.016

8- Murofushi T (2016) Clinical application of vestibular evoked myogenic potential (VEMP). Auris Nasus Larynx. 43:367–76. https://doi.org/10.1016/j.anl.2015.12.006

9- Godha S, Upadhyay Mundra A, Mundra RK, Bhalot L, Singh A (2020) VEMP: An Objective Test for Diagnosing the Cases of BPPV. Indian J Otolaryngol Head Neck Surg. 72:251–6. https://doi.org/10.1007/s12070-020-01802-3

10- Manzari L, Tedesco AR, Burgess AM, Curthoys IS (2020) Ocular and cervical vestibular-evoked myogenic potentials to bone conducted vibration in Ménière's disease during quiescence vs during acute attacks. Clin Neurophysiol. 121:1092–101. https://doi.org/10.1016/j.clinph.2010.02.003

11- Chihara Y, Iwasaki S, Murofushi T, Yagi M, Inoue A, Fujimoto C, Egami N, Ushio M, Karino S, Sugasawa K, Yamasoba T (2012) Clinical characteristics of inferior vestibular neuritis. Acta Otolaryngol. 132:1288–94. https://doi.org/10.3109/00016489.2012.701326

12- Fu W, Wang Y, He F, Wei D, Bai Y, Han J, Wang X (2021) Vestibular and oculomotor function in patients with vestibular migraine. Am J Otolaryngol. 42:103152. https://doi.org/10.1016/j.amjoto.2021.103152

13- Hassannia F, Misale P, Harvey K, Yu E, Rutka JA (2021) Elevated ocular VEMP responses in the absence of a superior semicircular canal dehiscence. Am J Otolaryngol. 42:102789. https://doi.org/10.1016/j.amjoto.2020.102789

14- Korres SG (2014) Contribution of Vestibular-Evoked Myogenic Potential (VEMP) testing in the assessment and the differential diagnosis of otosclerosis. Med Sci Monit. 20:205–13. https://doi.org/10.12659/MSM.889753

15- Maia N de PD, Lopes K de C, Ganança FF (2020) Vestibular evoked myogenic potentials in the prognosis of sudden hearing loss a systematic review. Braz J Otorhinolaryngol. 86:247–54. https://doi.org/10.1016/j.bjorl.2019.10.001

16- Shimizu K (2020) Vestibular evoked myogenic potentials in multiple sclerosis. J Neurol Neurosurg Psychiatry. 69:276–7. https://doi.org/10.1136/jnnp.69.2.276

17- Murofushi, Hideki Takegoshi T (2000) Vestibular Evoked Myogenic Potentials in Patients with Spinocerebellar Degeneration. Acta Otolaryngol. 120:821–4. https://doi.org/10.1080/000164800750061660

18- Chen C-H, Young Y-H (2003) Vestibular Evoked Myogenic Potentials in Brainstem Stroke. Laryngoscope. 113:990–3. https://doi.org/10.1097/00005537-200306000-00014

19- de Natale ER, Ginatempo F, Paulus KS, Manca A, Mercante B, Pes GM, Agnetti V, Tolu E, Deriu F (2015) Paired neurophysiological and clinical study of the brainstem at different stages of Parkinson's Disease. Clin Neurophysiol . 126:1871–8. https://doi.org/10.1016/j.clinph.2014.12.017

20- Nguyen KD, Welgampola MS, Carey JP (2010) Test-retest reliability and age-related characteristics of the ocular and cervical vestibular evoked myogenic potential tests. Otol Neurotol. 31:793–802. https://doi.org/10.1097/MAO.0b013e3181e3d60e

21- Ochi K, Ohashi T (2003) Age-related changes in the vestibular-evoked myogenic potentials. Otolaryngol - Head Neck Surg. 129:655–9. https://doi.org/10.1016/s0194-5998(03)01578-x

22- Chihara Y, Iwasaki S, Ushio M, Fujimoto C, Kashio A, Kondo K, Ito K, Asakage T, Yamasoba T, Kaga K, Murofushi T (2009) Ocular vestibular-evoked myogenic potentials (oVEMPs) require extraocular muscles but not facial or cochlear nerve activity. Clin Neurophysiol. 120:581–7. https://doi.org/10.1016/j.clinph.2008.12.030

23- Huang Y-C, Yang T-L, Young Y-H (2012) Feasibility of ocular vestibular-evoked myogenic potentials (oVEMPs) recorded with eyes closed. Clin Neurophysiol. 123:376–81. https://doi.org/10.1016/j.clinph.2011.06.024

24- Bayram A, Kalkan M, Ünsal N, Kale A, Küçük B, Mutlu C (2018) Does blindness affect ocular vestibular evoked myogenic potentials? Am J Otolaryngol. 39:290–2. https://doi.org/10.1016/j.amjoto.2018.03.010

25- Govender S, Rosengren SM, Colebatch JG (2009) The effect of gaze direction on the ocular vestibular evoked myogenic potential produced by air-conducted sound. Clin Neurophysiol. 120:1386–91. https://doi.org/10.1016/j.clinph.2009.04.017

26- Rosengren SM, Colebatch JG, Straumann D, Weber KP (2013) Why do oVEMPs become larger when you look up? Explaining the effect of gaze elevation on the ocular vestibular evoked myogenic potential. Clin Neurophysiol. 124:785–91. https://doi.org/10.1016/j.clinph.2012.10.012

27- Sandhu JS, George SR, Rea PA (2013) The effect of electrode positioning on the ocular vestibular evoked myogenic potential to air-conducted sound. Clin Neurophysiol. 124:1232–6. https://doi.org/10.1016/j.clinph.2012.11.019

28- Singh NK, Kadisonga P, Ashitha P (2014) Optimizing stimulus repetition rate for recording ocular vestibular evoked myogenic potential elicited by air-conduction tone bursts of 500 Hz. Audiol Res. 4:88. https://doi.org/10.4081/audiores.2014.88

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Original Research

Correlation of Diffusion-weighted MR imaging and FDG PET/CT in the Diagnosis of Metastatic Lymph Nodes of Head and Neck Malignant Tumors

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ABSTRACT

Objective: The aim of this study was to investigate the efficacy of diffusion-weighted magnetic resonance imaging (DW-MRI) as a reliable imaging modality for detecting metastatic neck lymph nodes of head and neck squamous cell carcinoma (SCC).

Methods: Thirty-two patients underwent positron emission tomography computed tomography (PET/CT) and DW-MRI were evaluated. Histopathologic analysis of lymph node metastases was used as the gold standard for assessment. We analyzed differences in sensitivity, specificity, accuracy, positive predictive value and negative predictive value among the imaging modalities using the Chi-square test. Their discriminative power evaluated using the Receiver-Operating Characteristic curve and calculation of the area under the curve. The correlation between ADCmin and SUVmax was calculated using the Spearman test. SPSS 24 was used for statistical analyses. P value of 0.05 indicates a statistically significant difference.

Results: A total of 32 patients with 50 neck dissections with head and SCC included. Sensitivity, specificity, accuracy, positive and negative predictive value of neck palpation was 72%, 60%, 70%, 62% and 80% respectively. Sensitivity, specificity, accuracy, positive and negative predictive value of DW-MRI was 87.5%, 96.2%, 92%, 95.5% and 89.3% respectively, according to ADCmin cutoff value 0.82×10-3s/mm2 . Sensitivity, specificity, accuracy, positive and negative predictive value of FDG-PET/CT was 91.7%, 100%, 96%, 100% and 92.9%, respectively, according to SUVmax cutoff value 3.4. For all neck dissections, there was a statistically significant inverse correlation between ADCmin and SUVmax (P<001).

Conclusion: DW-MRI may be as reliable as FDG-PET/CT in detecting cervical lymph node metastases. DWI and FDG PET/CT can play a complementary role in clinical evaluation. Further research is needed.

Keywords: Diffusion-weighted magnetic resonance imaging, head and neck cancer, squamous cell carcinoma, Fluoro-2-deoxy-d-glucose-Positron emission tomography

INTRODUCTION

Head and neck tumors are 5% of all malignant tumors, the sixth most common among all cancers, and the incidence is increasing in developing countries [1,2]. Squamous cell carcinoma(SCC) is the most common histopathological type and constitutes approximately 90% of all head and neck tumors [3]. The stage of the tumor is important in determining the treatment method of the patient. Lymph node involvement has an important place in the staging of the patient and significantly affects the prognosis and survival of the patient [1]. Therefore, the presence of lymph node metastases must be accurately determined.

Fluoro-2-deoxy-d-glucose-Positron emission tomography (FDG-PET) is a non-invasive imaging technique using positron

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emitting isotopes. Positron emission tomography/ Computed tomography (PET/CT) is a hybrid imaging method formed by the combination of Positron Emission Tomography and Computed Tomography devices. Because PET/CT scans the whole body, it successfully reveals the extention of the cancer [4].

Diffusion weighted imaging (DWI), one of the Magnetic Resonance Imaging (MRI) methods, is a functional method examining the random movements and microscopic diffusion of water molecules in tissues [5]. This phenomenon can be measured and can be expressed as the diffusion coefficient. Complete free diffusion of molecules is not possible in biological tissues due to constraints such as cell membranes or molecular boundaries. The measured magnitude of the conducted diffusion of molecules in the human body is known as the Apparent Diffusion Coefficient-Apparent Diffusion Coefficient (ADC). The ADC value expresses the rate of diffusional motion and is obtained by measuring and calculating the signal intensity on a series of diffusion-weighted MRI images. While malignant lesions show low ADC values, high ADC values are observed in benign lesions [6].

The aim of our study is to investigate the usability of DW-MRI, which has become widespread in recent years, as a reliable imaging method as PET/CT, which is the preferred imaging method in classical metastasis scanning, in detecting lymph node metastasis of head and neck squamous cell carcinomas.

METHODS

This study was carried out in the Ear Nose Throat Clinic and Radiology Clinic of a tertiary hospital between June 2017 and December 2017. The study was approved by the Ethics Committee on 28.02.2017 with the barcode number 4656.

121 neck dissection specimens that were applied to 91 patients who were diagnosed with head and neck SCC in our clinic between December 2014 and December 2017 and underwent neck dissection with primary tumor surgery were included in the study. Patients who did not undergo any of the PET/CT and DW-MRI methods, had an MRI performed in an external center, and whose imaging methods could not be performed in accordance with the standards due to technical deficiencies were excluded from the study. After inclusion and exclusion criteria, 50 neck dissections performed in 32 patients were included in the study (Figure 1). There was a maximum interval of 20 days between both imaging modalities.

Neck MRI examinations of 32 patients in the study series were performed on a 1.5 Tesla MR device (Siemens Avanto). T1 weighted with SE technique with 4 mm section thickness in coronal plane, T2 weighted with FAT SAT FSE technique with 4 mm section thickness in coronal plane, T1 weighted with SE technique with 6 mm section thickness in axial plane, T2 weighted with FSE technique with 6 mm section thickness in axial plane, T1-weighted sequences were added in the axial and coronal planes after intravenous contrast agent administration. Diffusion-weighted images and ADC maps were obtained for each patient by applying diffusion sensitive gradients in all three directions (x, y, z) at two different b values (0 and 1000 mm2/s). ADC maps of the lesions were automatically constructed on the main console. Then, the signal intensity of the lesion was measured by the radiologist in the radiology clinic of our hospital, and the region of interest (ROI) was defined. ROI was measured from solid areas in lymph nodes with a short axis greater than 1 cm. ADC values of the lesions were calculated from the ROI.

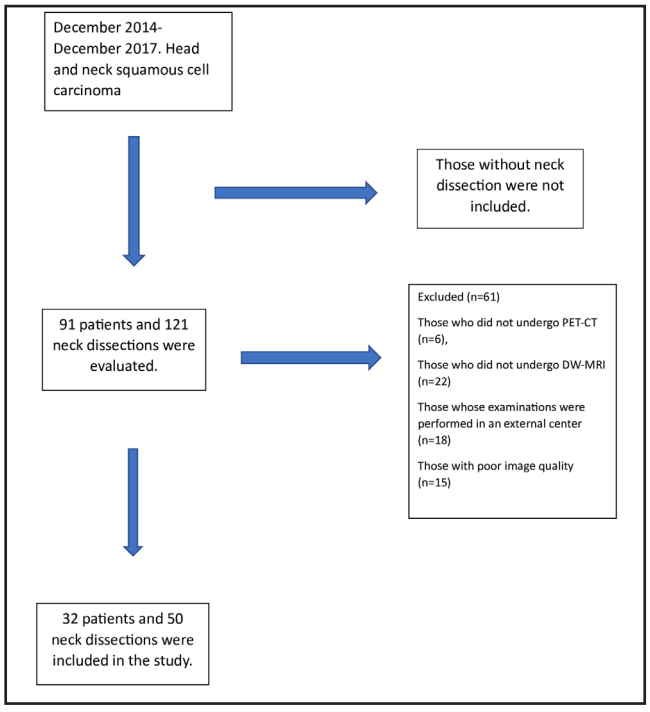


Figure 1. Inclusion criteria of patients

Before the PET/CT study, patients were fasted for an average of 10 hours. One hour before the radiopharmaceutical injection, 30 cc of oral contrast agent diluted with 1.5 liters of water was administered. Before the FDG injection, the blood glucose levels of all patients were checked. Imagimgs of patients with blood glucose levels above 200 mg/dl were not performed. 9-15 mCi (333-555 MBq) of F-18 FDG was given intravenously to the patients. The patients were rested without chewing or talking in a calm and room temperature environment until the post-injection imaging began. Whole body PET/CT imaging was performed 60-90 minutes after injection.

PET/CT imaging, with enhanced detector technology with increased sensitivity and spatial resolution, 17 cm field of view (FOV) and 5.47mm for 2D, 6mm for 3D, retractable septal allowing imaging in 2D and 3D modes, 8 Helical CT section was performed with PHILIPS Gemini TF 64 Slice PET/CT device. The patients were imaged in the supine position with their arms to the side or with the arms up. The patients were instructed to breathe normally during the acquisition. Following the CT topogram image, CT images covering the vertex-upper thigh were acquired at a tube current of 60 mA and a tube voltage of 140 kV at a rotation rate of 0.8 seconds per rotation. PET imaging started immediately after CT imaging. PET acquisition time was 2-3 minutes per bed position, according to the patient's weight and 2D/3D acquisition protocol. Scatter and attenuation corrections of PET images were

performed with the CT data. Evaluation was made by obtaining MIP (maximum intensity projection) and PET, CT and PET/CT fusion images in the transaxial, coronal and sagittal planes. The suvmax values of the lymph nodes defined in the PET/CT report of the patients, which were defined as malignant lymph node in the foreground and benign lymph node in the foreground, were added together and averaged.

All neck triangles of the patients were palpated bilaterally. The size, location, stiffness of the palpable lymph nodes and their relationship with the surrounding tissues were noted. Sensitivity, specificity and accuracy in neck palpation were evaluated by comparing with histopathological results.

While evaluating the findings obtained in the study, SPSS 2.4 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency) were used while evaluating the study data. The chi-square test was used to compare qualitative data. ROC (Receiver Operating Characteristic) analysis was applied to determine the cut-off point for SUVmax and ADC. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

RESULTS

32 patients included in the study, 29 (90.6%) were male and 3 (9.6%) were female, with a mean age of 60.47 (SD: 12.72). The 50 types of neck dissections performed are shown in Table 1.

At least 1 lymph node was detected on the same side as the primary tumor in 21 (65%) patients, and at least 1 bilateral lymph node was detected in 4 (12%) patients. Lymph nodes were detected on palpation in 29 of 50 neck dissections performed in 32 patients. The calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive values of palpation were 72%, 60%, 70%, 62% and 80%, respectively (Table 2).

At least 1 lymph node was detected on the same side as the primary tumor in 14 (43%) patients, and at least 1 lymph node bilaterally in 4 (6%) patients. DW-MRI detected lymph nodes in 22 of 50 neck dissections performed in 32 patients (Figure 2). Lymph nodes below the ADC value of 0.82×10-3s/mm2 were evaluated as benign and above as malignant. Taking the ADC cut-oFF value as 0.82×10-3s/mm2, the calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive value values were 87.5%, 96.2%, 92%, 95.5% and 89.3%, respectively (Table 2). Upon the usability of the ADC value in the differential diagnosis of malignant and benign lymph nodes, the area under the curve (AUC) was 0.965 and the standard error was 2.4% in the obtained ROC curve (Figure 3).

Table 1. Data of gender, age and Primary cancer site and neck dissection

		Functional neck dissection	Radical neck dissection	Supraomohyoid neck dissection	One side Functional, other side Radical neck dissection	
Primary Tumour	Larynx	12 (66.6%)	4 (22.2%)	0	2 (11.2%)	18
	Tonsil	1 (50%)	1 (50%)	0	0	2
	Oral Cavity	6 (54.5%)	0	4 (36.3%)	1 (9.2)	11
	Parotid Gland	0	1 (100%)	0	0	1
Total		19 (59.3)	6 (18.8)	4 (12.5%)	3 (9.4%)	32
Sex		Male		Female		
		29 (90.6%)		3(9.4%)		32
Mean age(sd)		71.17(21.07)		56.33(9.56)		p=0.09

Table 2. Sensitivity, specificity, accuracy, positive predictive value and negative predictive values of neck palpation, DW-MRI and PET-CT

Method	Sensitivity	Specificity	Accuracy	PPV	NPV
Neck Palpation	72%	60%	70%	62%	80%
DW-MRI	87.5%,	96.2%	92%	95.5%	89.3%
PET-CT	91.7%	100%	96%	100%	92.9%

DW-MRI: Diffusion-weighted magnetic resonance imaging
PET-CT: positron emission tomography – computed tomography
PPV: positive predictive value
NPV: negative predictive value

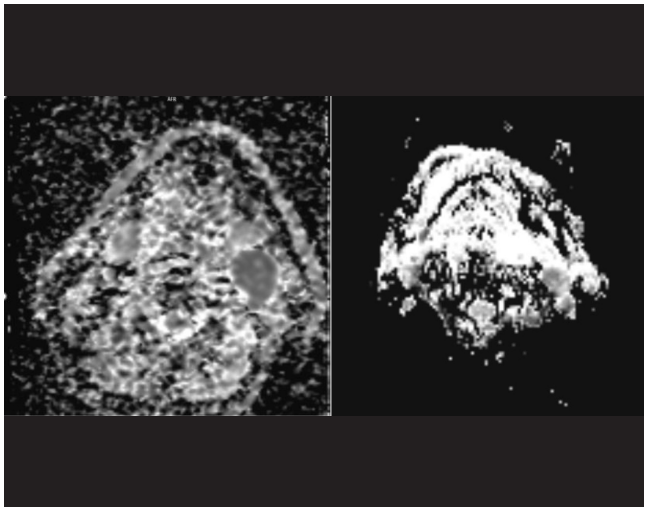


Figure 2. DW-MRI image

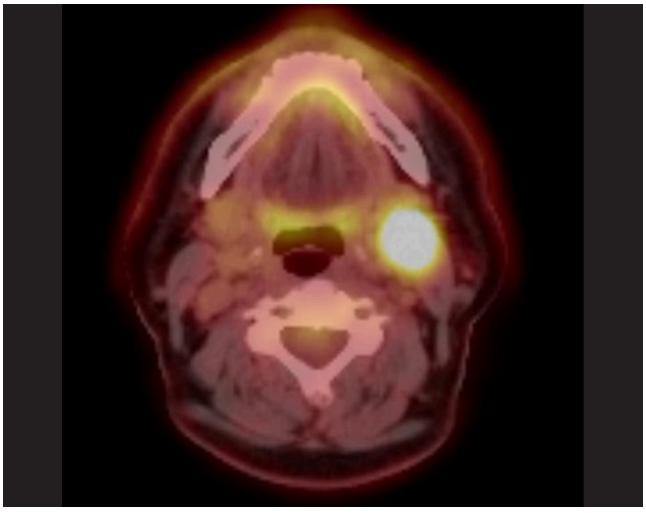
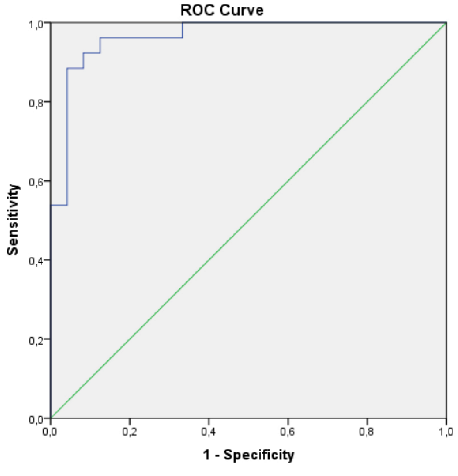


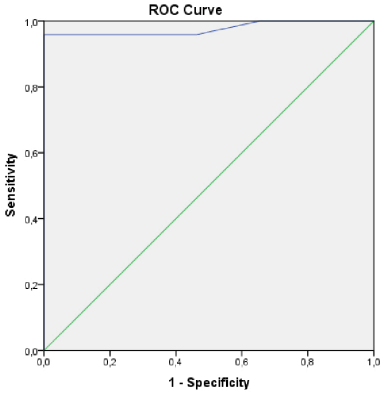
Figure 4. PET-CT image

At least 1 lymph node was detected on the same side as the primary tumor in 14 (43%) patients, and at least 1 bilateral lymph node was detected in 4 (12%) patients. PET/CT detected lymph nodes in 22 of 50 neck dissections performed on 32 patients (Figure 4). Lymph nodes with a SUVmax level below 3.4 were considered benign and above it malignant. Taking SUVmax cut-off value of 3.4, we calculated sensitivity as 91.7%, specificity as 100%, accuracy as 96%, positive predictive value as 100%, and negative predictive value as 92.9% (Table 2). Based on the utility of SUVmax in the differential diagnosis of malignant and benign lymph nodes, the area under the curve (AUC) was 0.977 and the standard error was 2.4% in the obtained ROC curve (Figure 5).



Area Under the Curve				
ADC				
Area	Std. Error(a)	P	95% (Confidence Interval)	
			Upper	Lower
0,965	0,024	0,000	0,918	1,000

Figure 3. ADC- Roc Curve. (AUC:0.965 Std Error:0.024). ADC has high reliability in detecting lymph node metastases.



Area Under the Curve				
SUVmax				
Area	Std. Error(a)	P	95% (Confidence Interval)	
			Upper	Lower
0,977	0,024	0,000	0,931	1,000

Figure 5. SUVmax- Roc Curve. (AUC:0,977 Std Error:0,024). SUVmax has high reliability in detecting lymph node metastases.

16 (50%) patients had at least 1 SCC metastasis on the same side as the primary tumor, and 3 (9%) patients had at least 1 bilateral lymph node with SCC metastasis. Lymph nodes with SCC metastases were detected in 22 of 50 neck dissections performed in 32 patients. In the pathological staging, 24 (75%) of the patients were in the advanced stage and 8 (25%) were in the early stage.

The correlation between SUVmax and ADCmin was analyzed by Spearman Correlation test. It was found that there was a statistically significant inverse correlation between both parameters. ($p<0.001$) (Figure 6).

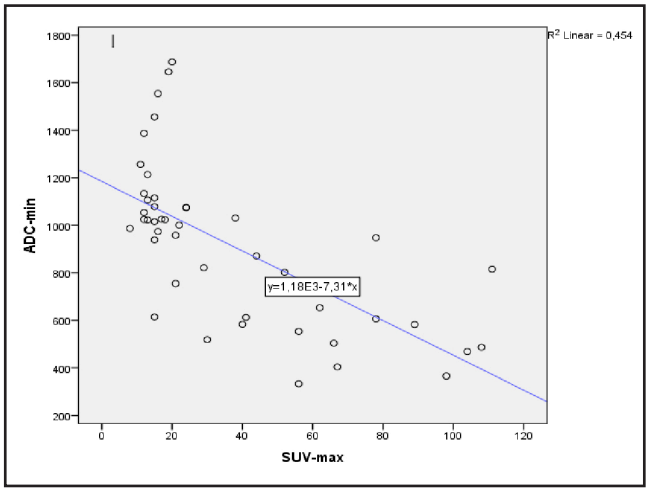


Figure 6. SUV–max and ADC correlation curve There is a statistically significant inverse correlation between SUVmax and ADC.

DISCUSSION

In our study, patients who were diagnosed with SCC in the head and neck and underwent neck dissection with primary surgical treatment were discussed. Preoperative PET/CT and DW-MR imaging and postoperative histopathological results of the patients were evaluated in terms of lymph node metastasis based on the relevant neck side. It has been found that DW-MRI is at least as successful and reliable as PET/CT in recognizing neck metastases of head and neck squamous cell carcinomas.

The most important feature of head and neck malignancies in general is that they spread to lymph nodes in the neck before spreading anywhere in the body. In other words, while distant metastases are rare in patients with head and neck malignant tumors, cervical lymph node metastasis is quite common [7]. It is accepted that lymph node metastasis is a major prognostic factor for these patients and neck relapses are the main cause of treatment failure in these patients [8,9]. For this reason, it is necessary to accurately evaluate the condition of the neck at the stage of diagnosis of the disease. The basic examination method in the evaluation of the neck is primarily palpation. However, in order for the lymph nodes to be palpable clinically, they should be 0.5 cm in diameter in the superficial regions and at least 1 cm in the deep regions. However, it has been suggested that the probability of histologically positive lymph node in a patient with negative neck palpation is between 4-60% [10]. In general, it has been reported that the correct detectability of neck metastases by palpation is between 60-65%, and false positive and negative results can be obtained [11]. Therefore, advanced radiological imaging is needed in addition to palpation in neck evaluation. These radiological methods basically enable the detection of pathological lymph nodes that cannot be detected by physical examination, the evaluation of extranodal spread in the existing lymph node, and the determination of vital organ invasions adjacent to the lymph nodes.

In our study, the rate of lymphatic metastases was 59.4%. The neck evaluation of our patients was first performed by detailed palpation method including all neck regions. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value ratio of palpation were 72%, 60%, 70%, 62% and 80%, respectively. These results were found to be similar to the results of some studies in the literature [10,11]. In accordance with the results of our study, we also think that the rate of bias and error will be high in the evaluation of pathological lymph nodes in the neck by palpation.

When the literature is examined, diffusion-weighted MR imaging has found to be useful in different parts of the head and neck. The first study in this area was on the characterization of head and neck masses by Wang et al [6]. As a result of the study, they found the mean ADC values of benign masses to be significantly higher than the average ADC values of malignant masses. Sumi et al. studied the differential diagnosis of metastatic neck lymph nodes with diffusion-weighted MRI in 2003 [12]. In a study on neck lymph nodes, it was found that the differentiation of necrotic and non-necrotic solid parts of malignant masses can be done by making ADC mapping of the mass as a new technique [13].

In the study by Sumi et al., ADC values in metastatic lymph nodes were shown to be significantly higher than in benign lymph nodes [12]. On the other hand, in the study by Abdel Razek et al., the mean ADC values measured in metastatic and lymphomatous lymph nodes were significantly lower than those measured in benign nodes [13]. Although the reason for the discrepancy between these two studies is unclear, continuing research using larger patient groups will help to clarify the uncertainty on this issue. In our study, unlike Sumi et al., metastatic mean ADC values were significantly lower than benign lymph nodes ($p<0.05$), but overlap was observed in some cases. Another factor that increases the ADC value in metastatic lymph nodes is necrosis foci, and necrosis is frequently observed in carcinoma metastases. The high ADC values of malignant lymph nodes in the study of Sumi et al. may be due to foci of necrosis.

The use of DW-MRI to differentiate malignant from benign lymph nodes has been investigated in a limited number of studies. Studies have shown that the sensitivity of DW-MRI in differentiating lymph nodes from benign and malignant ranges between 52-98% and specificity between 88-97% [6,12–14]. In the study conducted by Wang et al. in 2001, it was stated that 1.22 x 10-3mm2/s could be used as the cut-off point, with 84% sensitivity and 91% specificity, as the ADC value in the differential diagnosis of benign and malignant masses in head and neck masses. The study included a series of 97 lesions in 97 patients [6]. In the study conducted by Abdel Razek et al. in 2008 in a series of 78 pediatric head and neck masses, the cut-off value was taken as 1.25X10-3mm2/s and 1.25X10-3mm2/s can be used with a 94.4% sensitivty and specificity of 91.2% in benign and malignant head and neck masses [13]. Vandecaveye et al. evaluated the superiority of DW-MRI over other MRI techniques in the detection of head and neck squamous cell carcinoma metastases in 33 patients in 2009, taking the cut-off value of 0.94X10-3mm2/s, with a sensitivity of 84%, a specificity of 94% and an accuracy of 91% [14]. In our study, the ADC cut-

off value was 0.82×10-3s/mm2 in the detection of neck lymph node metastasis in 32 patients diagnosed with head and neck squamous cell carcinoma, and the calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive value values were 87.5%, 96.2%, 92%, 95.5% and 89.3% respectively. Consistent with the literature, we found that the use of DW-MRI in lymph node metastasis has a high diagnostic value.

Threshold values for diagnosing malignancy, separating lymphoma from carcinoma and separating malignant lymph nodes from benign lymph nodes have generally been studied on 1.5 T magnets to date, and these values should be defined for each MRI system separately. Because there are several variations between MRI units, pulse sequences, and functioning of the units [6]. Huisman et al. showed that ADC and fractional anisotropy values measured in brain gray and white matter were different in 1.5 and 3T devices. Therefore, it is necessary to investigate whether the ADC differences measured with 1.5T in benign and malignant neck masses are also valid at higher magnetic field strengths [15]. In the study of Srinivasan et al., a total of 33 patients with malignant and benign lesions were evaluated in a 3T MRI device, and the threshold value could be determined [16]. Magnetic resonance neck imaging of the patients in our study was studied using 1.5 Tesla magnets. Since there are limited number of studies with small patient groups in the literature on this subject, it is necessary to continue research and compare the results in different magnetic fields.

PET/CT imaging, in which both the metabolic and morphological features of the disease can be evaluated, has important advantages in staging head and neck cancers, identifying the tumor of unknown primary, monitoring the treatment, and determining the residual-recurrent tumor. Especially in oral cavity tumors, the sensitivity of PET is higher than CT and MR. The diagnostic performance of PET/CT in oral cavity tumors is 96.3%, 77.8% of CT and 85.2% of MRI [17].

PET/CT is the method of choice for staging locally advanced head and neck cancers due to its high sensitivity in distant metastasis research. In newly diagnosed oral cavity cancers, 24% additional (not detected by clinical examination, chest X-ray and thorax CT) distant metastases and a second primary tumor were detected with PET/CT. TNM staging was changed in 31% of patients with head and neck cancer staged by CT-MR. Distant metastases are unlikely in T1 disease and radiological staging is unnecessary. The necessity of radiological staging in T2 patients is controversial. PET/CT is the imaging modality of choice in locally advanced (T3-T4) patients [17].

The sensitivity of the use of FDG-PET/CT in the detection of lymph node metastases in head and neck squamous cell carcinomas was found to be 50-100% [4,18-19]. Ng et al. found that the diagnostic accuracy of FDG-PET/CT in the detection of lymph node metastasis in patients with head and neck squamous cell carcinoma was calculated according to neck levels with a sensitivity of 74.7% and a specificity of 93% [20]. Few studies have been reported evaluating SUVmax of metastatic lymph nodes in the neck. Murakami et al. calculated SUVmax cut-off 1.9 <10 mm diameter, cut-off 2.5 for 10-15 mm, and cut-off 3.0 for >15 mm, calculated according to neck levels with FDG-PET/CT sensitivity of 79% and specificity of 99% [21]. In our study, we calculated the SUVmax cut-off value as 3.4.

Sun et al. evaluated a total of 1270 patients in 24 studies in their Review study. As a result, number-based sensitivity/specificity was 91%(82-95%)/87%(80-92%), neck side-based sensitivity/specificity was 84%(75-90%)/83%(77-88%), and neck level-based sensitivity/specificity was calculated as 80% (71-87%)/96% (94-97%) [22]. In the study conducted by Kitajima et al. in 2015 on the clinical importance of SUVmax in 18F-FDG PET/CT scan for the detection of nodal metastases in patients with oral squamous cell carcinoma, the sensitivity was 67%, the specificity was %94.6 , accuracy 91.6%, positive predictive value 61.3%, negative predictive value 95.9% ; in the analysis performed according to the number of neck sides with a cut-off value of 3.5, sensitivity was 84.6%, specificity was 87%, accuracy was 86.1%, positive predictive value was 78.5% ,negative predictive value was 90.9% [23]. In our study, in the detection of neck lymph node metastasis of 32 patients diagnosed with head and neck squamous cell carcinoma, taken the SUVmax cut-off value as 3.4 in the calculation based on neck dissection, we calculated the sensitivity 91.7%, specificity 100%, accuracy 96%, positive predictive value 100%, negative predictive value as 92%. In accordance with the literature, we found that the use of PET/CT in lymph node metastasis has a high diagnostic value.

In the study conducted by Nakamatsu et al. in which 24 patients were included, lymph nodes whose pathology results were interpreted in favor of metastasis were detected in DW-MRI and PET/CT, and an inverse correlation was found between ADCmin and SUVmax values [24]. In our study, which included 32 patients based on the number of neck side and dissection, a statistically significant inverse correlation was found between ADCmin and SUVmax, similar to those of Nakamatsu et al. ($p<0.001$).

There were several limitations in our study. First, our study was retrospective. Second, relatively few patients were included in the study after the inclusion criteria. Due to the small number of patients, it was difficult to draw definitive conclusions. Further studies with prospective and larger patient series are needed.

CONCLUSION

PET/CT and DW-MRI have high reliability in detecting lymph node metastasis of head and neck squamous cell carcinomas. Combined use of both imaging modalities can be used as a guide when planning neck treatment.

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Ethics Committee Approval: This study was carried out in the Ear Nose Throat Clinic and Radiology Clinic of a tertiary hospital between June 2017 and December 2017. The study was approved by the Ethics Committee on 28.02.2017 with the barcode number 4656.

REFERENCES

1. Gormley M, Creaney G, Schache A, Ingarfield K (2022) Conway DI. Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors. Br Dent J. 233(9):780-786. https://doi.org/10.1038/s41415-022-5166-x
2. Dyba T, Randi G, Bray F, et al (2021) The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer. 157:308-347. https://doi.org/10.1016/j.ejca.2021.07.039
3. Rogers SJ, Harrington KJ, Rhys-Evans P, O-Charoenrat P, Eccles SA (2005) Biological significance of c-erbB family oncogenes in head and neck cancer. Cancer Metastasis Rev. 24(1):47-69. https://doi.org/10.1007/s10555-005-5047-1
4. Di Martino E, Nowak B, Hassan HA, et al (2000) Diagnosis and Staging of Head and Neck Cancer. Arch Otolaryngol Neck Surg. 126(12):1457. https://doi.org/10.1001/archotol.126.12.1457
5. Sakamoto J, Yoshino N, Okochi K, et al (2009) Tissue characterization of head and neck lesions using diffusion-weighted MR imaging with SPLICE. Eur J Radiol. 69(2):260-268. https://doi.org/10.1016/j.ejrad.2007.10.008
6. Wang J, Takashima S, Takayama F, et al (2001) Head and Neck Lesions: Characterization with Diffusion-weighted Echo-planar MR Imaging. Radiology. 220(3):621-630. https://doi.org/10.1148/radiol.2202010063
7. Aksoy F, Veyseller B, Binay O, Apuhan T, Yildirim YS, Ozturan O (2010) Patterns of cervical metastasis from squamous cell carcinoma of the head and neck. Kulak Burun Bogaz Ihtis Derg. 20(5):249-254.
8. Ying M, Bhatia KSS, Lee YP, Yuen HY, Ahuja AT (2013) Review of ultrasonography of malignant neck nodes: greyscale, Doppler, contrast enhancement and elastography. Cancer Imaging. 13(4):658-669. https://doi.org/10.1102/1470-7330.2013.0056
9. Meng W, Xing P, Chen Q, Wu C (2013) Initial experience of acoustic radiation force impulse ultrasound imaging of cervical lymph nodes. Eur J Radiol. 82(10):1788-1792. https://doi.org/10.1016/j.ejrad.2013.05.039
10. Cho JK, Hyun SH, Choi N, et al (2015) Significance of Lymph Node Metastasis in Cancer Dissemination of Head and Neck Cancer. Transl Oncol. 8(2):119-125. https://doi.org/10.1016/j.tranon.2015.03.001
11. Mathers CD, Shibuya K, Boschi-Pinto C, Lopez AD, Murray CJL (2002) Global and regional estimates of cancer mortality and incidence by site: I. Application of regional cancer survival model to estimate cancer mortality distribution by site. BMC Cancer. 2(1):36. https://doi.org/10.1186/1471-2407-2-36
12. Sumi M, Sakihama N, Sumi T, Morikawa M (2003) Discrimination of Metastatic Cervical Lymph Nodes with Diffusion-Weighted MR Imaging in Patients with Head and Neck Cancer. Am J Neuroradiol. 24:1627-1634.
13. Abdel Razek AAK, Soliman NY, Elkhamary S, Alsharaway MK, Tawfik A (2006) Role of diffusion-weighted MR imaging in cervical lymphadenopathy. Eur Radiol. 16(7):1468-1477. https://doi.org/10.1007/s00330-005-0133-x
14. Vandecaveye V, De Keyzer F, Vander Poorten V, et al (2009) Head and Neck Squamous Cell Carcinoma: Value of Diffusion-weighted MR Imaging for Nodal Staging. Radiology. 251(1):134-146. https://doi.org/10.1148/radiol.2511080128
15. Huisman TAGM, Loenneker T, Barta G, et al (2006) Quantitative diffusion tensor MR imaging of the brain: field strength related variance of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) scalars. Eur Radiol. 16(8):1651-1658. https://doi.org/10.1007/s00330-006-0175-8
16. Srinivasan A, Dvorak R, Perni K, Rohrer S, Mukherji SK (2008) Differentiation of Benign and Malignant Pathology in the Head and Neck Using 3T Apparent Diffusion Coefficient Values: Early Experience. Am J Neuroradiol. 29(1):40-44. https://doi.org/10.3174/ajnr.A0743
17. Brouwer J, Senft A, de Bree R, et al (2006) Screening for distant metastases in patients with head and neck cancer: Is there a role for 18FDG-PET? Oral Oncol. 42(3):275-280. https://doi.org/10.1016/j.oraloncology.2005.07.009
18. Paulus P, Sambon A, Vivegnis D, et al (1998) 18 FDG-PET for the assessment of primary head and neck tumors: Clinical, computed tomography, and histopathological correlation in 38 patients. Laryngoscope. 108(10):1578-1583. https://doi.org/10.1097/00005537-199810000-00029
19. Kresnik E, Mikosch P, Gallowitsch H, et al (2001) Evaluation of head and neck cancer with 18F-FDG PET: a comparison with conventional methods. Eur J Nucl Med. 28(7):816-821. https://doi.org/10.1007/s002590100554
20. Ng SH, Yen TC, Liao CT, et al (2005) 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: A prospective study of 124 patients with histologic correlation. J Nucl Med. 46(7):1136-1143.

21. Murakami R, Uozumi H, Hirai T, et al (2007) Impact of FDG-PET/CT Imaging on Nodal Staging for Head-And-Neck Squamous Cell Carcinoma. Int J Radiat Oncol. 68(2):377-382. https://doi.org/10.1016/j.ijrobp.2006.12.032

22. Sun R, Tang X, Yang Y, Zhang C (2015) 18FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: A meta-analysis. Oral Oncol. 51(4):314-320. https://doi.org/10.1016/j.oraloncology.2015.01.004

23. Kitajima K, Suenaga Y, Minamikawa T, et al (2015) Clinical significance of SUVmax in 18F-FDG PET/CT scan for detecting nodal metastases in patients with oral squamous cell carcinoma. Springerplus. 4(1):718. https://doi.org/10.1186/s40064-015-1521-6

24. Nakamatsu S, Matsusue E, Miyoshi H, Kakite S, Kaminou T, Ogawa T (2012) Correlation of apparent diffusion coefficients measured by diffusion-weighted MR imaging and standardized uptake values from FDG PET/CT in metastatic neck lymph nodes of head and neck squamous cell carcinomas. Clin Imaging. 36(2):90-97. https://doi.org/10.1016/j.clinimag.2011.05.002

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Original Research

Evaluation of the Image Quality of Ultra-Low-Dose Paranasal Sinus CT

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ABSTRACT

Objective: We aimed to investigate the image quality of paranasal sinus computed tomography (CT) scans obtained with the "Advanced intelligent Clear-IQ Engine" (AiCE) software and ultra-low dose parameters in patients with pre-diagnosed rhinitis, sinusitis or nasal septum deviation.

Methods: The first 50 patients (31 men and 19 women, aged 18-70 years) who agreed to participate in our prospectively planned study were included in the study. Imaging of the patients was performed with a 160-slice multidetector CT device Canon Aquilion Prime SP (Canon Medical Systems, Otawara, Japan). Tube voltage of 80 kV and tube current of 40 mA were chosen. The effective radiation dose (ED) was calculated based on the "dose-length product" (DLP) information of each patient. Evaluation of images was made on reformat images made with "AiCE Bone" filter in the axial and coronal planes. All images were double-blindly evaluated by 2 radiologists out of 5 points (5 = very good; 1 = not diagnostic). The visibility of 17 bilateral important anatomical landmarks examined on paranasal sinus CT was scored (0 = not visible; 2 = completely visible). In the evaluation of images, the agreement between radiologists was evaluated with Kappa statistics.

Results: The median ED value of the CT protocol was 0.015±0.001 mSv [range 0.012-0.017 mSv]. The overall image quality of the images in our study was interpreted as 4 (good) or 3 (moderate) for all patients. Inter-research agreement was 92%. Most of the anatomical landmarks evaluated were completely visible. Six (bilateral of three) anatomical landmarks could be partially visible in some patients.

Conclusion: Combining the ultra-low dose CT protocol and the AiCE reconstruction algorithm makes it possible to achieve very low ED values in paranasal sinus CT scans and still obtain sufficient image quality in indications such as septum deviation and sinusitis.

Keywords: Multidetector Computed Tomography; Paranasal Sinus; Radiation Exposure

INTRODUCTION

Computed Tomography (CT) is a diagnostic method that is widely used in the radiological diagnosis of many diseases and uses ionizing radiation. With the increasing use of CT, the exposure of people to ionizing radiation is constantly increasing. Ionizing radiation damages cells and tissues, disrupts the structure of genetic material and increases the risk of cancer in the long term [1]. For these reasons, techniques to reduce the radiation dose used in CT are constantly being developed.

CT is widely used for diagnostic purposes in almost all body imaging. It is also the gold standard for the evaluation of the paranasal sinus cavities and facial bones for most indications [2]. It provides important information about surgically important anatomical details, variations, soft tissues and bone structures, especially in the management of sinus inflammation [3]. In paranasal sinus CT, the presence of organs that are more sensitive to radiation, such as eye lens and thyroid, near the scanning area makes the radiation dose in this scan even more important [4]. The fact that the scanning is mostly done with young people and in some cases the need for follow-up imaging makes the issue even more serious. For these reasons, protocols containing as low radiation dose as possible should be arranged in every hospital.

In parallel with technological developments, advanced iterative dose reduction methods are applied in current CT devices. One of the most up-to-date among these is the "Advanced intelligent Clear-IQ Engine" (AiCE) dose reduction technology. In our study, we aimed to investigate the image quality of paranasal sinus CT scan obtained with AiCE software and ultra-low dose parameters in patients with prediagnosed rhinitis, sinusitis or nasal septum deviation.

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METHODS

The first 50 patients admitted to our radiology department between November 2019 and September 2022, and agreed to participate in our prospectively planned study were included in the study. Patients with a pre-diagnosis of rhinitis, sinusitis or septum deviation were determined as inclusion criteria. Patients under the age of 18 and those with a history of craniofacial trauma were not included in the study. Patients who moved during the scanning were excluded from the study.

Our study included 31 male and 19 female patients aged 18-70 years. Imaging of the patients was performed with a 160-slice multidetector CT device, Canon Aquilion Prime SP (Canon Medical Systems, Otawara, Japan). The settings were used as follows; tube voltage: 80 kV; rotation time: 0.35 s; tube current: 40 mA (14 mAs); collimation: 80x0.5 mm; pitch: 1.388. The patients were in the supine position and their images were taken in the axial plane. The scanning area was chosen from the roof of the frontal sinus to the end of the maxilla. Evaluation was made on reformat images with a section thickness of 2 mm made with "AiCE Bone" filter in the axial and coronal planes.

Volume CT dose index (CTDIvol) and dose-length product (DLP) of each patient were recorded. For the calculation of the effective radiation dose (ED), the product of the constant coefficient of 0.0023 mSv/(mGy.cm) recommended by the European Working Group for facial bones and the DLP value was used [5].

All images were evaluated double-blindly by 2 radiologists with 13 years and 11 years of experience, respectively. Initially, overall diagnostic image quality was scored out of 5 points (5=very good; 4 = good; 3 = moderate; 2 = low; 1 = not diagnostic). Then, the visibility of the borders of the nasal septum, bone septa of ethmoid cells, uncinate process of ethmoid bone, maxillary sinus ostium, ethmoid infundibulum, nasolacrimal duct, fovea ethmoidalis, cribriform plate and lamina papyracea were scored for each patient (Figure 1). The scoring system used for this was as follows; 0 (not visible), 1 (partially visible), or 2 (completely visible). Except for the nasal septum, other anatomical structures were evaluated separately for the right and left. The scores of the anatomical structures were recorded separately by both radiologists.

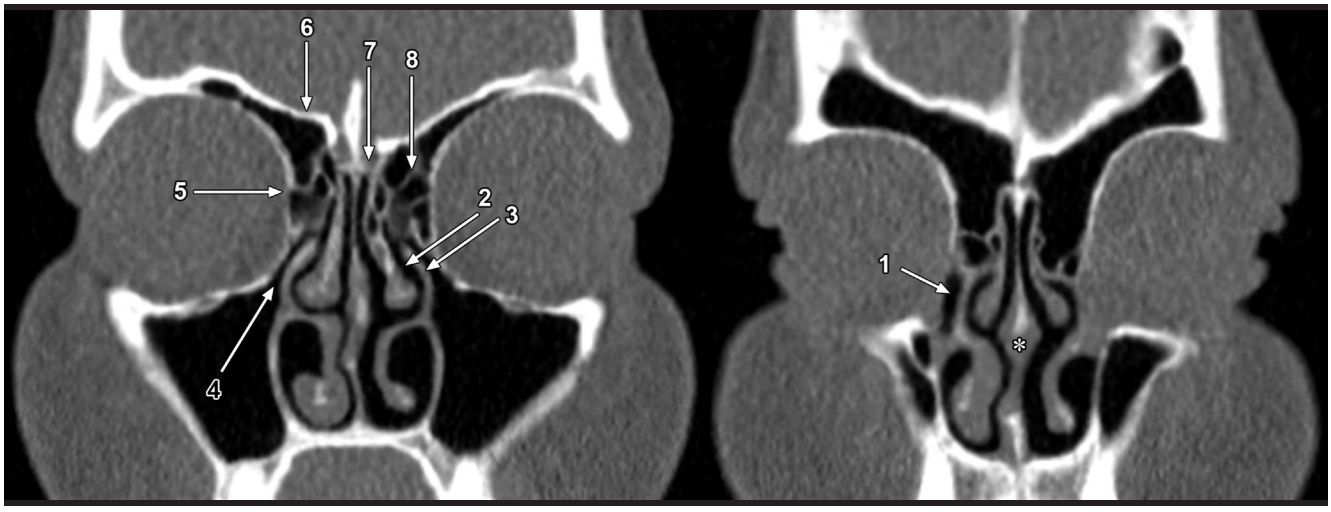

Figure 1. Anatomical structures scored. 1: nasolacrimal duct; 2: ethmoid infundibulum; 3: uncinate process of ethmoid bone; 4: maxillary sinus ostium; 5: lamina papyracea; 6: fovea ethmoidalis; 7: cribriform plate; 8: ethmoid cells; * nasal septum

Main Points:

- The most important disadvantage of CT is that it uses ionizing radiation.
- Image quality is the most important limiting factor in reducing the radiation dose in CT protocols.
- In paranasal sinus CT scans performed with AiCE, a contemporary dose reduction algorithm, it is possible to achieve sufficient image quality in pre-diagnoses such as rhinitis, sinusitis and septum deviation, even at very low doses.

Statistical Analysis

Descriptive statistics of the data obtained from the study were given with mean, standard deviation for numerical variables, and frequency and percentage analysis for categorical variables. In the evaluation of images, the agreement between 2 different radiologists was evaluated with Kappa statistics. Analyzes were performed with the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, New York, United States) and $p<0.05$ was chosen as the significance level.

Power Analysis: The total number of patients required for a moderate agreement (r=0.5) between the scores given by 2 different radiologists to the image quality of the images to be obtained by CT was determined as 29 ($\alpha=0.05$, $1-\beta= 0.80$). Analysis was done in Gpower version 3.1.

RESULTS

A total of 50 patients, 31 male (62%) and 19 female (38%), were included in the study. The mean age of the patients was 30 and the age range was 18-70.

The CTDIvol value of the applied protocol was 0.40 mGy. The median DLP value was 6.5±0.5 mGy.cm [range 5.20-7.50 mGy.cm], and the calculated median ED was 0.015±0.001 mSv [range 0.012-0.017 mSv].

The overall image quality of the images in our study was interpreted as 4 (good) or 3 (moderate) for all patients (Figure 2). There were no patients whose image quality was interpreted as 5 (very good), 2 (low), or 1 (not diagnostic). The agreement between radiologists was 92% (Table 1). Nasal septum, bony septa of ethmoid cells, uncinate process of ethmoid bone, maxillary sinus ostium, ethmoid infundibulum and nasolacrimal duct borders were completely visible in all patients. The borders of one or more of the fovea ethmoidalis, cribriform plate and lamina papyracea structures were partially visible in some patients (Figure 3). There was no patient in whom the borders of these structures were not visible at all (Table 2).

Figure 2. General image quality: Images of 2 different patients whose image quality was interpreted as "good" (A) and moderate (B) by both radiologists. Although the image quality and clarity are different, septum deviation and bone spur formation (arrows) can be easily evaluated in both patients.

Table 1. Evaluation of the images in terms of overall image quality

	Number of Patients	
	Radiologist 1	Radiologist 2
Scoring of image quality		
1: Not diagnostic	0	0
2: Low	0	0
3: Moderate	25	27
4: Good	25	23
5: Very good	0	0
Agreement	%92	
Reliability	κ =0.84	

κ: Kappa value

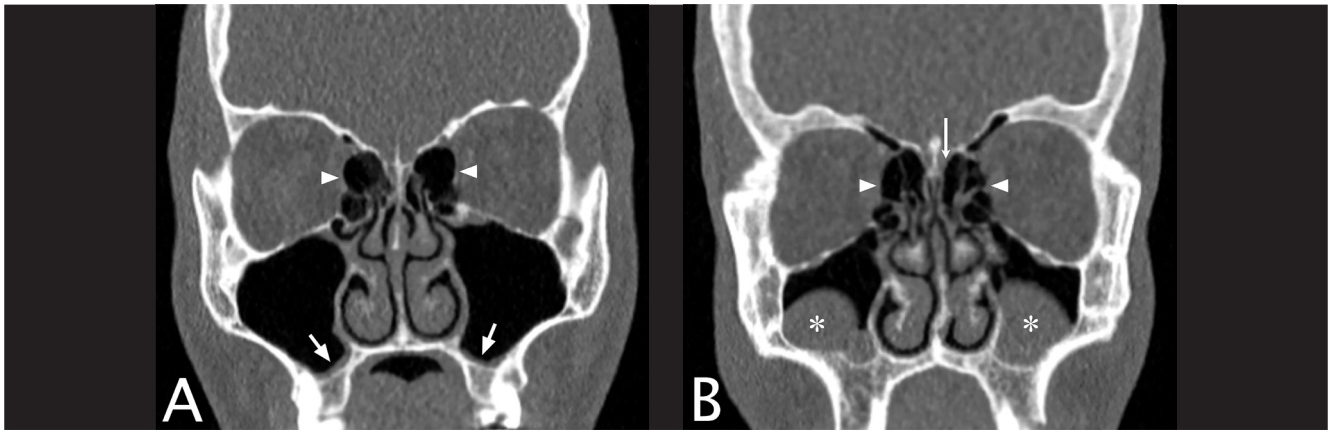

Figure 3. Examples of partially visible anatomical structures: **A)** A patient whose image quality was interpreted as "good" by both radiologists. Minimal mucosal thickening (arrows) is observed in the bilateral maxillary sinus. In this patient, both radiologists evaluated that the bilateral lamina papyracea (arrowheads) were partially visible. **B)** A patient whose image quality was interpreted as "moderate" by both radiologists. Retention cysts (asterisks) are observed in the bilateral maxillary sinus. In this patient, both radiologists evaluated that the borders of the bilateral lamina papyracea (arrowheads) and the left cribriform plateau (arrow) were partially visible.

Table 2. Evaluation of the visibility of anatomical structures

	NS		Ethmoid Cells				Uncinate Process				Maxillary Ostium				Ethmoid Infundibulum				Nasolacrimal Duct				Fovea Ethmoidalis				Cribriform Plate				Lamina Papyracea			
			R		L		R		L		R		L		R		L		R		L		R		L		R		L		R		L	
	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
0: NV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1: PV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	7	3	5	12	17	13	16	21	24	20	24
2: CV	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	44	43	47	45	38	33	37	34	29	26	30	26
Ag (%)	100		100		100		100		100		100		100		100		100		100		100		98		96		90		94		94		92	
Reli *	1		1		1		1		1		1		1		1		1		1		1		0.912		0.73		0.76		0.855		0.879		0.839	

R: Right; L: Left; R1: Radiologist1; R2: Radiologist2; NV: Not visible; PV: Partially visible; CV: Completely visible; NS: Nasal Septum; Ag: Agreement; Reli: Reliability* The reliability line shows the calculated kappa value (κ).

DISCUSSION

The CTDIvol value of the protocol in our study (tube voltage: 80 kV; tube current: 14 mAs; rotation time: 0.35 s; pitch value: 1.388 and AiCE reconstruction algorithm) is 0.4 mGy. The same value in the protocol we use in routine paranasal sinus CT scans with the same device in our hospital (tube voltage: 100 kV; tube current: 75 mAs; rotation time: 0.5 s; pitch value: 1.388 and AiCE reconstruction algorithm) is 4.0 mGy. Thus, with the parameters we used in the study protocol, we achieved a 90% dose reduction compared to our routine daily practice. The ED values in our study are in the range of 0.012-0.017 mSv. In a study, the mean ED value was found to be 0.0398 mSv in paranasal sinus radiographs [6]. So, the ED values we obtained are even below the radiographic ED value.

The overall image quality of our study protocol was not excellent, but was quite good according to the results of the evaluation by both radiologists with high agreement. We believe that with the AiCE reconstruction algorithm and the parameters we have chosen, adequate image quality can be obtained for indications such as evaluation of septum deviation and sinusitis detection in paranasal sinus CT scans, despite very low ED values. To date, different methods such as low tube voltage, low tube current-time value, high pitch value and iterative dose reduction methods have been tried to reduce ionizing radiation exposure in paranasal sinus CT scans, and the most important parameter limiting the use of these methods is image quality [7-11]. There are other studies in the literature combining iterative dose reduction method and low dose scanning protocol. In a study performed with Adaptive Iterative Dose Reduction 3 Dimensional (AIDR 3D) on the Toshiba Aquilion Prime device, the mean DLP value was found to be 33.12±4.53 and the mean ED value was 0.08±0.07 mSv [12]. Although the ED values we obtained in our study were lower than in this study, no serious problems were encountered in the distinguishability of anatomical structures. In another study performed with the Siemens Somatom Force device and ADMIRE reconstruction, the median ED value was calculated as 0.012 mSv, and it was stated that acute inflammatory sinus diseases can be reliably excluded with these images [2]. The ED values obtained in our study are similar to these values. Since our study was not planned only for patients with a prediagnosis of sinusitis, the detection rate of sinusitis was not investigated. However, no difficulties were encountered in the evaluation of the sinus cavities in terms of inflammation or mucosal thickening in our patients. Similarly, septum borders, deviation and bone spur formation, if any, could be easily observed.

The most important perhaps the only significant weakness in the image quality of the patients included in our study was the incomplete demarcation of thin bone structures. This situation was encountered especially in the evaluation of the cribriform plate and lamina papyracea, and sometimes in the fovea ethmoidalis. Of course, in patients with a prediagnosis of septum deviation, this situation cannot be expected to have a negative effect on the diagnosis. However, we think that the integrity of these bones cannot be adequately evaluated in paranasal sinus masses that thin or erode the sinonasal bone structures and require malignant/benign distinction, and this method may also be insufficient in the evaluation of trauma.

Limitations

There were some limitations in our study. First, the quality assessment in our study was subjective and there was no numerical criterion. However, we thought that this would not pose a serious problem due to the high agreement between researchers. Secondly, the image quality of a fixed protocol was investigated in our study and no comparison was made with the standard scanning protocol, different parameters, or different device. Finally, CT scans for a limited number of indications were included in our study, and the effectiveness of the method in patients with suspected malignancy was not investigated. Therefore, evaluations were made only through the bone window and the image quality of the soft tissue filter was not investigated.

CONCLUSION

Combining the ultra-low-dose acquisition protocol with the AiCE reconstruction algorithm makes it possible to achieve very low ED values in paranasal sinus CT scans and still obtain sufficient image quality in indications such as septum deviation and sinusitis.

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REFERENCES

1- Desouky O, Ding N, Zhou G. (2015) Targeted and non-targeted effects of ionizing radiation. J Radiat Res Appl Sci. 8(2):247-54. https://doi.org/10.1016/j.jrras.2015.03.003

2- Petritsch B, Kosmala A, Weng AM, Bley TA (2019) Tin-filtered 100 kV ultra-low-dose CT of the paranasal sinus: Initial clinical results. PLoS One. 14(5):e0216295. https://doi.org/10.1371/journal.pone.0216295

3- O'Brien Sr WT, Hamelin S, Weitzel EK (2016) The preoperative sinus CT: avoiding a "CLOSE" call with surgical complications. Radiology. 281(1):10-21. https://doi.org/10.1148/radiol.2016152230

4- Diklić A, Zujić PV, Šegota D, Debeljuh DD, Jurković S, Brambilla M, Kalra MK (2020) Optimization of paranasal sinus CT procedure: Ultra-low dose CT as a roadmap for pre-functional endoscopic sinus surgery. Phys Med. 78:195-200. https://doi.org/10.1016/j.ejmp.2020.09.014

5- Bongartz G. European guidelines on quality criteria for computed tomography: 1999.

6- Chaparian A, Tavakoli I, Karimi V (2013) Organ doses, effective dose, and radiation risk assessment in radiography of pediatric paranasal sinuses (Waters view). Asian Biomed. 7(5):695-8. https://doi.org/10.5372/1905-7415.0705.228

7- Bodelle B, Wichmann JL, Klotz N, Lehnert T, Vogl TJ, Luboldt W, Schulz B (2015) Seventy kilovolt ultra-low dose CT of the paranasal sinus: first clinical results. Clin Radiol. 70(7):711-5. https://doi.org/10.1016/j.crad.2015.03.002

8- Kearney SE, Jones P, Meakin K, Garvey CJ (1997) CT scanning of the paranasal sinuses--the effect of reducing mAs. Br J Radiol. 70(838):1071-4. https://doi.org/10.1259/bjr.70.838.9404216

9- Brem MH, Zamani AA, Riva R, Zou KH, Rumboldt Z, Hennig FF, Kikinis R, Norbash AM, Schoepf UJ (2007) Multidetector CT of the paranasal sinus: potential for radiation dose reduction. Radiology. 243(3):847-52. https://doi.org/10.1148/radiol.2433050207

10- Bulla S, Blanke P, Hassepass F, Krauss T, Winterer JT, Breunig C, Langer M, Pache G (2012) Reducing the radiation dose for low-dose CT of the paranasal sinuses using iterative reconstruction: feasibility and image quality. Eur J Radiol. 81(9):2246-50. https://doi.org/10.1016/j.ejrad.2011.05.002

11- Aksoy EA, Özden SU, Karaarslan E, Ünal ÖF, Tanyeri H (2014) Reliability of high-pitch ultra-low-dose paranasal sinus computed tomography for evaluating paranasal sinus anatomy and sinus disease. J Craniofac Surg. 25(5):1801-4. https://doi.org/10.1097/scs.0000000000000966

12- Schaafs LA, Lenk J, Hamm B, Niehues SM (2016) Reducing the dose of CT of the paranasal sinuses: potential of an iterative reconstruction algorithm. Dentomaxillofac Radiol. 45(7):20160127. https://doi.org/10.1259/dmfr.20160127

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Original Research

Prevalence of Accessory Sacroiliac Joint and Its Clinical Significance

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ABSTRACT

Objective: To determine the prevalence of the accessory sacroiliac joint (ASIJ) on both computed tomography (CT) images and dry bones.

Methods: CT images archived in the Radiology Department of Gaziantep University Medical Faculty obtained from 145 individuals (104 males and 41 females) as well as 92 sacral bones were examined.

Results: The prevalence of ASIJ among 92 sacral bones was 15.2%. The ASIJ was more commonly (52%) located at the posterior portion of the SIJ at the level of the second dorsal sacral foramen. In 48% of the bones, ASIJ was identified just above the first dorsal sacral foramen. Unilateral ASIJ was observed in 10.8% and bilateral ASIJ in 4.4% of the sacral bones. On CT images, ASIJ was found in 7.8% of the males and 7.2% of the females. The total prevalence of sacroiliac joint variations was 28.9%, and 6.8% of them were ASIJs.

Conclusion: It should be kept in mind that ASIJ may be a source of arthritis and chronic hip pain. The presence of ASIJ should be sought through imaging studies for early diagnosis of ASIJ.

Keywords: Accessory sacroiliac joint, variation, computed tomography, dry bone

INTRODUCTION

Several anatomists have investigated accessory sacroiliac joints within the confines of the articulation area of the sacroiliac joint (SIJ) [1-8]. Since the joint space width is used in the diagnosis of SIJ pathologies, knowledge of the normal anatomic structure of the SIJ and its variations have gained importance for the radiological assessment of diseases including inflammatory sacroiliitis [9].

Accessory sacroiliac joint (ASIJ) is a common anatomical variation of the sacrum [10-13]. While this accessory joint can be found bilaterally, it is often unilateral [4-6,11]. Located at the posterior aspect of the SIJ, ASIJ has usually been described as having a superficial structure at the level of the second dorsal sacral foramen and a deep structure just above the first dorsal sacral foramen [13-18]. In a 1984 study, an axial sacroiliac joint was found to be located extracapsularly at the dorsocranial level of the SIJ. The presence of fibrocartilage was demonstrated on the articular surface in several samples. Since the axial joint was histologically identified in the joint space, it was defined as "syndesmosis" due to presence of loose connective tissue and its articular surface structure [14]. In contrast, accessory sacroiliac joints are true synovial joints [4-6,14,15,18-20]. Since both are located in the same region, the axial sacroiliac joint can be confused with the accessory sacroiliac joint especially on radiographs [5,14,18]. Although ASIJ is defined as a syndesmosis by some researchers, it is more commonly described as a synovial joint [4-6,17,18].

ASIJ has a higher prevalence in older people, obese individuals and women with a history of 3 or more deliveries [13]. Looking at the literature, the reported prevalence of ASIJ varies from 1.7% to 50% across studies using CT scans and examination of dried skeletons [9,10,12,17,18,21] (Table 1).

Since most ASIJ cases are asymptomatic and often detected incidentally, clinical significance of ASIJ may be overlooked. However, there are studies reporting that ASIJ is associated with degenerative arthritis and may be a source of chronic hip or back pain [7-11,16,21-23].

This study was presented as an oral presentation at the 3rd International Zeugma Scientific Research Congress held in Gaziantep, Turkey on 22.11.2019.

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Table 1. Studies on the accessory sacroiliac joint and the prevalences reported.

Study	Materials Examined	Prevalence
Petersen (1905) (27)	skeletal specimens	16%
Derry (1911)(15)	skeletal specimens	10.4%
Jazuta (1929) (28)	skeletal specimens	27%
Kaibo (1932) (29)	skeletal specimens	10%
Trotter (1937, 1964) (4, 19)	skeletal specimens and cadavers	21–50%
Hadley (1952) (6)	skeletal specimens	18%
Ehara et al. (1988) (1)	CT images, skeletal specimens	16%–13%
Vleeming et al. (1990) (17)	CT images	18%
Valojerdy and Hogg (1990) (8)	skeletal specimens	18%
Prassopoulus et al. (1999) (3)	CT images	19.1%
Demir et al. (2007) (23)	CT images	17.5%
Fortin and Ballard (2009) (7)	CT images	3.6%
Klang et al. (2017) (20)	CT images	4.5%
El Rafei et al. (2018) (26)	MRI scans	11%
Tok Umay and Korkmaz (2020) (9)	CT images	1.7%
Teran-Garza et al. (2021) (24)	CT images	19.8%
Ziegeler et al. (2021) (25)	CT images	16.8%
Current study	CT images, skeletal specimens	6.8%–15.2%

With this study, we aimed to provide data on the prevalence of anatomical variations of the SIJ in the general population, to review and interpret CT images for the ASIJ and ultimately, to contribute to the literature.

METHODS

For this study, CT images of 145 individuals (104 males and 41 females) referred to the Radiology outpatient clinic of Gaziantep University Medical Faculty between 2013 and 2018 as well as 92 sacral bones were examined. Dry bones used in this study were obtained from the bone collections of the anatomy departments of Gaziantep and Çukurova Universities (southern Turkey). There was no information on the age and sex of the sacral bones included in the study.

CT images were acquired using a GE LightSpeed Pro 32-slice CT scanner (GE Healthcare Systems, USA) with the patient in supine position. Images were reconstructed using a bone algorithm with 7 mm thickness and 5 mm increments in axial and coronal planes. CT images allowing visualization of the SIJ were included in the study.

Main Points

- Accessory sacroiliac joint (ASIJ) may be a cause of arthritis and chronic hip pain.
- For early diagnosis of chronic hip pain, the presence of an ASIJ should be investigated by imaging studies.

Statistical Analysis

Statistical analysis was not performed because a prevalence study was conducted. The frequency values of the parameters are given as numbers and percentages.

RESULTS

Examination of the dry sacral bones (n=92) revealed an ASIJ prevalence of 15.2%. The ASIJ was more commonly (52%) located at the posterior portion of the SIJ (between the posterior superior iliac spine and sacral crest), at the level of the second dorsal sacral foramen. In 48% of the bones, ASIJ was identified just above the first dorsal sacral foramen (Figure 1). Unilateral ASIJ was observed in 10.8% and bilateral ASIJ in 4.4% of the sacral bones (Figure 2) (Table 2).

On CT images of 145 individuals, the frequency of ASIJ was 7.8% (n=7) in males and 7.2% in females (n=3) (Figure 3) (Table 3). In the study population, the total prevalence of SIJ variations was 28.9% and the prevalence of ASIJ was 6.8%.

Table 2. Prevalence of the accessory sacroiliac joint by its position and location relative to sacral foramen in dry bone specimens.

	S1		S2		Total	
	n	%	n	%	n=92	15.2%
Bilateral	2	50%	2	50%	4	4.4%
Unilateral	4	40%	6	60%	9	10.8%

Table 3. Prevalence of accessory sacroiliac joint within sacroiliac joint variations by age and gender (CT images).

	18 to 29 years	30 to 39 years	40 to 49 years	50 to 60 years	Total
	n=74	n=24	n=25	n=22	n=145
Female (n= 41)	2			1	3 (7.2%)
Male (n=104)	1	2	3	1	7 (7.8%)
Total	3	2	2	2	10 (6.8%)

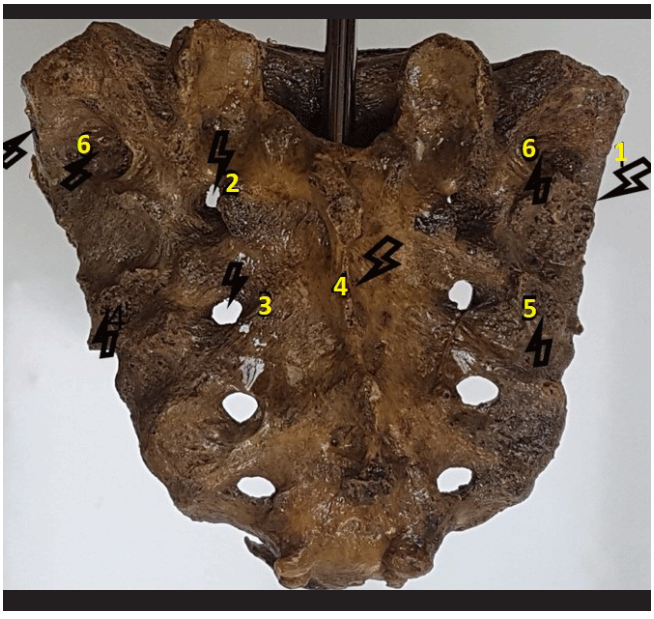

Figure 1. Posterior view of the sacral bone: 1) Sacroiliac joint, 2) 1st Dorsal sacral foramen, 3) 2st Dorsal sacral foramen, 4) Median sacral crest, 5) Accessory sacroiliac joint, 6) Axial sacroiliac joint.

Figure 2. Posterior view of the sacral bone and pelvis; yellow circled area indicates a unilateral accessory sacroiliac joint (right).

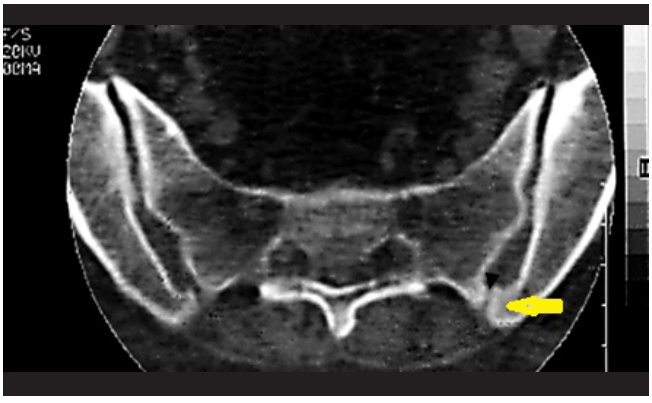

Figure 3. On the CT image, the yellow arrow shows the left side accessory sacroiliac joint.

DISCUSSION

The etiology of the variations of the sacroiliac joint and the ASIJ remains unclear. It is also unknown whether the ASIJ is a congenital or acquired joint [20,23]. This accessory joint may either be a true diarthrodial joint and present at birth or acquired as a fibrocartilaginous joint after childbirth [12]. Petersen (1905) and Jazuta (1929) found hyaline cartilage and joint capsule in some of the specimens, suggesting that ASIJ may be present at birth [20,23]. In contrast, Rixey et al. [21] did not observe ASIJ in children aged 0 to 15 years, and suggested that it is unlikely to be a congenital variant present at birth. However, they argued that the curvature of the SIJ in the expected location of the ASIJ, which increases in prevalence and severity with age, may predispose individuals to the development of an ASIJ later in life.

Unilateral or bilateral ASIJ is associated with degenerative changes such as subchondral sclerosis, osteophytes and ankylosis [7, 11, 23]. Statistically, patients with ASIJ were reported to present with a higher frequency of sclerosis and osteophytes compared to individuals with normal joint anatomy [24].

Slobodin et al. [22] reported that younger patients often have complaints of chronic or recurrent sacroiliac pain in the presence of an ASIJ with surrounding bone marrow edema and periarticular soft tissue inflammation, which correlate with the clinical picture.

Computed tomography is not the diagnostic tool of choice for younger patients with chronic hip or low back pain. However, CT aids in the detection of structural changes or anatomical variations,

and is also useful in differentiating the cause of sacroiliitis other than ankylosing spondylitis or axial spondyloarthritis. A reason for delayed diagnosis is that many clinicians are unaware of the fact that ASIJ may be a cause of chronic hip or low back pain [16, 22].

In a study by Demir et al. [23] using CT images, ASIJ was the most common variation of the sacroiliac joint (17.5%) and most of the patients with ASIJ did not have low back pain complaints. However, there are studies reporting that ASIJ is the source of chronic hip or low back pain, especially with severe arthritis and degenerative changes [9,12,21,22]. Klang et al. [20] identified abnormal sacroiliac joints in 31% of individuals less than 40 years of age with complaints of low back pain, and ASIJ was shown on CT images in 4.5% of them. In another study, an ASIJ surrounded by bone marrow edema was detected on MRI scan in in a 53-year-old patient with low back pain and buttock pain [10].

As a result of our review of CT images, we found that 28.9% of the study sample had SIJ variations and among them, 6.8% had ASIJ. In a study involving healthy subjects, Ziegeler et al. [25] reported an ASIJ prevalence of 8.3%. Of the 818 joints examined in that study, this variant was present in 51 females and 17 males. In a study examining anatomical variations of the SIJ in the Hispanic population, the prevalence of ASIJ was 19.8%, with a higher frequency of SIJ variants found in females and individuals older than 40 years of age [24].

The discrepancy between our results and some of the previous reports may be related to the difference in the populations studied.

Former osteological studies have reported on the prevalence of ASIJ in relation to sex, age and race. In a comprehensive study involving 958 pelvic bones, Trotter [19] reported an increase in the prevalence of ASIJ with advancing age as well as a higher frequency in whites (50%) than in blacks (21%) [4,15,19,20].

When we examined the sex distribution of the subjects with ASIJ, 7 (7.8%) of them were male and 3 (7.2%) were female. In a study by Fortin et al. [7], ASIJ was identified in 20 individuals, of whom 5 were males and 15 were females. Contrastingly, Valojerdy and Hogg [8] reported that sex does not have an impact on the prevalance of ASIJ.

In a study of the anatomical variations of the SIJ on MRI images, the prevalence of ASIJ was 11%. While 53% of these variations were bilateral, 45% were at the level of the first dorsal sacral foramen and 55% at the second dorsal sacral foramen. In the same study, it was reported that the occurrence of ASIJ did not differ between sexes [26]. When we examined the prevalence of ASIJ in relation to its location, 9.8% of the cases were unilateral and 4.4% were bilateral. Thus, our current results are consistent with the aforementioned findings.

If the anatomical variations of the SIJ are correlated with edematous or structural changes, they can be easily misdiagnosed on MRI scans. ASIJ is common in the general population and may be associated with the coexistence of back and sacroiliac joint pain. Therefore, rheumatologists, physical therapists, orthopedists and algologists should be familiar with this anatomical variation and be able to differentiate imaging features of other diseases (e.g., axial spondyloarthropathy) that mimic sacroiliitis mimicking [1,10-13,16,18].

Limitations

A number of limitations should be noted for this study. Firstly, this was a single-center study with a sample size. Since the study had a retrospective design, it was not possible to obtain any information on the complaints of the population studied. It would have been useful to classify the subjects as those with or without hip pain. Further multicenter studies involving greater numbers of CT images and dry bones are needed to corroborate our findings.

CONCLUSION

ASIJ can be a cause of arthritis or chronic hip pain. The differential diagnosis of hip pain should include ASIJ, which can be identified through additional imaging studies and allows for early diagnosis.

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REFERENCES

1. Ehara S, el-Khoury GY, Bergman RA (1988) The Accessory Sacroiliac Joint: A Common Anatomic Variant. AJR Am J Roentgenol. 150(4):857-859. https://doi.org/10.2214/ajr.150.4.857

2. Friedman L, Silberberg PJ, Rainbow A, Butler R (1993) A Limited, Low-Dose Computed Tomography Protocol to Examine The Sacroiliac Joints. Can Assoc Radiol J. 44(4):267-272.

3. Prassopoulos PK, Faflia CP, Voloudaki AE, Gourtsoyiannis NC (1999) Sacroiliac Joints: Anatomical Variants on CT. J Comput Assist Tomogr. 23(2):323-327. https://doi.org/10.1097/00004728-199903000-00029

4. Trotter M (1964) Accessory Sacroiliac Articulations in East African Skeletons. Am J Phys Anthropol. 22(2):137-141. https://doi.org/10.1002/ajpa.1330220213

5. Hadley LA (1950) Accessory Sacroiliac Articulations with Arthritic Changes. Radiology. 55(3):403-409. https://doi.org/10.1148/55.3.403

6. Hadley LA (1952) Accessory Sacro-Iliac Articulations. J Bone Joint Surg Am. 34-a(1):149-155.

7. Fortin JD, Ballard KE (2009) The Frequency of Accessory Sacroiliac Joints. Clin Anat. 22(8):876-877. https://doi.org/10.1002/ca.20772

8. Valojerdy MR, Hogg DA (1990) Anatomical Note: The Occurrence of Accessory Sacroiliac Joints in Man. Clin Anat. 3(4):257-260. https://onlinelibrary.wiley.com/doi/abs/10.1002/ca.980030403

9. Tok Umay S, Korkmaz M (2020) Frequency of Anatomical Variation of The Sacroiliac Joint in Asymptomatic Young Adults and its Relationship with Sacroiliac Joint Degeneration. Clin Anat. 33(6):839-843. https://onlinelibrary.wiley.com/doi/10.1002/ca.23539

10. Toussirot E, Aubry S, Runge M (2018) Unilateral Accessory Sacroiliac Joint with Bone Marrow Edema Mimicking Sacroiliitis. J Rheumatol. 45(9):1327-1328. https://doi.org/10.3899/jrheum.180030

11. Kim DK, McKenzie GA (2019) Accessory Sacroiliac Joint Injection for Relief of Buttock Pain. Pain Med. 20(2):412-413. https://doi.org/10.1093/pm/pny254

12. Song R, Lee S, Lee SH (2019) Progressive Sacroiliitis Due to Accessory Sacroiliac Joint Mimicking Ankylosing Spondylitis: A Case Report. Medicine (Baltimore). 98(16):e15324. https://doi.org/10.1097/MD.0000000000015324

13. Kang JH, Kim MW, Moon EH, Kim YJ, Yu KP (2017) The Accessory Sacroiliac Joint Diagnosed with Bone SPECT/CT. Clin Nucl Med. 42(6):483-484. https://doi.org/10.1097/rlu.0000000000001623

14. Bakland O, Hansen JH (1984) The "Axial Sacroiliac Joint". Anat Clin. 6(1):29-36. https://doi.org/10.1007/BF01811211.-

15. Derry DE (1911) Note on Accessory Articular Facets between the Sacrum and Ilium, and their Significance. J Anat Physiol. 45(3):202-210.

16. Rosa Neto NS, Vitule LF, Gonçalves CR, Goldenstein-Schainberg C (2009) An Accessory Sacroiliac Joint. Scand J Rheumatol. 38(6):496. https://doi.org/10.3109/03009740903036008

17. Vleeming A, Van Wingerden JP, Dijkstra PF, Stoeckart R, Snijders CJ, Stijnen T (1992) Mobility in The Sacroiliac Joints in The Elderly: A Kinematic and Radiological Study. Clin Biomech (Bristol, Avon). 7(3):170-176. https://doi.org/10.1016/0268-0033(92)90032-Y

18. Mahato NK (2016) Sacroiliac Joints. Bergman's Comprehensive Encyclopedia of Human Anatomic Variation. 165-175. https://doi.org/10.1002/9781118430309.ch18

19. Trotter M (1937) Accessory Sacro-Iliac Articulations. American Journal of Physical Anthropology. 22(2):247-261. https://onlinelibrary.wiley.com/doi/abs/10.1002/ajpa.1330220205

20. Klang E, Lidar M, Lidar Z, Aharoni D, Eshed I (2017) Prevalence and Awareness of Sacroiliac Joint Alterations on Lumbar Spine CT in Low Back Pain Patients Younger than 40 Years. Acta Radiol. 58(4):449-455. https://doi.org/10.1177/0284185116656490

21. Rixey A, Murthy N, Amrami K, Frick M, McKenzie G (2021) The Pediatric Accessory Sacroiliac Joint: Does It Exist? Skeletal Radiol. 50(3):579-583. https://doi.org/10.1007/s00256-020-03608-4

22. Slobodin G, Lidar M, Eshed I (2017) Clinical and Imaging Mimickers of Axial Spondyloarthritis. Semin Arthritis Rheum. 47(3):361-368. https://doi.org/10.1016/j.semarthrit.2017.05.009

23. Demir M, Mavi A, Gümüsburun E, Bayram M, Gürsoy S, Nishio H (2007) Anatomical Variations with Joint Space Measurements on CT. Kobe J Med Sci. 53(5):209-217

24. Teran-Garza R, Verdines-Perez AM, Tamez-Garza C, Pinales-Razo R, Vilchez-Cavazos JF, Gutierrez-de la OJ, et al. (2021) Anatomical Variations of The Sacro-Iliac Joint: A Computed Tomography Study. Surg Radiol Anat. 43(6):819-825. https://doi.org/10.1007/s00276-021-02714-9

25. Ziegeler K, Kreutzinger V, Diekhoff T, Roehle R, Poddubnyy D, Pumberger M, et al. (2021) Impact of Age, Sex, and Joint Form on Degenerative Lesions of The Sacroiliac Joints on CT in The Normal Population. Sci Rep. 11(1):5903. https://doi.org/10.1038/s41598-021-85303-5

26. El Rafei M, Badr S, Lefebvre G, Machuron F, Capon B, Flipo RM, et al. (2018) Sacroiliac Joints: Anatomical Variations on MR Images. Eur Radiol. 28(12):5328-5337. https://doi.org/10.1007/s00330-018-5540-x

27. Petersen O (1905) Ueber Artikulationsflchen an Der Hinterflchedes Os Sacrum. Anat Anz. 26:521-524.

28. Jazuta K (1929) Die Nebengelenkflachen an Kreuz-Und Huftbein. Anat Anz. 68:137-144.

29. Kaibo K (1932) Tıber Die Akzessorische Gelenkfiache Des Sakroiliakalge- Lenkes Am Kreuz- Und Darmbein. Gyoseki IX: Japanese J Med Sciences. 2:20-22.

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Original Research

Evaluation of Errors Encountered in Photogrammetric Studies on Lower Extremities

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ABSTRACT

Objective: The aim of our study is to reveal the errors that can be encountered during the shooting of photogrammetric studies on the lower extremities.

Methods: We revealed the necessary tools that used during photogrammetry measurements of the lower limb. Also, the errors have been encountered of our two previous studies performed on photogrammetry of lower limbs. The technical errors or incorrect positioning of 20 from 220 volunteers were encountered.

Results: The identified errors of 20 volunteers' photographs related to lower limb were about the inadequate quality image, calibration, poor lightining, positioning error of trunk or parts of lower limb and clothes that cover the anatomical points affected the measurements.

Conclusion: Photogrammetry is an important and useful tool for evaluation, diagnosis, treatment, and efficacy monitoring. In anatomy, it is frequently used as a time-saving method in terms of measurement and evaluation in the laboratory, which can be applied and repeated for research. For this reason, errors that occur during the lower extremity have been reported and we think that it will be useful for studies on this part of the body and can be a guide.

Keywords: photogrammetry, lower extremity, lower limb, tools of photogrammetry, errors of photogrammetry

INTRODUCTION

The word "photogrammetry" comes from the Greek words " φως» meaning «light» and «γραμμετρια" meaning "something written or drawn" [1]. It was first used by British scientist Sir John Herschel in 1839 (Figure 1) [2]. The research in this area, which began in the early 19th century, has found that photography can express a great deal more detail than other disciplines like painting and sculpting. The first known photograph that left a permanent mark was produced by Nicéphore Niepce in 1822. "View from the Window at Le Gras," which he photographed in 1826, was the first ever permanent nature image. However, since these shootings can be done in about 8 hours, he tried to find new systems in this field with Louis Daguerre [3]. Daguerre, on the other hand, discovered the method of obtaining images by exposing silver plates known as daguerotype to mercury vapor for a period of 10-20 minutes [4]. Contrarily, a sight captured using this method in 1838, when a man had his shoes painted on the streets of Paris, is considered to be the first human picture in history. During the 19th century, there were many developments such as the transition from silver and copper plates to glass plates. By 1884, George Eastman invented film instead of photographic plates [5]. Photogrammetric measurement, on the other hand, is a method of obtaining reliable information about physical objects and the environment in the process of recording, measuring and interpreting photographic images and patterns of electromagnetic radiant images and other phenomena [6]. This method is used with high accuracy to detect, measure and interpret the properties of living or non-living things. The primary benefit of photogrammetry is that measurements are obtained from photographic representations rather than directly on objects [7]. Making measurements repeatedly became convenient as a result of this. This approach first appeared about the same time as the photograph. With the advancements, it has also been extensively employed in the field of medical, in addition to areas like maps and architecture [8]. In 1863, American physician Holmes used it for the first time in medicine [9, 10]. This made it possible for him to create prosthetic limbs for Civil War troops who had lost their arms or legs [9,10]. Its use has expanded as development

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has progressed. Yet, despite declines throughout the world wars, it spread and the region of its utilization continuously grew. As a reproducible replication technique for planning and observing therapeutic treatment for bodily structures, photogrammetry has grown in significance in medicine [11].

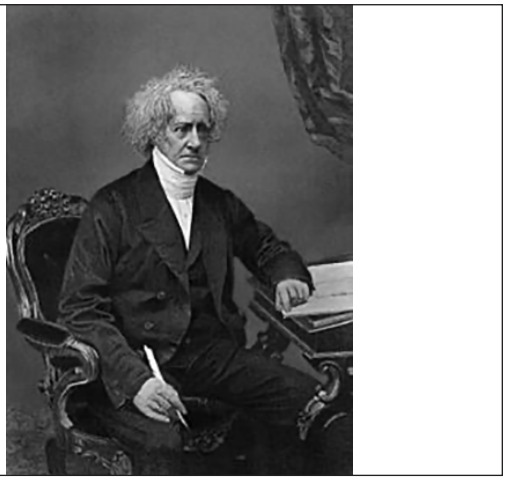

Figure 1. British scientist Sir John Herschel (1839) who was first used the photogrammetry.

Photography in medicine was first used by the French physician Alfred François Donnê. Donnê, who was also the inventor of photomicrography, used the materials he revealed using the "daguerrotype" method in his lectures, and collected what he took under the microscope in his book titled "Cours de Microscopie, Complementaire des Études Médicales: Anatomie Microscopique et Physiologie des Fluides de L'Economie" [12,13]. The first daguerrotype taken in the field of dermatology was a photograph of skin disease in 1848, and the photographs taken before and after surgery in the field of orthopedics in 1852 [12]. Taking photos from inside the body was not realized until 1883 due to the light problem [12].

For the design and evaluation of therapeutic treatment and its outcomes, photogrammetry has grown in popularity in medicine [14]. It is a technique for reproducing bodily structures in a reproducible manner. As photogrammetry is non-invasive and precise technique that uses photographs to measure and analyze the shape, size, and position of objects. In medicine, photogrammetry has a wide range of applications, where the most common used now is in orthopedics. They provide rapid measurements of the whole body or specific body parts, such as in screening exams for spinal curvatures, determining the craniofacial anthropometric features or lower limb [15-19].

Main Points:

- The importance of correct use of the necessary tools that used during photogrammetry measurements (camera, tripod, light source, White background, calibration object, markers, foot support, software and computer)
- Correct positioning of the volunteer before shooting and planning the preparations correctly.
- Removing clothes or accessories from the area(s) where the photo will be taken and ensuring the hygiene of the area.

METHODS

During our studies of the "Variable Lower Limb Alignment of Clinical Measures With Digital Photographs" [18] and "Physical attractiveness: analysis of buttocks patterns for planning body contouring treatment" [19], the detection of difficulties and errors we encountered in photogrammetry was examined. Although a total of 220 adult volunteers (115 male, 105 female) between the ages of 19-21 participated in the study, 200 of them have been included in the study. Twenty volunteers' photos were excluded from the study due to low resolution, incorrect extremity position, etc. The reasons for 20 individuals who were not included in the study were explained in the result section. None of the participants had a history of surgery or reported trauma, lower extremity fractures, or pain in the lumbar spine and lower extremity until at least 3 months prior to measurement. The studies were ethically approved by Ege University Faculty of Medicine and complies with the Declaration of Helsinki.

Research Plan and Procedure of Photogrammetry

Five characteristics the thigh, knee, leg, ankle and foot of lower limb were assessed in this study. Utilizing a variety of measurement techniques, including the Image J tool to measure digital photos. A standard posture was used to acquire weight-bearing, full-length, antero-posterior, and lateral digital photos of the lower limb. Participants were asked to stand in a neutral position, which is described as having the feet shoulder-width apart, the toes looking forward, and the upper extremities crossed over the chest, in order to assess the static lower limb alignment factors. The anatomical body landmarks indicating the center (kneecap, tibial tuberosity, the knee joint center, lateral femoral condyle, ankle joint, and lateral malleolus) were marked on the skin with nontoxic color pencils. Each participant was assigned a number before the picture shoot, and the photographs that matched that number were subsequently uploaded to a digital folder. Care was also taken to ensure that the picture session was done in metric (Figure 2).

Figure 2. The standart positions of the lower limb during photo shoot from anterior, posterior and lateral views.

As the feet were more swollen towards the end of the day, we performed the photo taking both feet accurately in the morning/afternoon. The procedure of picture shoot of the foot was done with a glass-supported setup. Obtained digital pictures were imported into Image J software (http://rsbweb.nih.gov/ij) in order to calculate the determined parameters (Figure 3).

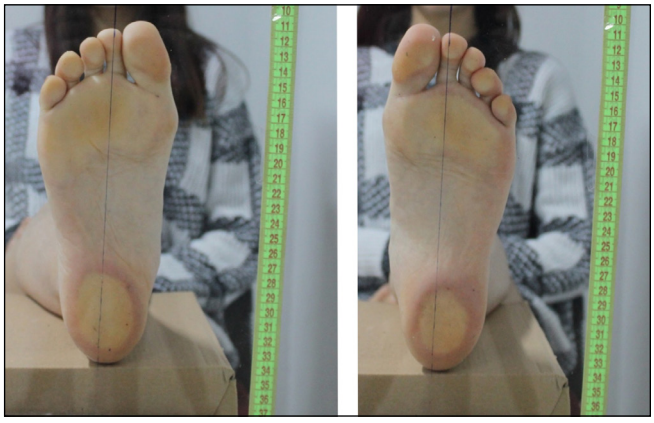

Figure 3. The standart position of the plantar surface of foot

The necessary tools that used during photogrammetry measurements of the lower limb were as follows:

a) Camera: A digital camera with high resolution and good image quality was essential for capturing detailed images of the foot.
b) Tripod: A tripod was necessary to keep the camera steady and ensure that the images were in focus.
c) Light source: A consistent and even light source was important for capturing clear and accurate images. A softbox or diffused light source was used to reduce shadows and glare.
d) White background: A plain white background was used to provide contrast and enhance the visibility of the markers on the images.
e) Calibration object: A calibration object (the green metric) was used to establish the scale of the images and ensure accurate measurements. It was a green plastic meter stick or a custom-made object of known size.
f) Markers: Markers were used to identify specific anatomical landmarks on the foot, which were necessary for accurate measurements. The skin was marked with nontoxic color pencils.
g) Foot support: A foot support was used to position the foot in a standardized position for imaging. It was a custom-made support or a commercially available one.
h) Software: Photogrammetry software was necessary to process the images and obtain accurate measurements. Some popular photogrammetry software options included Agisoft Metashape, Pix4D, and RealityCapture.
i) Computer: A powerful computer with sufficient storage and processing power was necessary to handle the large image datasets and process the images using photogrammetry software. Overall, photogrammetry of the lower limb, especially the foot, requires specialized equipment and software to ensure accurate measurements and reliable results.

RESULTS

It was observed that 20 of the 220 volunteers who were photographed had errors in their images. The technical errors or incorrect positioning were encountered in our study (Figure 1 and Figure 2).

Errors identified in a photogrammetric study of lower limb:

a) clothing and underwear covering the anatomical points made it impossible to make the planned measurements (Figure 4).
b) incorrect rotational trunk (Figure 5) or lower extremity (Figure 6) position: It was important that the planned parameters were realized in a static upright posture. Therefore, rotations of different parts of the body were not preferred during shooting.
c) inadequate technical error-picture quality (Figure 7): Poor image quality not only made the analysis with the photogrammetric method difficult, but also led to inaccuracies in measurement.

Errors identified in a photogrammetric study of the foot and the plantar surface:

a) it was observed that the possible reflection of the sole of the foot, which occurred due to the glass apparatus used during the photo shoot, affected the measurements (Figure 8). In addition, it was another mistake that the clarity of the metric (green meter) placed on the glass was insufficient for measurement. It was also necessary to prevent reflections that might be caused by the glass material used during photo shoots. For this, it was necessary to control the light and camera before shooting.
b) removal of digitus secundus from the midline (Figure 9): The parameters planned to be measured should be done with the foot in a standard position.
c) insufficient hygiene of the plantar surface (Figure 10): The parameters that were planned to be measured must be clear and understandable. In this case, care should be taken to ensure that the plantar surface of the foot was hygienic.
d) clothes (thin socks) that cover the anatomical points affected the measurements (Figure 11): Clothing that covers the landmarks determined during the measurement should be avoided.

Figure 4. Clothes and underwear that cover the anatomical points of the lower limb.

Figure 5. Incorrect position of trunk.

Figure 7. Inadequate picture quality durig the photo shoot of lower limb resulting in poor image.

Figure 6. Incorrect position of the lower limb.

Figure 8. Inadequate picture quality durig the photo shoot of the foot resulting in poor image.

Figure 9. Incorrect position of the plantar surface of the foot where the digitus secundus has been removal from the midline.

Figure 10. Insufficient hygiene of the plantar surface.

Figure 11. Undesired clothes such as socks that cover the anatomical points of the lower limb.

DISCUSSION

Photogrammetry is a technique that involves taking measurements and making three-dimensional models of objects or scenes from photographs [20]. It has a wide range of applications, including in the field of medicine, where it is used for measurements of lower limb and foot. One of the most common uses of photogrammetry in lower limb and foot measurements is for orthopedic purposes [21]. By taking precise measurements of the foot and lower limb, orthopedic specialists can identify any anomalies or abnormalities, such as flat feet or misaligned joints [18, 22]. These measurements can then be used to create customized orthotics or other devices to help correct these issues. Another use of photogrammetry in lower limb and foot measurements is in the field of biomechanics [23]. Biomechanists use photogrammetry to study the movement and mechanics of the lower limbs and feet during various activities, such as walking, running, and jumping [24]. By analyzing these movements, areas of potential injury or strain can be identified and develop strategies to prevent or reduce these issues. Therefore, photogrammetry is a valuable tool in the field of lower limb and foot measurements, allowing for precise and accurate measurements that can aid in diagnosis, treatment, and prevention of various foot and lower limb issues [25].

Photogrammetry can also be used to design custom orthotics, which are shoe inserts that are used to correct foot posture and improve foot function. By taking photographs of the foot in different positions, photogrammetry can be used to create a 3D

model of the foot that can be used to design custom orthotics. So, the photogrammetry is a useful tool in the assessment and treatment of foot-related conditions, as well as in the design of custom orthotics and footwear [26].

In studies to be carried out with the photogrammetric method, the marked anatomical points and the photographs taken should be clear. Especially during the measuring of determined parameters with the Image J software is crucial. The software which has been used in this study is a free, open-source image analysis software developed by the National Institutes of Health (NIH). It is widely used in scientific research, particularly in the fields of biology and biomedical research [27]. It allows users to analyze digital images and videos by performing measurements, processing, and enhancing of images. The software provides a wide range of functions, such as filtering, thresholding, segmentation, and morphological operations. It also offers tools for image registration, colocalization analysis, and 3D rendering. In research, Image J is commonly used to analyze images obtained from various techniques such as anatomy [28], histology [29], and radiology [30-33].

Although the photogrammetry is a non-invasive technique that involves using photographs to measure the shape and size of objects easly, there are some disadvantages to using photogrammetry in the lower limb analysis, which are discussed below:

a) inaccuracy: one of the main disadvantages of photogrammetry is the potential for measurement errors. The accuracy of photogrammetry depends on several factors, including the quality of the camera, the angle and distance of the camera from the subject, and the presence of any obstructions in the image. These factors can affect the accuracy of the measurements, resulting in errors in the data.
b) limited range: another disadvantage of photogrammetry is the limited range of motion that can be captured. To obtain accurate measurements, the subject must remain still during the imaging process, which can be difficult for some individuals, particularly those with mobility issues or pain. Additionally, the range of motion that can be captured is limited by the angle of the camera and the distance from the subject, which can be problematic in assessing dynamic movements such as walking or running.
c) equipment requirements: photogrammetry requires specific equipment, including a high-quality camera and software, which can be expensive. Additionally, the process requires a trained professional to capture the images, which can further increase the cost of the analysis.
d) image quality: the quality of the images captured can also affect the accuracy of the measurements. If the images are blurry, overexposed, or underexposed, the measurements may be inaccurate, making it difficult to obtain reliable data.
e) complex data analysis: photogrammetry data analysis can be complex and time-consuming. The images must be processed using specialized software, and the data must be carefully analyzed to obtain meaningful results. This requires a skilled and experienced professional, which can further increase the cost of the analysis.
f) ethical considerations: Finally, there are ethical considerations to consider when using photogrammetry in lower limb analysis.

This technique involves taking photographs of the subject's body, which can be intrusive and uncomfortable for some individuals. Additionally, there is the potential for the images to be used inappropriately, which can lead to privacy concerns.

The encountered errors of photogrammetry related to lower limb have been explained in this study. However, other than the lower limb errors, may be encountered in studies performed on other parts of the body (upper limb, face, etc.). Although this study has been described the encountered errors during the photogrammetry of young Anatolian adults, a number of other errors related to photogrammetry may also be encountered depending on race or age. Therefore, it is thought that this study may be a guide for photogrammetric measurements to be made about the lower limb, as well as encouraging new studies to reveal the errors that may be encountered in different ethnic groups, ages or demographic features.

In conclusion, photogrammetry is a useful tool for lower limb analysis, but it is not without its limitations. The potential for measurement errors, limited range of motion, equipment requirements, image quality issues, complex data analysis, and ethical considerations must be carefully considered before using this technique. Despite the disadvantages of photogrammetry, it is thought that this method will contribute to patient control, treatment planning / treatment follow-up, and revealing the morphometric and morphological characteristics of the lower limb as a method to reduce radiation preference.

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All authors read and approved the final version.

REFERENCES

1. Μαστραπάς Α (2009) Βελτίωση ψηφιακής φωτογραφίας. University of Patras, Doctoral dissertation.

2. Sutton MA (1974) Sir John Herschel and the development of spectroscopy in Britain. Br J Hist Sci. 7(1):42-60. https://doi.org/10.1017/S0007087400012851

3. Braive MF (1973) Birth of Photography. Chest. 63(6):951. https://doi.org/10.1378/chest.63.6.951

4. Benjamin W (1972) A short history of photography. Screen. 13(1):5-26. https://doi.org/10.1093/screen/13.1.5

5. Jenkins RV (1975) Technology and the market: George Eastman and the origins of mass amateur photography. Technol Cult. 16(1):1-19. https://doi.org/10.2307/3102363

6. Mitchell HL, Newton I (2002) Medical photogrammetric measurement: overview and prospects. J Photogramm Remote Sens. 56(5-6):286-94. https://doi.org/10.1016/S0924-2716(02)00065-5

7. Petriceks AH, Peterson AS, Angeles M, Brown WP, Srivastava S (2018) Photogrammetry of human specimens: an innovation in anatomy education. J med educ curric dev. 5:2382120518799356. https://doi.org/10.1177/2382120518799356

8. Magnani M, Douglass M, Schroder W, Reeves J, Braun DR (2020) The digital revolution to come: Photogrammetry in archaeological practice. Am Antiq. 85(4):737-60. https://doi.org/10.1017/aaq.2020.59

9. Struck R, Cordoni S, Aliotta S, Pérez-Pachón L, Gröning F (2019) Application of photogrammetry in biomedical science. Biomed Vis. 1:121-30. https://doi.org/10.1007/978-3-030-06070-1_10

10. Lane HB (1983) Photogrammetry in medicine. Photogramm Eng Remote Sensing. 49(10):1453-6.

11. Ey-Chmielewska H, Chrusciel-Nogalska M, Fraczak B (2015) Photogrammetry and its potential application in medical science on the basis of selected literature. Adv Clin Exp Med. 24(4):737-41. https://doi.org/10.17219/acem/58951

12. Harting MT, DeWees JM, Vela KM, Khirallah RT (2015) Medical photography: current technology, evolving issues and legal perspectives. Int J Clin Pract. 69(4):401-9. https://doi.org/10.1111/ijcp.12627

13. Donné A (1844) Cours de microscopie complémentaire des études médicales: anatomie microscopique et physiologie des fluides de l'économie. Baillière.

14. Barut C, Ertilav H (2011) Guidelines for standard photography in gross and clinical anatomy. Anat Sci Educ. 4(6):348-56. https://doi.org/10.1002/ase.247

15. Furlanetto TS, Sedrez JA, Candotti CT, Loss JF. (2016) Photogrammetry as a tool for the postural evaluation of the spine: a systematic review. World J Orthop. 7(2):136. https://doi.org/10.5312/wjo.v7.i2.136

16. Bahşi I, Orhan M, Kervancioğlu P, Karatepe Ş, Sayin S (2021) Craniofacial anthropometry of healthy Turkish young adults: analysis of head and face. J Craniofac Surg. 32(4):1535-1539. https://doi.org/10.1097/SCS.0000000000007219

17. Bahşi I, Orhanc M, Kervancioğlu P (2021) Confusion of the Standardization in Craniofacial Soft Tissue Measurements: Frankfort Horizontal Plane or Natural Head Position?. J Craniofac Surg. 32(8):2578-9. https://doi.org/10.1097/SCS.0000000000007883

18. Govsa F, Nteli Chatzioglou G, Hepguler S, Pinar Y, Bedre O (2020) Variable lower limb alignment of clinical measures with digital photographs and the footscan pressure system. J Sport Rehabil. 30(3):437-44. https://doi.org/10.1123/jsr.2018-0283

19. Nteli Chatzioglou, G, Govsa F, Bicer A, Ozer MA, Pinar Y (2019) Physical attractiveness: analysis of buttocks patterns for planning body contouring treatment. Surg Radiol Anat. 41:133-40. https://doi.org/10.1007/s00276-018-2083-4

20. Lowe DG (1987) Three-dimensional object recognition from single two-dimensional images. Artif Intell. 31(3):355-95. https://doi.org/10.1016/0004-3702(87)90070-1

21. Pérez Pico AM, Marcos Tejedor F, de Cáceres Orellana LC, de Cáceres Orellana P, Mayordomo R (2022) Using Photogrammetry to Obtain 3D-Printed Positive Foot Casts Suitable for Fitting Thermoconformed Plantar Orthoses. Processes. 11(1):24. https://doi.org/10.3390/pr11010024

22. Sacco ICN, Picon AP, Ribeiro AP, Sartor CD, Camargo-Junior F, Macedo DO, et al. (2012) Effect of image resolution manipulation in rearfoot angle measurements obtained with photogrammetry. Braz J Med Biol. 45:806-10. https://doi.org/10.1590/S0100-879X2012000900003

23. Larsen PK, Simonsen EB, Lynnerup N (2010) Use of photogrammetry and biomechanical gait analysis to identify individuals. Proceedings of the 18th European signal processing conference; 1660-4.

24. Morales-Acosta L, Ortiz-Prado A, Jacobo-Armendáriz VH, González-Carbonell RA (2019) Biomechanical analysis of weeding labor in mexican farmers through the simultaneous use of photogrammetry and accelerometry. Proceedings of the 8th Latin American Conference on Biomedical Engineering and XLII National Conference on Biomedical Engineering; 2019 Oct 2-5; Cancún, México. 850-7. https://doi.org/10.1007/978-3-030-30648-9_111

25. Zahra SU, Kervancioğlu P, Bahşi İ (2018) Morphological and topographical anatomy of nutrient foramen in the lower limb long bones. Eur J Ther. 24(1):36-43. https://doi.org/10.5152/EurJTher.2017.147

26. Shilov L, Shanshin S, Romanov A, Fedotova A, Kurtukova A, Kostyuchenko E, et al. (2021) Reconstruction of a 3D

Human Foot Shape Model Based on a Video Stream Using Photogrammetry and Deep Neural Networks. Future Internet. 13(12):315. https://doi.org/10.3390/fi13120315

27. Schneider CA, Rasband WS, Eliceiri KW (2012) NIH Image to ImageJ: 25 years of image analysis. Nat Methods. 9(7):671-5. https://doi.org/10.1038/nmeth.2089

28. Akcay E, Chatzioglou GN, Gayretli O, Gurses IA, Ozturk A (2021) Morphometric measurements and morphology of foramen ovale in dry human skulls and its relations with neighboring osseous structures. Medicine. 10(3):1039-46. https://doi.org/10.5455/medscience.2021.04.149

29. Shintaku H, Yamaguchi M, Toru S, Kitagawa M, Hirokawa K, Yokota T, et al. (2019) Three-dimensional surface models of autopsied human brains constructed from multiple photographs by photogrammetry. PloS one. 14(7):e0219619. https://doi.org/10.1371/journal.pone.0219619

30. Arslan D, Ozer MA, Govsa F, Kitis O (2019) Surgicoanatomical aspect in vascular variations of the V3 segment of vertebral artery as a risk factor for C1 instrumentation. J Clin Neurosci. 68:243-9. https://doi.org/10.1016/j.jocn.2019.07.032

31. Adanir SS, Bakşi YE, Bahşi I, Kervancioğlu P, Yalçin ED, Orhan M (2022) Evaluation of the Cranial Aperture of the Optic Canal on Cone-Beam Computed Tomography Images and its Clinical Implications for the Transcranial Approaches. J Craniofac Surg. 33(6):1909-13. https://doi.org/10.1097/SCS.0000000000008577

32. Ayvaz DK, Kervancıoğlu P, Bahşi A, Bahşi İ (2021) A radiological evaluation of lumbar spinous processes and interspinous spaces, including clinical implications. Cureus. 13(11):e19454. https://doi.org/10.7759/cureus.19454

33. Bahşi İ, Orhan M, Kervancıoğlu P, Yalçın ED (2019) The anatomical and radiological evaluation of the Vidian canal on cone-beam computed tomography images. Eur Arch Otorhinolaryngol. 276:1373-83. https://doi.org/10.1007/s00405-019-05335-6

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Original Research

Analysis of the Nutrient Foramen in Human Dry Ulnae of Turkish Population: An Anatomical Study and Current Literature Review

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ABSTRACT

Objective: The nutrient artery which enters through the nutrient foramen (NF) provides blood circulation and nutrition in long bones. This supply is essential during the growing period, the early phases of ossification, and in some surgical procedures. This study aimed to investigate NF in adult human ulnas in the Turkish population.

Methods: For this study, 155 (70 right and 85 left) Turkish dry adult human ulnas were used. The presence, number, and patency of NF were recorded as well as its topography and direction. The vertical distance between the most proximal point of the olecranon and the proximal edge of the NF (DONF), and the longitudinal distance between the most ventral point of the coronoid process on the sagittal plane and the proximal edge of the NF (DCpNF) was calculated. Additionally, the foraminal index (FI) was assessed.

Results: Single and double NFs were in 139 ulnas (89.67%), and 3 ulnas (1.94%), respectively. NFs were not observed in 13 ulnas (8.39%). The majority of NFs (93.12%) were situated on the anterior surface of the ulna. The direction of all NFs was towards the elbow. The mean DONF and DCpNF were 9.48 ± 1.57 cm, and 6.68 ± 1.44 cm, respectively. The FI was 37.45% in ulnas with a single NF, while it was 41.46% in ulnas with a double NF.

Conclusion: Our study has presented additional information such as the FI of ulnas with 2 NFs, and the distance between the coronoid process and NF in the Turkish population.

Keywords: Nutrient foramen, ulna, clinical importance, foraminal index.

INTRODUCTION

The long bone is supplied by a nutrient artery, which enters the bone obliquely through the nutrient foramen (NF), which is directed away, as a rule, from the growing end [1]. The nutrient artery is the principal source of blood supply to a long bone and is particularly important during its active growth period in the embryo and fetus, as well as during the early phase of ossification [2, 3]. During childhood, the nutrient arteries provide 70–80% of the interosseous blood supply to long bones: when this supply is compromised, medullary bone ischemia occurs with the metaphysis and growth plate both becoming less vascularized [1, 3, 4]. An understanding of the location and number of nutrient foramina in long bones is, therefore important in orthopedic surgical procedures such as joint replacement therapy, fracture repair, bone grafts and vascularized bone microsurgery, as well as in medicolegal cases [2]. Topographical knowledge of these nutrient foramina is useful in operative procedures to preserve circulation [1]. When a bone graft is taken, the vascularization of the remaining bones has to be considered [1]. The vascularity of this area allows various options in grafting [1]. It was reported that the ideal bone graft for free transfer should include endosteal and periosteal blood supply with good anastomosis [2]. Moreover, the presence of preserved nutrient blood flow is essential for the survival of osteocytes in cases of tumor resection, traumas, and congenital pseudoarthrosis [4]. However, there is still a need for a greater understanding of nutrient foramina in bones [5]. The goal of the present study was to investigate the number, position and direction of the nutrient foramen in adult human ulnas in Turkish population.

METHODS

This study was conducted on 155 (70 right and 85 left) Turkish dry adult human ulnas, whose ages and gender were not recorded in the İstanbul University, Faculty of Medicine, Department of

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Anatomy. All bones included in the study were normal bones without any pathological findings. Ethical approval was granted by the Clinical Research Ethical Committee of İstanbul University Faculty of Medicine (IRB Date: 25/06/2021, Number: 13].

Nutrient foramen (NF) was investigated and the following parameters related to NF were examined.

1. The number of NFs was macroscopically observed in each bone.
2. The patency and direction of the NF were determined by an acupuncture needle with dimensions of 0.25 X 30 mm. Foramen smaller than the size of the needle were not analysed or reported in this study.
3. The topography of the foramen in specific borders or surfaces of the bone body was analysed with the naked eye.
4. The vertical distance between the most proximal point of the olecranon and proximal edge of the NF (DONF) was determined (Figure 1 A).
5. The longitudinal distance between the most ventral point of the coronoid process on the sagittal plane and the proximal edge of the NF (DCpNF) was measured (Figure 1 B).
6. The total length of ulna (TL) was measured as the vertical distance between the most proximal point of the olecranon and styloid process (Figure 1 C).

Additionally, the foraminal index (FI) was calculated by using the following formula: FI = (DONF/TL) X 100 (6).
The position of the foramen according to FI was divided into 3 types according to the following limits:
Type 1: FI below 33.33%, proximal third of the ulna.
Type 2: FI between 33.33% and 66.66%, middle third of the ulna.
Type 3: FI above 66.66, distal third of the ulna.

The measurements were made by two independent researchers, and the mean value per parameter was written down as the final value. A digital caliper accurate to 0.01 mm (INSIZE Co., Ltd., Taiwan) was used for distances. In ulnas with 2 NF, DONF, DCpNF and FI values were measured separately for each foramen.

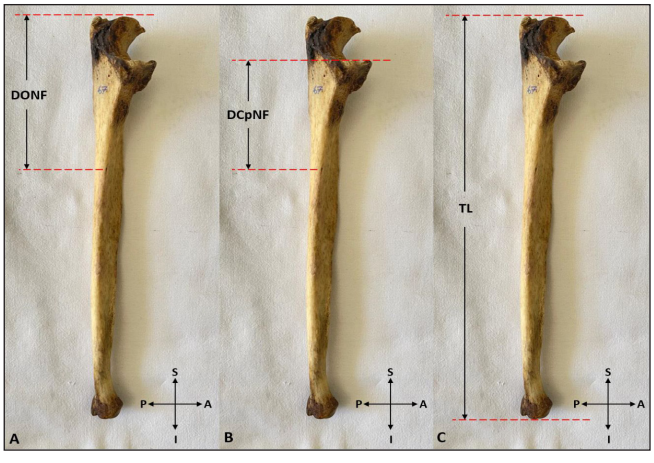

Figure 1. A–C. Main elements measured on the ulna. DONF: distance of olecranon–nutrient foramen. DCpNF: distance of coronoid process–nutrient foramen. TL: total length of ulna. S: superior. I: inferior. P: posterior. A: anterior.

RESULTS

In the current study, 155 ulnas were examined. Single NFs were detected in 89.67% (139 ulnas) (Figure 2 A) and double NFs in 1.94% (3 ulnas) of the bones (Figure 2 B), however, NFs were not found in 8.39% (13 ulnas) of the bones. The direction of all nutrient foramina was towards the elbow (Figure 3). Table 1 summarizes the side and number of nutrient foramina.

The majority of NFs (93.12%,135 NFs) were situated on the anterior surface of the ulna (Figure 4 A), whereas the remaining were on the anterior border and interosseous border at equal rates (3.44%, 5 NF) (Figure 4 B-C). Table 2 summarizes the topography of the NFs.

The total length of ulna (TL) was as a mean of 25.88 ± 3.79 cm and the distance between the most proximal point of the olecranon and proximal edge of the NF (DONF) was a mean of 9.48 ± 1.57 cm.

The DCpNF was calculated as a mean of 6.68 ± 1.44 cm in 139 ulnas with a single NF, while it was a mean of 6.77 ± 1.64 cm in 6 ulnas with a double NF. The mean FI was 37.45% in ulnas with 1 NF and 41.46% in ulnas with 2 NF. Additionally, 22.75% of NFs were type 1, and 77.25% of NFs were type 2. Table 3 summarizes the FI of the NFs.

Figure 2. A. Showing single NF on ulna. **B.** Showing double NF on ulna. NF: nutrient foramen. S: superior. I: inferior. M: medial L: lateral.

Figure 3. A–D. Photographs of showing NF directed proximally. S: superior. I: inferior. M: medial. L: lateral. P: posterior. A: anterior.

Figure 4. A. Ulna with NF on the anterior surface. **B.** Ulna with NF on the anterior border. **C.** Ulna with NF on the interosseus border. NF: nutrient foramen. AS: anterior surface. AB: anterior border. IB: interosseus border. S: superior. I: inferior. M: medial. L: lateral. P: posterior. A: anterior.

Table 1. Side and number of the nutrient foramen of ulna

Number of NF	Right	Left	Total
	N (%)	N (%)	N (%)
0	3 (4.29%)	10 (11.77%)	13 (8.39%)
1	64 (91.42%)	75 (88.23%)	139 (89.67%)
2	3 (4.29%)	0	3 (1.94%)
Total	70 (100%)	85 (100%)	155 (100%)

NF: Nutrient foramen

Table 2. The topography of nutrient foramen

Location of nutrient foramen	Right	Left	Total
	N (%)	N (%)	N (%)
AS	66 (93.76%)	69 (92%)	135 (93.12%)
AB	2 (3.12%)	3 (4%)	5 (3.44%)
IB	2 (3.12%)	3 (4%)	5 (3.44%)
Total	64 (100%)	75 (100%)	145 (100%)

AS: Anterior Surface, AB: Anterior Border, IB: Interosseous Border

Table 3. Classification of nutrient foramen on the basis of foraminal index

FI	The number of NF		
	Right (n=70)	Left (n=75)	Total (n=145)
Type I (<33.33%)	16 (22.85%)	17 (22.66%)	33 (22.76%)
Type II (33.33%-66.66%)	54 (77.15%)	58 (77.34%)	112 (77.24%)
Type III (> 66.66%)	-	-	-

FI: Foraminal Index, NF: Nutrient foramen

DISCUSSION

This study investigated the number, position, and direction of NF and measured the mean distance between the coronoid process and NF. Similarly, the current paper indicated the mean FI in ulnas that had double NF.

The number of nutrient foramina

Although studies in the literature have shown that NF is mostly single, investigations in which NF is absent or double have also been reported. Parmar et al. [5] reported that the total number of ulna was 60, all of which had a single NF. Subsequent studies (Mishra et al., Charan et al., Uzuner et al.) [7, 8, 9] highlighted similar results as well. In their studies on adult human long bones of the upper and lower limbs, Kizilkanat et al. [2] observed that 101 ulnas (99%) had one NF and 1 ulna (1%) had two NFs. Pereira et al. [10] documented similar results to the findings of Kizilkanat et al. [2]. In the next three studies [1, 11, 12], the number of single foramina was obtained at a lower rate, however, the number of double foramina was found at a relatively higher rate. Solanke et al. [13] indicated that 96.25% (77 ulnas) of specimens had a single NF and 3.75% (3 ulnas) had no NF. A study conducted by Chavda et al. [14] showed that 96.67% of the ulna (145 ulnas) had a single nutrient foramen, 1.33% (2 ulnas) had a double foramen and 2% (3 ulnas) had no nutrient foramen. Additionally, in their study, Kumari et al. [15] noted that 3% (3 ulnas) did not have NF, 92% (92 ulnas) had a single foramen and 5% (5 ulnas) had double NF. On the other hand, Rangasubhe and Havaldar [16] assessed 100 ulnas and reported that 86 (86%) of them had a single NF, 13 (13%) had a double NF and 1 (1%) had three NFs. In the present paper, 89.67% (139 ulnas) had a single NF, 1.94% (3 ulnas) had a double NF, and 8.39% [13] of ulnas had no NF. Our single NF results are closer to the results of Kumari et al. [15] and the double NF results of this study are compatible with the findings of Chavda et al. [14]. Nevertheless, our results of the absence of NF are not consistent with the results of previous studies, and this inconsistency may be due to the difference in sample size and ethnicity. Because the nutrient artery is the main source of blood supply to the bone, it plays an essential role in fracture healing. Therefore, it may be important for surgeons to know the number of NF to protect the nutrient artery. At the same time, the number of ulna without NF in our study was higher than that in studies in the literature. Accordingly, preoperative planning may need to be modified according to this result. Azizi and Danish [1] highlighted that the NF may be a potential region of weakness in some patients and, under stress due to increased physical activity or decreased quality of the bone, the foramen may allow the development of a fracture. In our study, double NFs were found in 1.94% (3 ulnas) of the bones. According to the results of our study, we think that the probability of developing the fracture mentioned by Azizi and Danish (1) may be relatively high.

Direction and topography of the nutrient foramen

Most of the previous studies reached a consensus that the opening of the NF is towards the elbow. Nevertheless, Rangasubhe and Havaldar [16] observed 115 NF in their study and reported that 97% of NF were directed upper oblique, 2% lower oblique and remaining horizontally. Similar to the previous studies, the direction of all NF in the present study was also towards the elbow.

In the majority of studies in the literature, it has been reported that NF has the highest rate on the anterior surface, followed by the anterior border and interosseous border. A few studies have noted that NF can be found in the posterior surface or medial surface of the ulna [1, 11, 13, 16]. In the present study, NF was located on the anterior surface, anterior border, and interosseous border at 93.12% (135 NF), 3.44% (5 NF), and 3.44% (5 NF), respectively. Our results highly correspond with those of former studies.

Another topographical perspective of the NF of the ulna, the FI has been noted in the literature. Pereira et al. [10] found FI to be a minimum of 27.4% and a maximum of 52.5% and reported that the mean FI was 37.9%. Ukoha et al. [4] highlighted that the majority of NF (73%) were in the middle third (type 2) while 27% were in the proximal third (type 1) of the bone and recorded the mean FI was 36.70%. A study performed by Udayasree et al. [12] reported that the average FI was 34.91% and noted that 13.2% of NFs (5 NFs) were in the proximal third (type 1) of the ulna and 86.8% of NFs (33 NFs) were in the middle third (type 2) of ulna. Chavda et al. [14] stated that 63.76% of NFs were in the middle third (type 2) of the ulna, 22.15% were in the upper third of the ulna and 14.09% were in the lower third of the bones. They also mentioned that the mean FI was 35.34% [14]. Similar to the study of Ukoha et al. [4], Azizi and Danish [1] indicated that most of the NF (80%) were located in the middle third, while the remaining (20%) were situated in the upper third of the ulna. Likewise, Rangasubhe and Havaldar [16] determined that 85.22% of NFs were in the upper third and 12.17% were in the middle third of the ulna. Priya et al. [11] calculated that the mean FI was 35.83 ± 6.12 and reported that 40% of NF were present in the type 1 category and 60% in type 2. On the other hand, Kumari et al. [15] showed that the location of NF in relation to the length of the ulna was 25.4% in the upper 1/3rd, 62.7% in the middle 1/3rd, 11.76 % at the junction of the middle and upper 1/3rd, and no NF in the distal 1/3rd of the ulna.

In the current study, the mean FI was 37.45% in ulnas with 1 NF and 41.46% in ulnas with 2 NF. Moreover, 22.75% of NFs were type 1 and 77.25% of NFs were type 2. Our classification results of NF are very close to the classification results of NF that were reported by Azizi and Danish [1] and our mean FI results are consistent with previous studies. Knowing the direction and location of NF may help surgeons who study joint replacement therapy, fracture repair, bone grafts, and vascularized bone microsurgery. Thus, the success rate of applications might increase.

Distance between the coronoid process and NF (DCpNF)

In applications related to NF of the ulna, DCpNF was conducted to easily reach NF. In 139 ulnas with a single NF, the DCpNF was a mean of 6.68 ± 1.44 cm. Additionally, this value was obtained as a mean of 6.77 ± 1.64 cm in 6 ulnas with double NF. No similar study could be found that measured this distance before. Knowledge of the accurate location of NF may aid surgeons in preventing intraoperative injuries in orthopedic, plastic and reconstructive surgery [2]. In this sense, the mean DCpNF value may be a guide for surgeons.

Limitations

We did not reach the records of gender and age of ulnas. Analyzing the ulnas according to their gender and age could have expressed more meaningful results. Difficulties in knowing the characteristics of dry bones such as age, gender, or race have been reported in the literature [17].

CONCLUSION

Anatomy has traditionally been a reliable source of information for surgical operations. The outcomes of this study corroborated those of previous studies on ulnar NF. The current study has provided additional information on the foraminal index, morphology and topography of the nutrient foramina in ulna bones. Accurate knowledge of the position and number of the nutrient foramen of ulna could be important in orthopedic surgical procedures such as vascularized bone microsurgery, bone grafts, joint replacement therapy and fracture repair. The anatomical data of this subject are enlightening to the clinician to avoid damage to the nutrient vessels during surgical procedures and can be of use for review by orthopedic surgeons for planning surgeries in the region of the forearm.

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REFERENCES

1. Azizi J, Danish H (2019) Anatomical study of nutrient foramen in the long bones of upper extremities. Int J Eng Appl Sci Technol. 4: 7-10.

2. Kizilkanat E, Boyan N, Ozsahin ET, Soames R, Oguz O (2007) Location, number and clinical significance of nutrient foramina in human long bones. Ann Anat. 189(1): 87-95. https://doi.org/10.1016/j.aanat.2006.07.004

3. Zahra SU, Kervancıoğlu P, Bahşi I (2018) Morphological and topographical anatomy of nutrient foramen in the lower limb long bones. Eur J Ther. 24(1): 36-43. https://doi.org/10.5152/EurJTher.2017.147

4. Ukoha UU, Umeasalugo KE, Nzeako HC, Ezejindu DN, Ejimofor OC, Obazie IF (2013) A study of nutrient foramina in long bones of Nigerians. NJMR. 3(04): 304-308.

5. Parmar AM, Vaghela B, Shah K, Patel B, Trivedi B (2014) Morphometric analysis of nutrient foramina in human typical long bones of upper limb. Natl J Integr Res Med. 5(5): 26-9.

6. Hughes H (1952) The factors determining the direction of the canal for the nutrient artery in the long bones of mammals and birds. Cells Tissues Organs. 15(3): 261-280. https://doi.org/10.1159/000140748

7. Mishra AK, Jaiswal S, Verma RK, Mishra G, Kumar N (2019) A topographical study of nutrient foramen in dry human long bones of the superior extremity. EJMR. 6(2): 67-70. https://doi.org/10.24041/ejmr2019.132

8. Charan KA, Parthasarathy M, Sharmadhakl PM, Parthasarathy KR, Krishnarjun P (2016) Morphological and topographical anatomy of nutrient foramina in human upper limb long bones and their surgical importance. IOSR-JDMS. 15(8): 80-5. https://doi.org/10.9790/0853-1709026368

9. Uzuner MB, Ocak M, Geneci F, Kocabıyık N, Sargon MF, Asaad AS (2018) Quantitative and morphometric evaluation of the foramina nutricia in the long bones of the upper and lower extremities in Anatolian population. Kafkas J Med Sci. 8(1): 30-34. https://doi.org/10.5505/kjms.2018.19327

10. Pereira GAM, Lopes PTC, Santos AMPV, Silveira FHS (2011) Nutrient foramina in the upper and lower limb long bones: morphometric study in bones of Southern Brazilian adults. Int J Morphol. 29(2): 514-20. https://doi.org/10.4067/s0717-95022011000200035

11. Priya DC, Durga JL, Chandrupatla M (2019) A morphological study of nutrient foramina of human ulna and their clinical importance. IJSR. 6: 75-9.

12. Udayasree L, Ravindranath G, Maheswari KB, Prasad SG (2017) Anatomical study of nutrient foramina in dried human upper limb bones and their clinical significance. J Evol Med Dent Sci. 6(2): 110-113. https://doi.org/10.14260/jemds/2017/28

13. Solanke KS, Bhatnagar R, Pokhrel R (2014) Number and position of nutrient foramina in humerus, radius and ulna of human dry bones of Indian origin with clinical correlation. OA Anatomy. 2(1): 4.

14. Chavda SR, Rathwa AJ, Akbari V (2018) A study on variations of nutrient foramen of ulna in Saurashtra region with its clinical relevance. Int J Anat Res. 6(4.2): 5844-47. https://doi.org/10.16965/ijar.2018.358

15. Kumari S, Sidhu V, Sharma RK, Kullar JS (2021) A Study Of Ulnar Diaphysial Nutrient Foramina In North Indian Population With Its Clinico-Anatomical Co-Relation. Eur J Mol Clin Med. 8(4): 1077-1085.

16. Rangasubhe P, Havaldar PP (2019) An osteological study on nutrient foramina of human dry adult ulna bones. Int J Anat Res. 7(1.2): 6149-53. https://doi.org/10.16965/ijar.2018.425

17. Bahşi İ (2019) An Anatomic Study of the Supratrochlear Foramen of the Humerus and Review of the Literature. Eur J Ther. 25: 295-303. https://doi.org/10.5152/EurJTher.2019.18026

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Original Research

Evaluation of the Readability of Turkish Online Resources Related to Laryngeal Cancer

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ABSTRACT

Objective: The aim of this study was to investigate the readability of patient education materials in Turkish about laryngeal cancer.

Methods: Patient education materials were determined by entering the term "gırtlak kanseri", which is the Turkish equivalent of laryngeal cancer, into the Google search engine. The first 50 websites were determined. Duplicates, academic journals, videos, only graphics or tables were excluded. The websites are categorized as Hospitals, Doctors, and General information websites. These websites were evaluated with the Ateşman readability scale.

Results: After applying inclusion and exclusion criteria, 40 websites were analyzed. 19 PEM articles were included on Hospitals websites, 14 on Doctors websites, and 7 on General Information websites. The mean Ateşman readability score of the articles was 58.5±7.06. Hospitals websites mean score was 59.16±6.87. Doctors' websites average score was 57.25±7.41. General information websites mean score was 59.28±7.59. There was no significant difference in readability scores of Hospitals websites, Doctors websites and General Information websites (P=0.569).

Conclusion: Patient education materials in Turkish about laryngeal cancer are above the desired reading level. Increasing the readability levels of websites to the desired level can help patients reach the right treatment and better compliance to the treatment process.

Keywords: laryngeal cancer, Ateşman readability index, patient education materials

INTRODUCTION

Laryngeal cancer is the second most common malignancy of the upper respiratory system [1]. 54% of laryngeal cancers are detected at an early stage [2]. In the early stage, especially in cancer at the glottic level, 5-year survival reaches 90% [3].

The use of the Internet as a source of information on health-related issues is increasing. According to the data of 2022 in our country, the rate of internet usage is 85% [4]. Patients diagnosed with cancer, or their relatives are more likely to refer to the internet for information about their disease. The internet has an important place in patients' decisions about their health. Considering the survival rates of laryngeal cancer - which reaches up to 90% -especially in the early stage and the morbidity in the treatment process, the importance of patient education materials (PEM) about laryngeal cancer on the internet is understood.

Patient information texts on the Internet; can be used to accurately inform patients about the diagnosis, treatment, benefits and possible risks of treatment types, and post-treatment follow-up processes. At the same time, these texts can provide patient-physician communication and facilitate patient compliance with treatment [5]. However, it is important that the texts are understandable. Approximately 40% of the American population has insufficient health literacy [6]. This rate is 57.9% in our country [7]. The American Medical Association (AMA) and the National Institutes of Health (NIH) recommend that complex medical information should be written in an effective manner that maximizes comprehension and should be understood at or below six-year education level, due to the poor health literacy of the majority of the population [8,9].

Readability is a concept that objectively measures how difficult a written text is to be read for the reader by using various mathematical formulas. Formulas can be prepared in accordance

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with the grammatical structure of each language. Ateşman readability formula, developed in accordance with the syllable and word structure of Turkish texts, is designed to determine the readability levels of Turkish texts [10]. According to the Ateşman readability formula, the texts are divided into five levels: very easy, easy, medium difficulty, difficult and very difficult. It is recommended that the texts should be easy and very easy to read [10] (Table 1).

The aim of this study is to investigate the readability of online resources written in Turkish for patients who apply to the internet for information about laryngeal cancer.

Table 1. Ateşman Readability Formula

Scores	Levels
90–100	very easy
70–89	easy
50–69	medium difficulty
30–49	difficult
1–29	very difficult

METHODS

Patient Education Materials (PEM) on "Laryngeal cancer" were identified by searching on Google Search. The search term used was "gırtlak kanseri", which is the Turkish equivalent of laryngeal cancer. Only "full sentence" and "Turkish language" are selected in the advanced search. The top 50 websites that come up as a result of the search are included. Only those containing graphics or tables, academic journals, videos, and repetitive websites were excluded. Since public data were used in our study, an ethics committee is not required.

The materials were divided into three categories: (1) Hospitals (2) Doctors (3) General Information websites. Hospitals were defined institutionally as the websites of private, public and foundation hospitals. Physicians were defined as websites belonging to the physicians' own names. General information websites, on the other hand, were defined as newspapers and general information websites in the field of health, excluding the first two groups.

Each meaningful text on laryngeal cancer was copied into a separate Microsoft Word (version 2010; Microsoft, Redmond, WA) document. Non-educational text such as web page navigations, copyright notices, disclaimers, author information, feedback polls, links, website URLs, references, figures, tables, footnotes, addresses, and phone numbers have been removed to avoid affecting readability scores.

The readability levels of the texts were calculated using the Ateşman readability formula (198.825-40.175x (total syllables/total words)-2.610x (total words/total sentences)) [10]. Mean, standard deviation, median, minimum, maximum value, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. Kruskal-Wallis was used to compare quantitative data. SPSS 28.0 program was used for statistical analysis.

Main Points:

- There were no very easy-level materials.
- There were only two materials on the easy level.
- There were no very difficult materials.
- 33 (82.5%) materials were at medium readability level.
- There was no difference between the materials prepared by hospitals and doctors and general information websites.
- Hospitals and health professionals have a duty to provide patients with easy-to-understand educational materials.

RESULTS

After applying the inclusion and exclusion criteria, 40 websites were reviewed. 19 PEM on Hospitals websites met the inclusion criteria. A total of 14 PEM were included on the Doctors websites. 7 PEM from General Information websites were included. Mean Ateşman readability scores of the materials were 58.5±7.06. While the lowest score was 45.4, the highest score was calculated as 73 (Table 2).

Hospitals websites mean score was 59.16±6.87, while the lowest score was 47, the highest score was 72.4. Doctors' websites average score was 57.25±7.41, lowest score was 45.7, highest score was 73. On the General information websites, the mean score was 59.28±7.59, the lowest score was 45.4, and the highest score was 69.4 (Table 3). There was no significant difference in readability scores of Hospitals websites, Doctors websites and General Information websites (p=0.569) (Table 4).

There were no very easy-level materials. There were two materials on the easy level. There were no very difficult materials. There were five materials on the difficult level. The remaining 33 materials were at medium difficulty level.

DISCUSSION

The aim of this study was to determine the readability of Turkish language online resources about laryngeal cancer. The materials were examined in three different groups as Hospitals, Doctors and General Information websites. Almost all of the related websites were above the readability level.

The use of the Internet to obtain health-related information has been increasing in recent years [11]. With the increase in Internet use in Turkey, they use search engines more frequently for health-related information [4]. An increasing number of doctors and health professionals create and share health-related content on the internet, and patients can access these resources with the help of search engines. The results of these searches affect patients' compliance to treatment. It is known that information obtained from accessible and safe sources positively affects the treatment process [12] and will play an increasingly important role in health care, especially for diabetes and other chronic diseases. Diabetes patients with limited health literacy have worse health outcomes, and limited health literacy may be a barrier to effectively utilizing internet-based health access

Table 2. Ateşman readability scores of all the resources

	N	Minimum	Maximum	Mean	Std. Deviation
VAR00001	40	45.40	73.00	58.5175	7.06493
Valid N (listwise)	40				

Table 3. Readability scores of Hospitals, Doctors and General İnformation websites

		N	Minimum	Maximum	Mean	Std. Deviation
Hospitals	VAR00001	19	47.00	72.40	59.1684	6.87645
	Valid N (listwise)	19				
Doctors	VAR00001	14	45.70	73.00	57.2500	7.41659
	Valid N (listwise)	14				
General Information	VAR00001	7	45.40	69.40	59.2857	7.59088
	Valid N (listwise)	7				

Table 4. Statistical analysis of readability scores

VAR00003	N	Mean Rank
Hospitals	19	21.58
Doctors	14	17.89
General Information	7	22.79
Total	40	
Test Statistics[a,b]		
Kruskal–Wallis H		1.126
df		2
Asymp. Sig.		**0.569**

a. Kruskal Wallis Test

b. Grouping Variable: VAR00003

services. We investigated use of an internet-based patient portal among a well characterized population of adults with diabetes. We estimated health literacy using three validated self-report items. We explored the independent association between health literacy and use of the internet-based patient portal, adjusted for age, gender, race/ethnicity, educational attainment, and income. Among 14.102 participants (28% non-Hispanic White, 14% Latino, 21% African-American, 9% Asian, 12% Filipino, and 17% multiracial or other ethnicity.

Laryngeal cancer is an important disease in terms of morbidity and mortality. It is quite understandable for patients to refer to the internet to get information about the process of the disease after being diagnosed. Online patient education materials can be useful to increase patient compliance with treatment. Although the content of the training materials contains correct information, it is important that it is understandable by the patient.

In the literature, there are different results according to the subject studied in the studies conducted with educational materials in Turkish language. In a study examining Turkish language materials on vertigo, the materials were generally found to be easy to read [13]. Kozanhan and Tutar, on the other hand, found that online materials on anesthesiology required academic literacy and were well above the recommended levels [14]. Özduran et al. found that Turkish educational materials on low back pain were at medium readability level [15]. Cifci et al., in their study examining the Turkish language materials on 'Substance Addiction', concluded that the materials were at difficult readability level [16]. In another study examining Turkish materials on skin cancer, it was concluded that the materials were at medium readability level [17]. Similarly, in the study on colorectal cancer, the materials were found to be at medium readability level [18]. The materials in our study were at medium difficulty level and this seems to be compatible with the literature studies in Turkish.

As far as we know, there is no study on the readability levels of laryngeal cancer education materials in Turkish. In a study on English language materials on laryngeal cancer, the materials were found to be difficult to read [19] cochleostomy (C. This is well above the recommended level. In our study, although the

materials were not at the desired level, they were not at a very difficult level. This shows that the Turkish language materials on laryngeal cancer are more readable. However, the limited number of studies indicates that more studies are needed.

In our study, 40 different educational materials in Turkish about laryngeal cancer were examined. None of these were at a very easy readability level. There were only 2 (5%) materials with easy readability. However, there was also material that was very difficult to read. There were 5 (12.5%) materials at the difficult readability level. The remaining 33 (82.5%) materials were at medium readability level. These data show us that patient education materials in Turkish about laryngeal cancer are not at the level that they should be. However, the fact that there is no material at very difficult level, only 12.5% of the material is at difficult level, and 82.5% of the material is at medium level, showing that these materials can be moved to a level that patients can understand better with a little effort. This can be considered as an opportunity to increase patients' compliance with treatment and to facilitate patient-physician communication.

In our study, there was no difference between the materials prepared by hospitals and doctors and general information websites. Hospitals and health professionals have a duty to provide patients with easy-to-understand educational materials. The low level of health literacy in our country makes this even more important.

Limitations

This study has some limitations. First, using only the Google search engine may not reflect the experience of all users. Search engines used other than Google are not included in this study. Google was used because it is the most frequently used search engine. Second, the readability score does not evaluate the scientific accuracy of websites. Third, only written materials are evaluated while calculating the readability scores. Whereas an online resource with a graphic or video may be much more understandable.

CONCLUSION

Laryngeal cancer is a disease that can be treated and has a high survival rate at an early stage. It is vital for patients to be able to receive information about their disease and to be compliant with the treatment. Having the readability scores of the websites at the recommended level, especially very easy level will ensure that the patients are informed correctly and will increase their compliance with the treatment.

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REFERENCES

1. Armstrong WB, Vokes DE, Tjoa T, Verma SP (2020) Malignant Tumors of the Larynx. In: Cummings Otolaryngology [Internet]. Seventh Ed. Elsevier Inc. 1564-1595.e11. Available from: https://doi.org/10.1016/B978-0-323-61179-4.00105-8
2. Society AC. Survival Rates for Laryngeal and Hypopharyngeal Cancers. https://www.cancer.org/cancer/laryngeal-and-hypopharyngeal-cancer/detection-diagnosis-staging/survival-rates.html.
3. Syme NP, Hoffman HT, Anderson C, Pagedar NA (2020) Management of Early Glottic Cancer. In: Cummings Otolaryngology [Internet]. Seventh Ed. Elsevier Inc. 1596-1616.e4. Available from: https://doi.org/10.1016/B978-0-323-61179-4.00106-X
4. Kurumu Tİ. Hanehalkı Bilişim Teknolojileri (BT) Kullanım Araştırması, 2022. https://data.tuik.gov.tr/Bulten/Index?p=Hanehalki-Bilisim-Teknolojileri-(BT)-Kullanim-Arastirmasi-2022-45587
5. Finnie RKC, Felder TM, Linder SK, Mullen PD (2010) Beyond reading level: a systematic review of the suitability of cancer education print and Web-based materials. J Cancer Educ. 25(4):497-505. https://doi.org/10.1007/s13187-010-0075-0
6. Ritterband LM, Thorndike FP, Cox DJ, Kovatchev BP, Gonder-Frederick LA (2009) A behavior change model for internet interventions. Ann Behav Med. 38(1):18-27. https://doi.org/10.1007/s12160-009-9133-4
7. Özdemir S, Akça HŞ, Algın A, Kokulu K (2020) Health Literacy in The Emergency Department: A Cross-sectional Descriptive Study. Eurasian J Emerg Med. 19(2):94-7. https://doi.org/10.4274/eajem.galenos.2019.38268
8. Affairs A complete list of the members of the AHC on HL and the members and staff of the C on S. Health literacy report of the Council on Scientific Affairs (1999) Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, American Medical Association. JAMA [Internet]. 281(6):552-7. https://doi.org/10.1001/jama.281.6.552
9. The National Library of Medicine (MedlinePlus) (2022) How to Write Easy-to-Read Health Materials [Internet]. 1-6. Available from: https://medlineplus.gov/pdf/health-education-materials-assessment-tool.pdf
10. Ateşman E (1997) Measuring readability in Turkish. AU Tömer Lang J. 58:71-4.

11. Lau JTF, Gross DL, Wu AMS, Cheng K man, Lau MMC (2017) Incidence and predictive factors of Internet addiction among Chinese secondary school students in Hong Kong: a longitudinal study. Soc Psychiatry Psychiatr Epidemiol. 52(6):657-67. https://doi.org/10.1007/s00127-017-1356-2

12. Sarkar U, Karter AJ, Liu JY, Adler NE, Nguyen R, López A, et al (2010) The literacy divide: Health literacy and the use of an internet-based patient portal in an integrated health system-results from the diabetes study of Northern California (DISTANCE). J Health Commun. 15(SUPPL. 2):183-96. https://doi.org/10.1080/10810730.2010.499988

13. Tahir E, Kent AE (2021) Baş Dönmesi İle İlgili İnternet Kaynaklı Hasta Bilgilendirme Metinlerinin Okunabilirlik Düzeyleri. KBB-Forum. 20(2):163-70.

14. Kozanhan B, Tutar MS (2017) Readability of Patient Education Texts Presented on the Internet in the Field of Anesthesiology. Turkiye Klin J Anesthesiol Reanim. 15(2):63-70. https://doi.org/10.5336/anesthe.2017-55537

15. Özduran E, Erkin Y, Hancı V, Taştan A, Tosun DD, Sayan EN (2022) Evaluation of The Readability Of Turkish Internet-Based Patient Education Materials Related To "'Low Back Pain.'" Dokuz Eylül Üniversitesi Tıp Fakültesi Derg. 36(2):135-50. https://doi.org/10.18614/deutip.1174522

16. Çiftçi HK, Kozanhan B, Solak İ (2020) Evaluation of Readability of Turkish Websites on Substance Addiction. J Depend. 21(1):56-63.

17. Eryılmaz UN, Külahçı UO (2019) Deri Kanseri Hasta Bilgilendirme Metinlerinin Okunabilirlik Düzeyleri. Dermatoz. 10(1):1-8.

18. Solak M (2019) Readability of Websites Containing Information About Colorectal Cancer. Harran Üniversitesi Tıp Fakültesi Derg. ;16(3):509-13. https://doi.org/10.35440/hutfd.623920

19. Narwani V, Nalamada K, Lee M, Kothari P, Lakhani R (2016) Readability and quality assessment of Internet-based patient education materials related to laryngeal cancer. Laryngoscope. 38(4):601-5. https://doi.org/10.1002/hed.23939

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Original Research

Determination of Reference Intervals of Biochemistry Parameters in Healthy Individuals in Gaziantep Province

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ABSTRACT

Objective: Reference values have gained universal acceptance as the most powerful material that helps the decision-making-implementation process of the clinical laboratory. These values may be affected by the geographical location, dietary habits and other lifestyle changes of individuals applying to the clinical laboratory. The aim of our study to determine the reference ranges for the biochemistry test panel, thyroid function tests, and insulin hormone levels, which are frequently needed by clinicians for the province of Gaziantep, with samples obtained from healthy individuals.

Methods: In the study phase, the selection of reference individuals was carried out using the direct method a priori. For the study group, healthy individuals (224 men, 243 women) between the ages of 18-45 were selected. Reference intervals (95% limit) were calculated according to the non-parametric method.

Results: When the reference intervals obtained in our study were compared with the reference intervals of the manufacturer, there were differences (> 10% lower or higher) in the upper and lower limits in urea (female and male), creatinine (male), HDL (female), AST (female and male), ALT (female), GGT (female), ALP (common), Lipase (common), CK (male), iron (male), TSH (female and male) markers. Male and female reference intervals for HDL, AST, ALT, and TSH were significantly different. Manufacturer reference ranges for these parameters were common to both sexes.

Conclusion: As a result, differences were determined between most of the the reference intervals obtained in our study and the reference intervals we routinely use. We think that the difference in the reference intervals is due to the differences in dietary habits and environmental factors.

Keywords: Reference range, biochemistry tests, direct method, regional differences

INTRODUCTION

Reference values have gained universal acceptance as the most powerful material that helps the decision-making-implementation process of the clinical laboratory [1]. Clinical laboratories provide services to clinicians and patients in order to evaluate health status, diagnosis of disease, degree of disease, drug dose, and sometimes surgical intervention with the tests they measure [2]. Reference values and ranges form the basis for the interpretation of laboratory test results and help the clinician to distinguish between healthy and sick individuals [3]. For this reason, each clinical laboratory should determine the reference values and reference interval of its own population or prove the suitability of the current values to the population.

The importance of reference intervals (RIs) has been recognized in the laws of the United States, and the Clinical Laboratory Improvement Amendments requests laboratories that offer, modify, or develop their own measurements of the FDA-approved test system, and manufacturers, to verify that the RIs are compatible for their own patient population [2]. Article 5.5.5 of the ISO 15189 Special Conditions for Quality and Competence Standard, which is a clinical laboratory accreditation standard, is related to RIs. Accordingly, before the analysis and after each update in the analysis procedures, the RIs are reviewed, and the necessary changes are provided by the laboratory specialists [4]. Having sufficient data is extremely important when determining the reference range. Statistical methods used in the reference range determination are highly dependent on the distribution type of the reference population and the number of data [5]. According to C28-A3 standards, at least 120 data will be sufficient for the statistical evaluation of data in reference range analysis. This number is also valid for main subgroups such as age and gender [6,7].

In this study, we determined the reference ranges for the most frequently studied biochemistry test panel, thyroid function tests, and insulin hormone levels in our central laboratory for Gaziantep province in accordance with the C28-A3 standards.

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METHODS

Subjects

The reference range determination study was planned as the 'Prior' choice of the 'Direct' method proposed by the International Federation of Clinical Chemistry, among many methods related to the subject [6]. Questionnaires with added questions were applied to individuals aged 18-45 in Gaziantep, selected as the study group, according to the US National Clinical Laboratory Standards Committee C28-A3 standards and by evaluating preanalytical factors. Exclusion criteria were: BMI ≥ 30, alcohol consumption ≥ 70 g/day, smoking >20 cigarettes/day, Hb (female) <12.5, Hb (male) <13.5, chronic systemic disease (CRP> 5 mg/L), having an acute disease within the last 14 days, currently known carrier state for HBV, HBC or HIV, pregnancy, and being in the postpartum first year. According to the preliminary evaluations of these questionnaires, taking into account the exclusion criteria, 224 male and 243 female healthy individuals.

This study was carried out in accordance with the Helsinki Declaration Decisions, Patient Rights Regulation and Ethics Committee Rules, and approval was obtained from the Gaziantep Ethics Committee (on May 5, 2011, with Decision No. 05/2011-55). Volunteers gave written informed consent to participate in the study and were briefed on the results upon request.

Biochemical Analysis

The subjects fasted prior to sample collection and the time of sampling was set at 7 to 10 am. Within 20 to 30 minutes of selection, the samples were centrifuged at 1200 x g for 10 min at room temperature. Blood samples were centrifuged within 20–30 minutes of withdrawal from each volunteer. One aliquot of 1 ml was prepared and stored at -80 ±2 oC for up to six months until analysis. The frozen serum samples were transferred to a refrigerator (+4–6 oC) for about 2–3 hours for thawing before examination and then transferred to the analyzer within 6 hours of thawing. Glucose, urea, creatinine, uric acid, total protein, albumin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, calcium, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), amylase, creatine kinase (CK), creatine kinase MB (CK-MB), iron, magnesium, sodium, potassium, chlorine, lipase and unsaturated iron binding capacity (UIBC) measurements were performed on the Abbott Architect C16000 autoanalyzer (Abbott Inc., Wiesbaden, Germany). Free T3 (fT3), free T4 (fT4), thyroid stimulating hormone (TSH) and insulin hormone measurements were made on the Abbott Architect I2000 (Abbott Inc., Wiesbaden, Germany). Hemoglobin (Hb) values measured in order to identify healthy individuals were measured on the Becman Coulter LH780 (Becman Coulter Inc, California, USA) device, and CRP and HbsAg values were measured using the Abbott Architect I2000 (Abbott Inc., Wiesbaden, Germany) device. Original kits from the company representative were used for each device.

Statistical Analysis

To calculate RIs, data were transferred into SPSS version 20.0 (SPSS Inc., Chicago, USA) and MedCalc version 14.12.0 (MedCalc Software, Mariakerke, Belgium). Reference limits describe the central 95% of the reference population. Non-parametric statistics were used for the determination of RIs. Non-parametric methods typically include the central 95th percentile of reference values and use the 2.5th and 97.5th percentile as the lower and upper reference limit, respectively. Dixon's range test, recommended by the IFCC for statistical analysis in reference interval studies, was used to detect and eliminate extreme values as outliers. Confidence intervals of 90% (90% CI) of reference limits were determinated following IFCC recommendations [8,9].

RESULTS

Five hundred forty-five samples were collected from candidate reference individuals between the ages of 18-45 (mean age 30.7±7.8 years) living in Gaziantep province. A total of 78 samples were excluded from the study because of Hb levels less than 12.5 g/dL in women (n=35) and less than 13.5 g/dL in men (n=13), CRP levels above five mg/L (female n=8, male n=5) and HbsAg (+) (female n=6, male n=11). After exclusions, the study group was formed with the remaining 467 samples (243 females, 224 males).

Table 1 includes the demographic and characteristic data for the male and female genders of the reference individuals in the study group. The degree of influence of the factors (alcohol, smoking, exercise) that might affect the reference ranges on the data was analyzed with the "Mann-Whitney U test". No statistically significant difference was found in terms of their effects (p> 0.05). Table 2 shows the RIs of 33 analytes determined by the direct method in males (n:224) and females (n:243) participants and 90% CIs of reference limits. It also includes a comparison of the reference ranges determined with the reference ranges from the literature and the manufacturer. When the reference intervals obtained in our study were compared with the reference intervals of the manufacturer, there were differences (>10% lower or higher) in the upper limits of urea (female and male), creatinine (female and male), HDL (female), TBIL (common), AST (female and male), ALT (female), GGT (female), ALP (common), Lipase (common), CK (male), iron (female and male), TSH (female and male) markers. There were differences (>10% lower or higher) in the lower limits of urea (female and male), creatinine (male), HDL (male and female), TBIL (common), AST (female and male), GGT (female and male), ALP (common), Mg (common), iron (male), TSH (female and male), fT3, fT4 markers. Male and female reference intervals for HDL, AST, ALT, and TSH were significantly different. Manufacturer reference ranges for these parameters were common to both sexes.

DISCUSSION

In this study, it was aimed to determine the RIs for the most frequently studied biochemistry tests in our central laboratory. At the beginning of this study, it was started with the question of why RIs are so important. Today, due to the developing technology and increasing test diversity, clinicians make more laboratory requests and decide on clinical diagnosis, patient follow-up, and surgical intervention with the interpretation of the results.

Table 1. Demographic and characteristic data of the reference population

	Female	Male
n	243	224
Age (years)	29.7±7.8	31.7±7.7
BMI (kg/m2)	24.6±4.9	25.8±3.1
Smoking (Yes)	19	24
Alcohol consumption (Yes)	5	12
Exercise (Yes)	7	20

Table 2. Reference intervals estimated with direct method using non-parametric calculation

Test Name	Unıt	Method	Gender	RIs			Manufac-turer	Literature (14)
				LL-CI	LL-UL	UL-CI		
Glucose	mg/dL	Hexokinase	C	68-71	70-103	101-106	70-105	74-100
Urea	mg/dL	Urease	F	11-12	11-34 (•,▪)	32-39	19-42	13-43*
			M	16-18	17-39 (•,▪)	38-44	15-55	
Creatinine	mg/dL	Jaffe/picrate	F	0.51-0,56	0.52-0.85 (▪)	0.81-0.92	0.57-1.1	0.45-0.75
			M	0.53-0.67	0.63-1.05 (•,▪)	1.01-1.09	0.72-1.25	0.62-1.1
Urıc Acıd	mg/dL	Urokinase	F	1.9-2.3	2.1-6 (•)	5.5-7.1	2.6-6	2.3-6.6
			M	2.8-3.5	3.1-7.9 (•)	7.3-8.1	3.5-7.2	4.4-7.3
Total Proteın	g/dL	Biuret	C	5.7-6.1	6-8.1	8-8.2	6.4-8.3	6.4-8.3
Albumın	g/dL	Bromocresol green	C	3.38-3.62	3.46-4.9	4.81-4.95	3.5-5	3.5-5.2
Total Cholesterol	mg/dL	Enzymatic	C	108-121	114-259	234-258	<200**	<200**
Trıglyceride	mg/dL	Enzymatic	F	30-46	40-220	189-225	<170**	<150**
			M	36-51	43-305	285-364		
LDL	mg/dL	Liquid se-lective de-tergent	C	48-58	54-159	156-174	<130**	<100**
HDL	mg/dL	Accelerator selective detergent	F	25-34	33-68 (•,▪)	66-75	40-60	40-60
			M	25-29	27-55 (•)	53-59		
Total Bilirubin	mg/dL	Colorimetric	C	0.2-0.25	0.23-1.32 (•,▪)	1.25-1.39	0.2-1.2	0-2
Direct Bilirubin	mg/dL	Colorimetric	C	0.08-0.1	0.09-0.51	0.48-0.64	0-0.5	0-0.2
AST	U/L	Enzymatic	F	8-10	9-27 (•,▪)	24-28	5-34	<31
			M	9-10	9-38 (•,▪)	34-43		<35
ALT	U/L	Enzymatic	F	4-5	4-32 (▪)	30-39	0-55	<34
			M	5-6	5-53	48-61		<45

ALP	U/L	Enzymatic	C	32–38	35–107 (•,▪)	101–122	40–150	42–98 53–128
GGT	U/L	Enzymatic	F M	5–7 9–11	6–27 (•,▪) 10–59 (•)	26–32 53–67	9–36 12–64	2–35 1–24
LDH	U/L	From lactate to pyruvate	C	105–115	112–231(•)	221–239	125–243	125–220
Amylase	U/L	Enzymatic	C	29–35	32–113 (•)	106–119	25–125	28–100
Lipase	U/L	Colorimetric	C	8–11	9–54 (▪)	49–56	8–78	<38
CK	U/L	Enzymatic	F M	25–35 41–49	29–141(▪) 44–225 (•,▪)	125–162 201–259	29–168 30–200	46–171 34–145
CK–MB	U/L	Colorimetric	C	4–7	5–27	26–28	<24	
Iron	µg/dL	Colorimetric	F M	25–31 31–46	28–160 (▪) 42–179 (•,▪)	143–164 173–212	31–144 25–156	65–175 50–170
Iron Binding Capacity	µg/dL	Colorimetric	F M	16–123 84–144	107–446 130–344 (•)	411–500 324–377	110–370	250–425
Ca	mg/dL	Arsenazo III Complex	C	8–8.4	8.2–10.1	10–10.3	8.4–10.2	8.6–10.2
Mg	mg/dL	Arsenazo III Complex	C	1.78–1.84	1.82–2.8 (•)	2.75–2.83	1.6–2.6	1.6–2.6
Phosphorus	mg/dL	Phospho–molybdate	C	2.3–2.6	2.49–4.5	4.4–4.7	2.3–4.7	2.5–4.5
Na	mmol/L	ISE	C	131–132	131–145	143–146	136–145	136–145
K	mmol/L	ISE	C	3.53–3.7	3.62–5.03	4.84–5.14	3.5–5.1	3.5–5.1
Cl	mmol/L	ISE	C	98–100	99–110	109–111	98–107	98–107
TSH	µIU/mL	CMIA	F M	0.44–0.67 0.38–0.57	0.55–4.11 (•,▪) 0.47–3.53 (•,▪)	4.04–4.38 3.24–3.69	0.35–4.94	0.4–4.2
Ft3	pg/mL	CMIA	C	2.39–2.57	2.53–3.93(•)	3.86–4.03	1.71–3.71	2.1–4.4
Ft4	ng/dL	CMIA	C	0.84–0.87	0.86–1.32(•)	1.28–1.36	0.7–1.48	0.4–2.7
Insulin	µU/mL	CMIA	C	3–4	4–20	17–21	–	3–25

(*) Calculated by converting blood urea nitrogen to urea
(**) Optimal values expected in healthy individuals
(•) LL of obtained RIs different (> 10% lower or higher) from manufacturer RIs
(▪) UL of obtained RIs different (> 10% lower or higher) from manufacturer RIs
F: Female, M: Male, C: Common, RIs: Reference Intervals, LL: Lower Limit, UL: Upper Limit, CI: Confidence intervals, ISE: Ion Selective Electrode, CMIA: Chemiluminescent microparticle immunological assay

Clinical laboratories, due to their responsibilities in health care, should provide clinicians and patients with the essential guides for the correct interpretation of all the tests they offer. The primary source that clinicians use when interpreting test results is reference ranges [10,11]. These values not only affect the physician's decision but also cause negativities in the patient's life. For this reason, the RIs to be included in the guidelines should represent the population served by the clinical laboratory and there should be no room for doubt in these values [7,12].

The suitability of the RIs in the prospectuses of the manufacturer according to the results of non-parametric methods was

evaluated [13]. Our results showed that; The reference ranges determined for the lower and upper limits in twelve parameters differed from those used in the routine. There were differences >10% lower or higher in the upper and lower limits. These changes are notable considering that sometimes seemingly minor differences are of great importance in clinical decisions. Unlike other parameters, RIs are not given in the kit package insert for the insulin hormone, and it is recommended by the manufacturer that the responsible clinical laboratory should conduct a reference study. Male and female reference intervals for HDL, AST, ALT, and TSH were significantly different. Manufacturer reference ranges for these parameters were common to both sexes.

As a result of reference value studies, the most important question is that 'can the determined reference values be applied in practice?' In fact, this is the most critical result of reference interval studies. Therefore, RIs determined by a team of biochemists and clinicians should be evaluated one by one before the results can be put into practice. If the determined reference values are compatible with the reference interval data in the literature and the package insert, it can be said that the reference interval of your society is similar to the RIs of other societies. If different reference values have been obtained, then you have the chance to say that your society's reference range is diverse and you have the opportunity to interpret this different result.

In our study, the upper reference value for total cholesterol was found as 259 mg/dL. When the literature and kit prospectuses are examined and clinical practice is examined, it is seen that the desired value for total cholesterol in healthy individuals is below 200 mg/dL. The blood lipid values we obtained bring to mind the question, "Are we administering unnecessary drug treatment to healthy individuals? or will we conclude that we have high blood lipid values depending on the nutritional habits of the society and these values cannot be a reference for a healthy person?" At this stage, the discussion can be continued over the decision limits. Yes, the values determined as a result of this study are the reference values of our society, but in clinical practice, there is also a need for decision limit studies for analytes such as glucose, total cholesterol, LDL-cholesterol, and triglycerides. These approaches also show that the use of determined RIs in routine practice is a process that should be supported by new ideas and studies.

For HDL-cholesterol, the manufacturer's reference ranges are given as 40-60 mg/dL without discrimination between men and women. However, both in our study and in studies conducted in Bursa and Denizli, HDL cholesterol values in men and women were significantly different. For HDL reference values, we found 27-55 mg/dL for men and 33-71 mg/dL for women in our study. In the study conducted in Bursa, values of 30-54 mg/dL in men and 31-65 mg/dL in women were reported [15], while values of 28-67 mg/dL in men and 35-83 mg/dL in women were obtained in the study conducted with individuals living in Denizli [13]. These results show us once again how reference values differ between individuals living in different parts of the same society, as well as gender.

These data and reference range studies provide essential information about the habits of our own society. It allows us to have information about the relationship between tests and lifestyle factors, such as hyperlipidemia, which is seen as an essential factor in terms of cardiovascular diseases, which has been discussed for many years in our country, and hyperglycemia, which is the leading cause of diabetes with a prevalence of 16.5% today [16].

In the thyroid test panel, narrower RIs were obtained than the RIs of the manufacturer. In our study, 2.53-3.93 pg/mL for fT3, 0.86-1.32 ng/mL for fT4, and 0.55-4.11 µIU/mL for TSH in women and 0.47-3.53 µIU in men /mL results obtained. Endemic goiter and iodine deficiency are important public health problems in Turkey. In the survey study of Kologlu et al. [17], it was determined that there is a significant problem of goiter in many regions of Turkey, and it was stated that this was due to the insufficient iodine content of the waters and soil. The differences in these values obtained in the RIs of thyroid function tests can be explained by geographical and ethnic differences such as population, lifestyle, salt iodination and nutrition [18].

Reference values for liver enzymes AST and ALT were significantly different in men and women ($p<0.01$). The company gives RIs as single RIs for both genders. These results suggest that separate reference values should be given for men and women.

The results of this study once again showed that reference values may vary according to the population served by the clinical laboratory. Gender, geographical location, socio-economic level and related nutrition, smoking and alcohol use, exercise may be the reasons for these differences. Therefore, each clinical laboratory should perform reference range studies for its own population. As stated in the accreditation documents regulating clinical laboratory service conditions and standards, the reference values used should be validated at least [4].

To summarize, most laboratories in our country, as in the world, use literature or test kit manufacturer reference intervals. This may affect the clinical interpretation of physicians and lead to misdiagnosis and treatments [19]. According to the European Union's regulation on in vitro diagnostic medical devices, test kit manufacturers are responsible for providing appropriate reference ranges for use with their devices. Due to the difficulties of the direct method, most laboratories use these reference ranges. However, it is the task of laboratories to determine the suitability of these externally sourced reference intervals for use [20].

Our study is the first reference interval study of our region and includes many biochemical markers. The 18-45 age range was a good choice to reach healthy individuals but it was also the main limitation of our study. Our targets are new reference interval studies to be carried out up to age 65. Also, RIs are representative of the population and are, therefore, not a perfect fit for the individual. An improved solution may be to use the data of individuals to derive a personalized RI. [21].

As a result, differences were determined between the RIs obtained in our study and the RIs in the manufacturer and the literature. We think that the difference in the RIs is due to the differences in dietary habits and environmental factors. The different RIs obtained will be used in diagnostic laboratories after meetings with clinicians.

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Ethics Committee Approval: Ethics committee approval was obtained from the Gaziantep University Clinical Research Ethics Committee on May 5, 2011, with Decision No. 05/2011-55.

REFERENCES

1- Grasbeck R (1983) Reference value philosophy. Bull Mol Biol Med. 8:1–11.

2- Aslan D, Turkish Biochemistry Association Reference Ranges Calculation Course Book. Izmır, 2010

3- Ilcöl YO, Aslan D (2006) Use of total patient data for indirect estimation of reference intervals for 40 clinical chemical analytes in Turkey. Clin Chem Lab Med. 44(7):867-76. https://doi.org/10.1515/CCLM.2006.139

4- ISO 15189: Medical Laboratories-Particular Requirements for Quality and Competence. Geneva 2003.

5- Sumbuloglu K & Sumbuloglu V. Biostatistics. 10. ed. Hatiboglu Yayinlari. Ankara, 2002.

6- Clinical and Laboratory Standards Institute. Defining, Establishing, and Verifying RIs in the Clinical Laboratory; Approved Guideline. 3rd ed.Wayne, PA: CLSI;2010.

7- Horn PS. Pesce AJ (2003) Reference Intervals: An Update. Clin. Chim. Acta. 334: 5-23. https://doi.org/10.1016/S0009-8981(03)00133-5

8- Solberg HE (1987) International Federation of Clinical Chemistry (IFCC). Approved recommendation on the theory of reference values. Part 5. Statistical treatment of collected reference values. J Clin Chem Clin Biochem. 25:645-56. https://doi.org/10.1515/CCLM.2004.121

9- Dixon WJ (1983) Processing data for outliers. Biometrics. 9:74- 89. https://doi.org/10.2307/3001634

10- Barth JH (2004) Who is responsible for reference ranges? Ann Clin Biochem. 41(Pt 6):429. https://doi.org/10.1258/0004563042466730

11- Barth JH (2009) Reference ranges still need further clarity. Ann Clin Biochem. 46(Pt 1):1-2. https://doi.org/10.1258/acb.2008.0081

12- Solberg HE (1987) Approved recommendation on the theory of reference values. Part 1. The concept of reference values. J Clin Chem Clin Biochem. 25:337–342. https://doi.org/10.1016/0009-8981(87)90151-3

13- Enli Y, Aslan D, Akalın N, Aydın Y, Yılmazturk CG, Goçhan I, Tekinturk S, Demir S (2003) Determination of Reference Ranges by Different Methods in Individuals aged 18-40 living in Denizli. Turkish Journal of Biochemistry. 28(4): 228-45.

14- Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5 st ed. St. Louis, Missouri; 2012, p95-118/ p.2131-2188

15- Ilçöl YO, Aslan D. Determination of Blood Biochemistry Profile Reference Ranges in Healthy Individuals in Bursa Province. TJB 2004; 29(2): 183-92

16- Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J (2013) Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. TURDEP-II Study Group. Eur J Epidemiol. 28(2):169-80. https://doi.org/10.1007/s10654-013-9771-5

17- Koloğlu S, Koloğlu B. Türkiye'de endemik guatr. Elif Matbaacılık, Ankara 1984:1-64.

18- Cavuşoğlu AC, Bilgili S, Erkızan O, Arıcan H, Karaca B (2010) Thyroid hormone reference intervals and the prevalence of thyroid antibodies, Turk J Med Sci. 40 (4): 665-672. https://doi.org/10.3906/sag-0906-62

19- Jones GR, Barker A, Tate J, Lim C-F, Robertson K (2004) The case for common reference intervals. Clin Biochem Rev. 25(2):99

20- Directive C. 98/79. EC concerning in vitro diagnostic devices 1998.

21- Personalized reference intervals: from theory to practice, Coskun A, Sandberg S, Unsal I, Serteser M, Aarsan A (2022) Crit Rev Clin Lab Sci. 59(7):501-516 https://doi.org/10.1080/10408363.2022.2070905

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Original Research

The Effect of Forced Exercise on Striatal and Serum Serotonin Levels in a Parkinson's Mouse Model

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ABSTRACT

Objective: The general treatment approach for Parkinson's disease (PD) is L-dopa administration. While L-dopa only relieves dopaminergic deficiency, it has no effect on the serotonergic system, which is thought to be impaired in the disease. The limitations of current treatment methods have made it necessary to discover new approaches to the treatment of the disease. Studies conducted in recent years report that different types of exercises lead to improvements in the symptoms of PD. Exercise decreases serotonin levels and increases dopamine levels. However, the effect of exercise on serotonin and dopamine levels in PD and its effect on non-motor symptoms such as anxiety and depression are unknown.

Methods: PD is created using MPTP. The exercise groups were given challenging treadmill exercises for six weeks. Serotonin and dopamine levels were measured in the striatum and serum. Parkinson's symptoms were examined with pole test and behavioral tests.

Results: Exercise significantly reduced bradykinesia, increased motor activity, and decreased anxiety behaviors in the exercise groups. While exercise increased striatal dopamine levels in all exercise groups, there was no difference in striatal serotonin levels. However, the serotonin serum level decreased in the PD model group. While treadmill exercise increased striatal dopamine levels in the Parkinson's mouse model, it did not cause any change in striatal serotonin levels. However, the decrease in serum serotonin level was determined only in the MPTP group.

Conclusion: The fact that the decrease in serotonin level was only in the disease group and the lower level of anxiety observed in behavioral experiments suggested that regular treadmill exercise was the reason. However, this improvement was not observed in cases where the anxiety level was very high.

Keywords: forced exercise, serotonin, treadmill exercise, Parkinson's disease, dopamine

INTRODUCTION

Dopaminergic neuronal loss is known as the main cause of Parkinson's disease (PD), and motor and non-motor symptoms are seen in this disease. Motor symptoms include bradykinesia, rigidity, and tremor, while non-motor symptoms include a variety of symptoms such as cognitive impairment, autonomic dysfunction, sleep disturbances, depression, and anxiety [1-3]. It is known that 60% of people with PD have non-motor symptoms [4]. While depression affects approximately 25-40% of people with PD, anxiety is seen in 40% [5]. Some studies also state that mood disorders appear years before the motor symptoms of the disease appear [6]. However, non-motor symptoms are generally not treated [7]. The pathophysiology underlying mood disturbances such as anxiety and depression in PD is still not fully understood. However, there is evidence showing that the cholinergic, dopaminergic, and noradrenergic systems in the brain have an effect on mood disorders [8]. It is known that dysfunction in the serotonergic [5-hydroxytryptamine) system contributes to mood disorders and cognition disorders [9]. An old systemic review stated that the use of antidepressants treated depression in PD, but the results were not consistent with each other. In addition, it has been reported that the drugs used show side effects at a rate of about 26% [8].

Physical activity's affirmative effects on health have been known for years. Regular physical exercise increases synaptic plasticity,

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modulates neurogenesis, and increases brain perfusion. It has even been reported that exercise has antidepressant and anxiety-reducing effects [10, 11].
In this research, we researched the effect of forced treadmill exercise on serotonin and its relationship with non-motor functions like anxiety and depression in a mouse model of Parkinson.

METHODS

Animal: 24 adult C57Bl/6 male mice were tested in the experiment. Standard rodent chow and water were placed in the cages of the animals. Animals were fed ad-libitum. The procedure of the experiment was confirmed by "the animal care and usage committee of Gaziantep University" and was in accordance with the "Declaration of Helsinki and International Association for the Study of Pain Guidelines". 24 mice were casually separated into four groups. Groups are 1) Control (CON), 2) MPTP (MPTP), (3) Control+Exercise (CON+EXE), and (4) MPTP+Exercise (MPTP+EXE).

Parkinson Model: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known as a neurotoxin. It was used to induce dopaminergic neurodegeneration in this experiment. The MPTP-Parkinson model very closely reflects the clinical symptoms of PD. MPTP (M-0896, Sigma-Aldrich, St. Louis, Mo. USA) solution was prepared with normal saline at 3mg/ml and injections were administered 4 times at a dose of 20 mg/kg intraperitoneally to reduce the risk of animal loss due to the toxin [12,20].

Exercise Protocol: The treadmill (The Ugo Basil, 47300) was used to apply a forced exercise protocol to the animals and had dimensions of 38x5x5 cm. Adaptation exercise was trained at 10 m/min for 5 days to measure the exercise compliance of the animals before applying the exercise protocol. Animals that did not comply with exercise were not included in the experimental group [13]. The mice in the exercise groups exercised five days a week. The exercise continued regularly for six weeks. Mice were subjected to moderate-intensity treadmill exercise for 40 minutes per day [14]. The exercise protocol is as follows: Speed for exercise is 15 m/min (5 min 6 m/min, 5 min 9 m/min, 20 min 12 m/min, 5 min 15 m/min, and 5 min 12 m/min) with 0° inclinations.

Pole test: The pole test is used for the assessment of bradykinesia symptom [15-19]. Animals injected with MPTP were applied to the pole test on the 7th day of the experiment. The application of the pole test is as follows: A rod's length, used in the pole test, is 50 cm, and its diameter is 0.8 cm. The mouse was put on the end of the rod with its head facing up. The time until he turned his head was considered Tturn, and the time until he turned his head down was considered Ttotal. The average of the three measurements in the experiment was recorded.

Open Field Test (OFT) and Elevated Plus Maze (EPM) Test: Both tests are used to qualify locomotor activities, and mood disorders such as anxiety and depression. EPM is a plus-shaped experimental setup with 2 open and 2 closed arms at a specific height from the ground, and OFT consists of a 50 x 50 cm square platform. A camera system is placed in full view of both test platforms to record behavioral data [26, 27]. Recording behavioral data were taken by the Axis M1145-L network camera system, and analysis was made using Etho Vision XT 11.5 in this study. Each mouse was put in the midpoint of the open field cage or the middle zone of the elevated place maze for testing all parameters, and the camera continued to record for 5 minutes. The area in both systems was completely cleaned with a 10% ethanol solution to wipe away the animal odors at the end of each experiment, and a new animal was included in the experiment after it was allowed to dry thoroughly [27].

Tissue preparation: All mice were anesthetized after a 6-week treadmill exercise. Xylazine was injected at a dose of 10 mg/kg, and ketamine was injected at a dose of 100 mg/kg. Injections are applied intraperitoneally for anesthesia. Animals were guillotined and euthanized 48 hours after the last exercise to exclude the acute effects of exercise.

Brain dissection and tissue homogenization: Brains were removed, and striatum tissues were immediately isolated [28]. Brain tissues and serum were preserved at -80°C until homogenization. The striatum was homogenized for 30 seconds, using a sonicator (Branson Sonifier® UNITS Model S-150D) on ice. Then, centrifugation (Thermo Scientific MicroCL Centrifuge) was performed at 5,000 g for 5 minutes at 8°C for the tissues, and supernatants were collected. Protein determination (BioTek, Synergy H1 Microplate Reader) was performed using 2 microliter samples from each different homogenate.

Determination of dopamine and serotonin levels: Dopamine and serotonin levels were determined by a sandwich enzyme-linked immunosorbent assay (ELISA) (Mouse Serotonin ELISA Kit, FineTest, China Cat: No: EM1465, Mouse Dopamine ELISA Kit, FineTest, China Cat: No: EM1712), following the indication provided by the manufacturer. Serotonin and dopamine levels were examined in both the striatum and serum.

Statistical assessment: Statistical Package for the Social Sciences (SPSS) software for Windows (version 20.0) was used for data analysis. Whether the data had a normal distribution or not was determined by the Kolmogrov-Smirnow test. A one-way analysis of variance (ANOVA) test was applied to normally distributed data. Kruskal Wallis was used for the analysis of non-normally distributed data. The Tukey Post Hoc Test was applied to parametric data to determine the differences between groups. Dunn's test was used to determine the differences between groups in the data that was not normally distributed. Data are presented as mean±SD. Data were considered significant if the p-value was less than 0.05 ($p<0.05$).

RESULTS

Bradykinesia assessment: The pole test, which measures impairments in starting and maintaining movement, shows two parameters. In our results, a significant prolongation was observed statistically in the time to start movement in the MPTP and MPTP+EXE groups compared to the CON and CON+EXE (Figure1). Total shows the time it takes to start and maintain

movement. This value was significantly longer only in the MPTP group compared to the CON and CON+EXE groups (Figure 2).

Motor performance assessment: Motor activities were evaluated with EPM and OFT tests. Mean distance moved in EPM (Figure 3) and velocity in OFT (Figure 4) decreased only in MPTP group compared to other groups.

Anxiety and depression assessment: Anxious and depressed animals spend longer in closed arms and shorter in open arms in EPM. Anxious and depressed animals spend longer in the EPM in closed arms and shorter in open arms. Figure 5 shows the average time spent by the groups in the open arms. According to Figure 5, the time spent in the open arms of the MPTP group in EPM decreased compared to the CON and CON+EXE groups. However, no significant difference was found between the disease model group and the exercise disability model group. In Figure 6, it is seen that the time spent in closed arms decreased only in the CON group compared to the MPTP and MPTP+EXE groups.

Anxious and depressed animals spend longer time in OFT in the peripheral area and shorter in the middle area. Compared to the other groups, the MPTP group passed less time in the middle area (Figure 7) and more time in the peripheral area (Figure 8).

Assessment of Dopamine and Serotonin Levels: Both neurotransmitter levels were measured in the striatum and serum. It was found to be statistically significantly reduced in striatal dopamine levels in the PD model group compared to the other groups (Figure 9). However, there was no difference in serum dopamine levels among groups (the figure is not shown). It was found to be statistically significantly reduced in serum serotonin levels in only the MPTP group compared to the control group (Figure 10). However, there was no difference in striatal serotonin levels among groups (the figure is not shown).

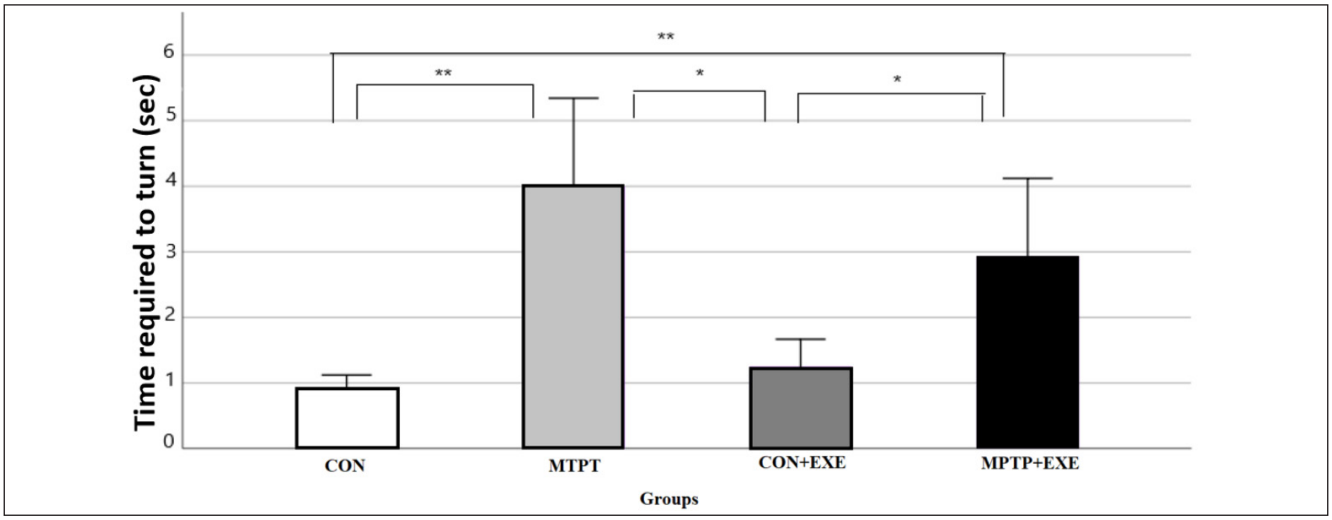

Figure 1. Tturn means the time it takes the animal to turn its head down after placing it on the pole. (n=6, *p < 0.05 vs. MPTP and CON+EXE groups, CON+EXE and MPTP+EXE groups, **p < 0.01 vs. CON and MPTP groups, CON and MPTP+EXE groups)

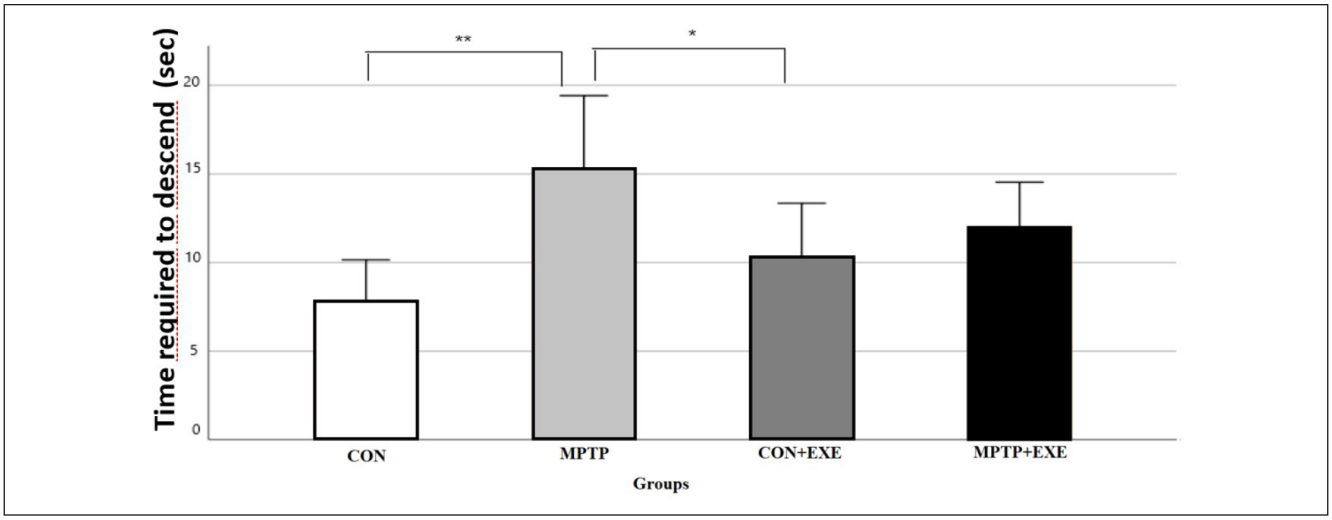

Figure 2. Total shows the time it takes to start and maintain movement. (n=6, *p < 0.05 vs. MPTP and CON+EXE groups, **p < 0.01 vs. CON and MPTP groups)

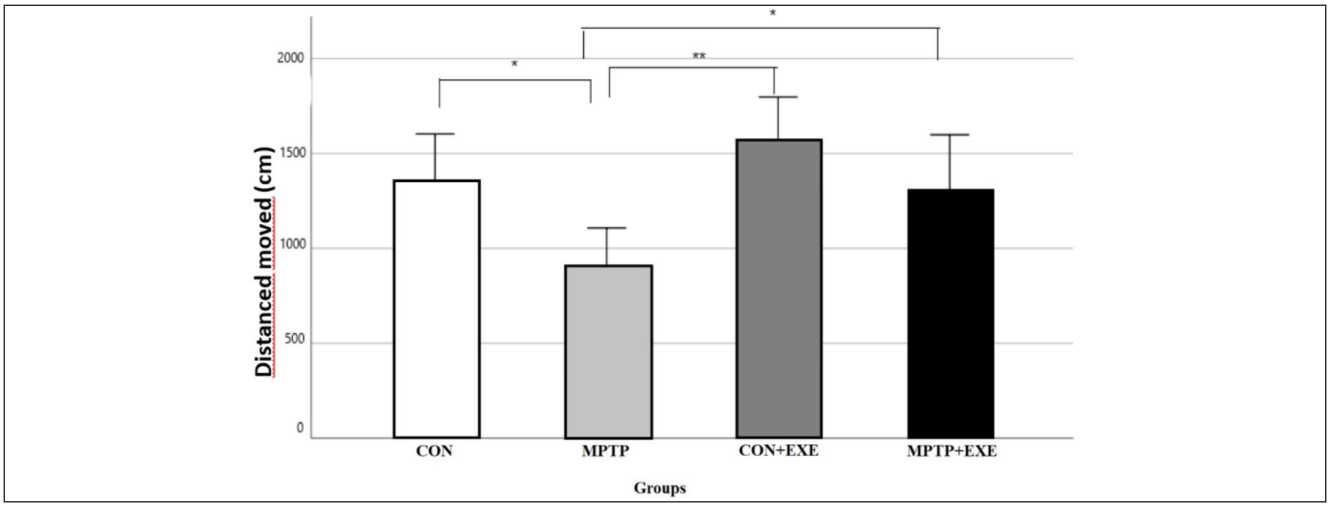

Figure 3. The mean distance moved in the EPM test (n=6, *p<0.05 vs. MPTP and CON groups, MPTP and MPTP+EXE groups, **p<0.01 vs. MPTP and CON+EXE groups)

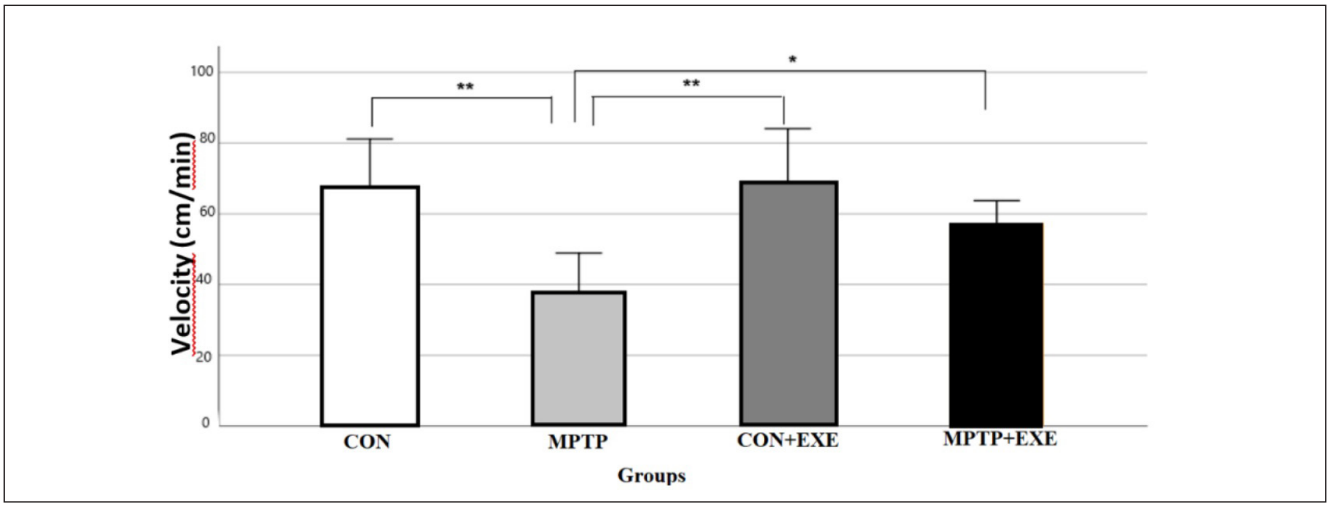

Figure 4. The velocity in the OFT test (n=6, *p<0.05 vs. MPTP and CON groups, MPTP and MPTP+EXE groups, **p<0.01 vs. MPTP and CON+EXE groups)

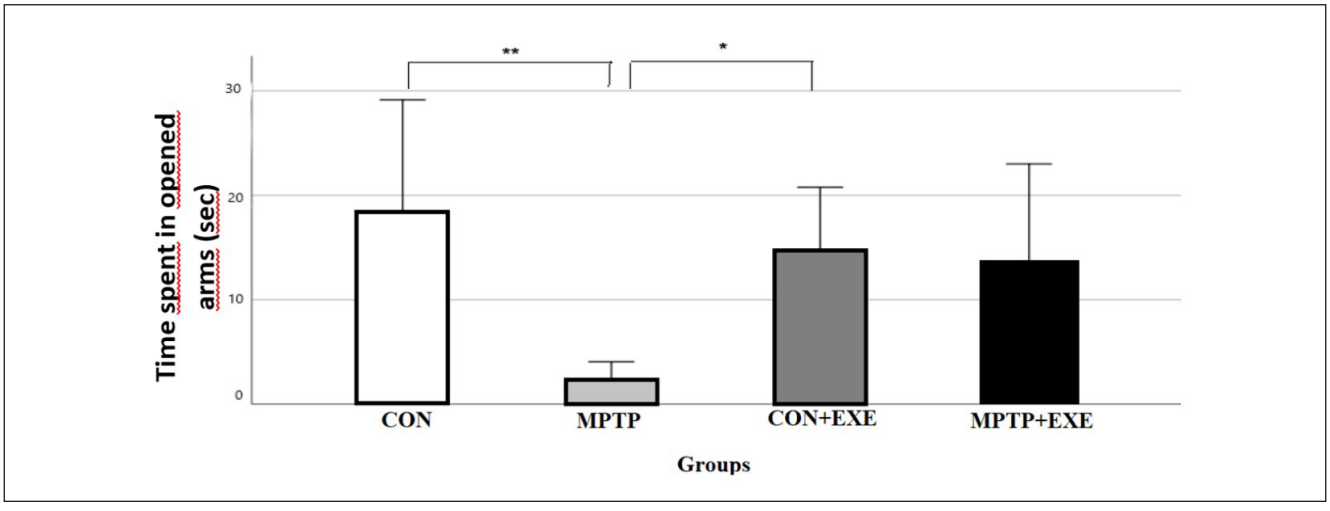

Figure 5. The spent time in the opened arms in the EPM test (n=6, *p < 0.05 vs. MPTP and CON+EXE groups, **p<0.01 vs. CON and CON+EXE groups)

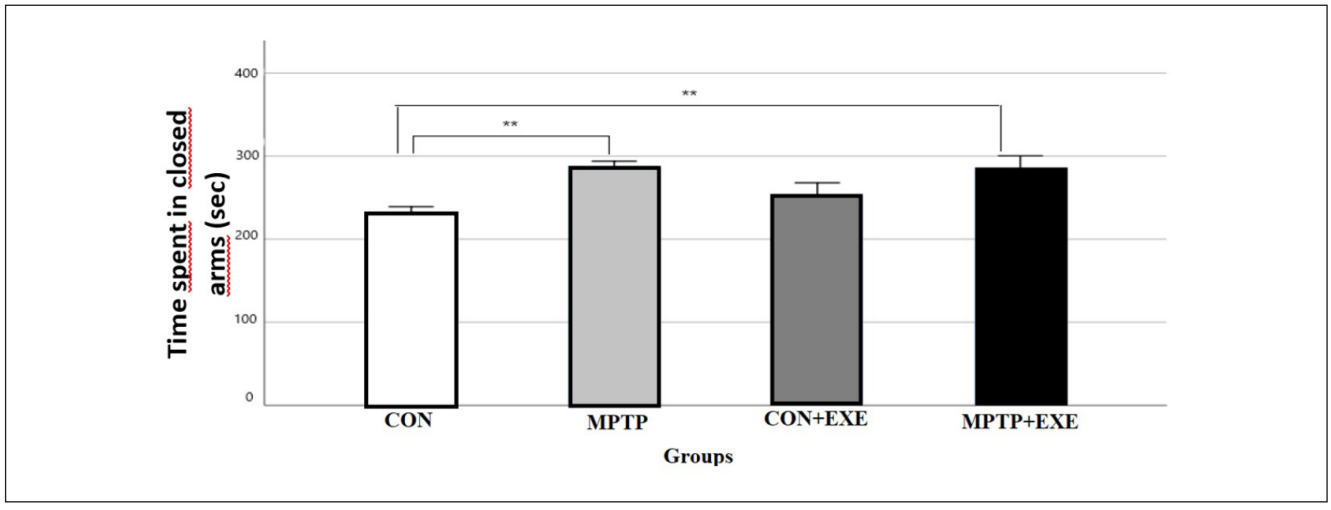

Figure 6. The spent time in the closed arms in the EPM test (n=6, **p<0.01 vs. CON and MPTP groups, CON and MPTP+EXE groups)

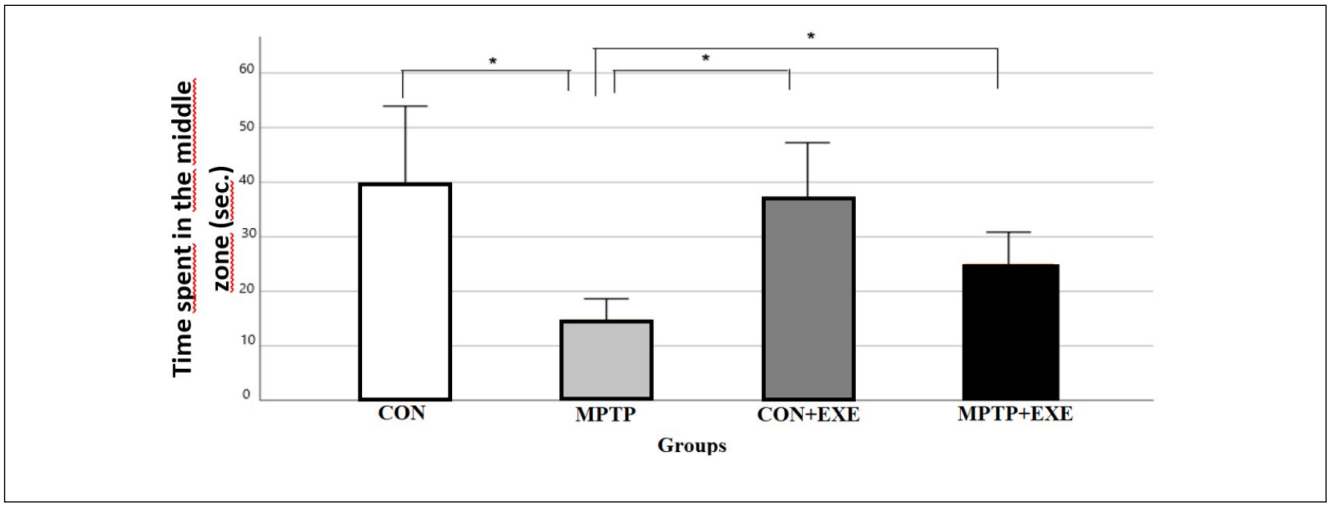

Figure 7. The spent time in the middle zone in the OFT test (n=6, *p < 0.05 vs. CON and MPTP groups, MPTP and CON+EXE groups, MPTP and MPTP+EXE groups)

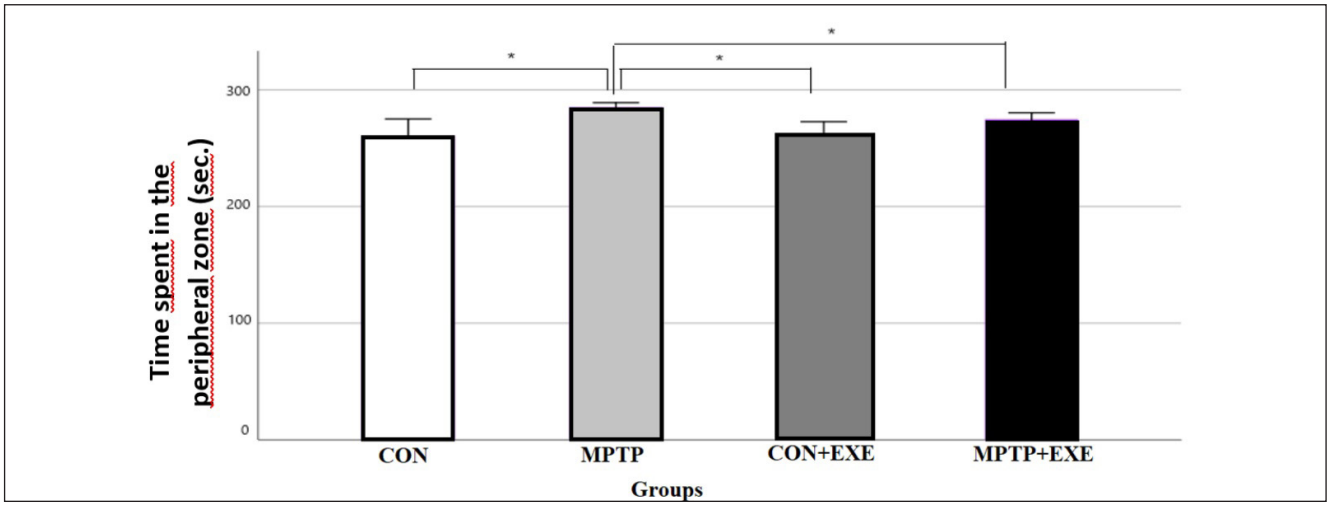

Figure 8. The spent time in the peripheral zone in the OFT test (n=6, *p<0.05 vs. CON and MPTP groups, MPTP and CON+EXE groups, MPTP and MPTP+EXE groups

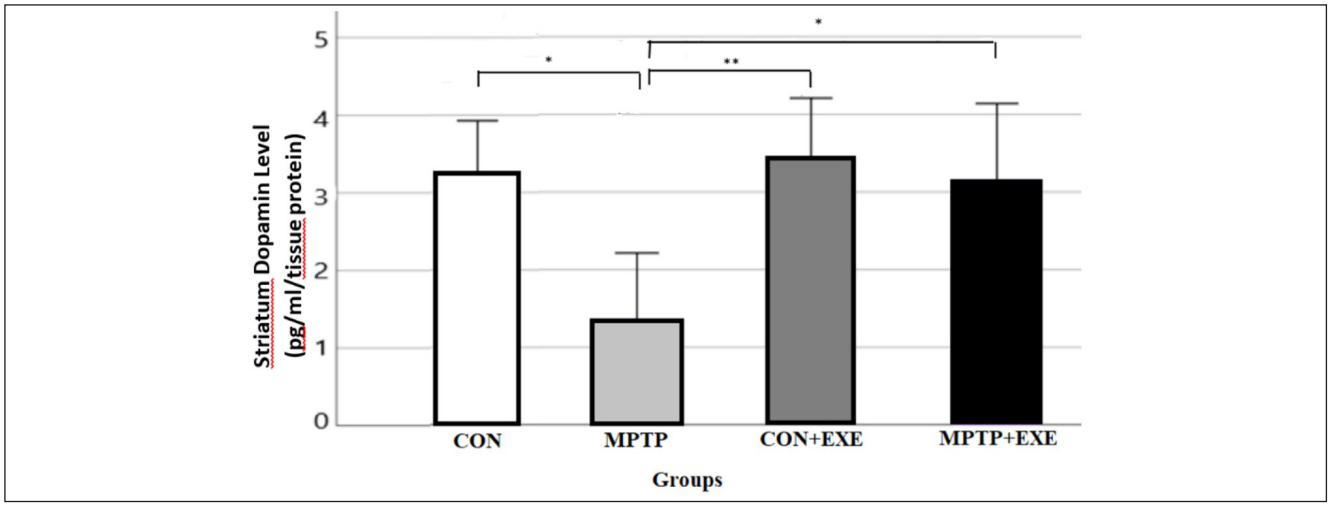

Figure 9. The striatal dopamine levels (n=6, *p<0.05 vs. CON and MPTP groups, MPTP and MPTP+EXE groups, **p<0.01 vs. MPTP and CON+EXE groups)

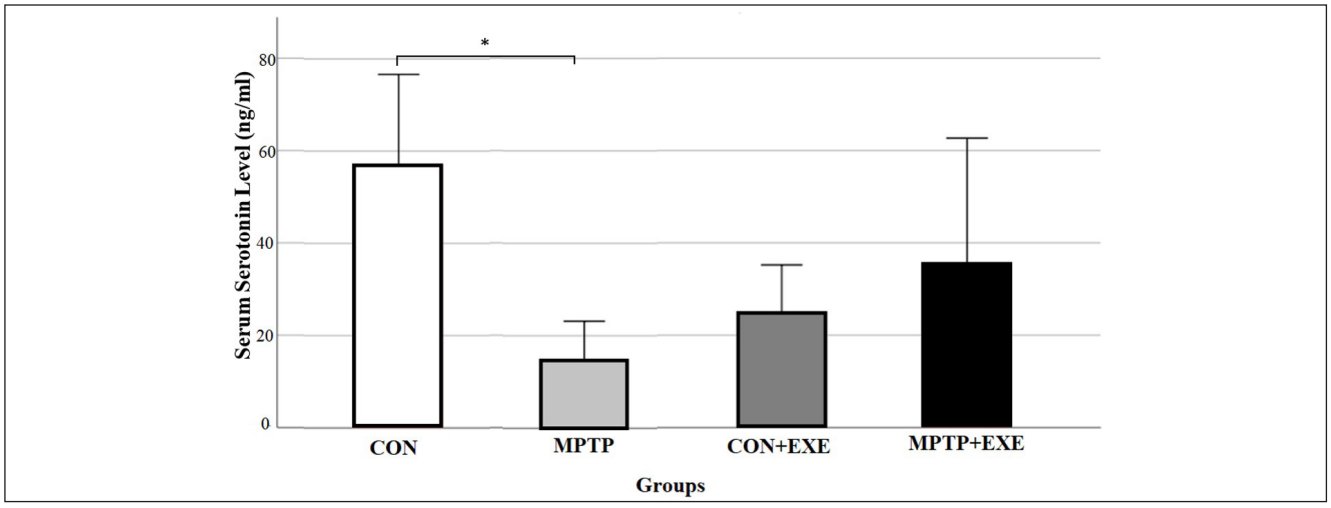

Figure 10. Serum serotonin levels (n=6, *p<0.05 vs. CON and MPTP groups)

DISCUSSION

PD is the second most common neurodegenerative disease [3,21]. The priority as a treatment approach is the treatment of motor symptoms, as motor symptoms further prevent the patient from continuing his daily life. However, it is known that non-motor symptoms occur long before the motor symptoms of the disease appear [6]. Treating non-motor symptoms together with motor symptoms will increase the patient's quality of life [7]. It is known that the main reason for the emergence of motor symptoms is dopamine deficiency. However, there is no definite information about the cause of non-motor symptoms. Studies show changes not only in the dopaminergic system but also in the cholinergic and noradrenergic systems in Parkinson's patients [8].

Parkinson's model with MPTP injection is accepted as the "gold standard" in the development of symptomatic treatment methods, evaluation of pharmacological agents, and development of new strategies. The advantages of the model created with MPTP are that mice cost less to purchase and house than other animals, MPTP does not require stereotaxic surgery, causes bilateral lesions, and shows most of the known biochemical features of PD [13].

In our pole test results, the time to start movement was extended in the MPTP group. However, exercising in the Parkinson model group did not significantly reduce the time to start movement (Tturn). Exercise does not improve the bradykinesia in PD. However, the time required to descend was prolonged only in the MPTP group. However, distance moved and velocity values decreased significantly in the solely Parkinson model group compared to others. Although the forced treadmill exercise did not shorten the starting time to move, it improved the ability to maintain movement by healing motor coordination. We reported in our previous study that moderate-intensity forced treadmill exercise provided restorative effects on motor coordination [22].

There are studies showing that exercise improves mood [23,41], and it even reduces anxiety in humans [24]. However, there is conflicting information regarding the alteration of anxiety in

exercising animals. In other words, many studies report that exercise decreases anxiety, while other researches report that exercise increases anxiety [25,26]. The study by Pietrelli et al. reported that moderate-intensity treadmill exercise reduced anxiety in rodents [11]. However, the study by Burghardt et al. reported that exercise had no effect on anxiety [27]. In our study, we found that moderate-intensity forced treadmill exercise reduces anxiety, a symptom of PD. Because parameters for locomotor activity [total distance and velocity of movement] decreased in animals with the MPTP injection in OFT [28] and spent more time in the peripheral area than in the middle region [29] are findings showing that anxiety develops. However, the results of the EPM test showed that anxiety did not decrease in the Parkinson's model group that exercised. Because the MPTP+EXE group spent more time in closed arms. It was known that the EPM test causes more anxiety in mice [30]. In other words, it is thought that the curative effect of forced exercise is relatively less at higher anxiety levels. In one study, the level of corticosterone, known as the stress hormone, was lower in the group that volunteered for 10 days compared to the groups that did the forced treadmill or forced spinning wheel exercise. Researchers have stated that voluntary exercise works like a reward system and increases motivation, and accordingly, corticosterone levels do not increase [31].

The effect of different types of exercise on brain neurotransmitters has been investigated for many years. It is known in the literature that both central dopaminergic and serotonergic activities change depending on exercise [32]. A deficiency of the dopamine neurotransmitter is accountable for the clinical symptoms of PD [33]. There is conflicting information in the published literature regarding the effect of treadmill exercise on dopamine levels in the striatum. Many scientific researches have reported that treadmill exercise increases dopamine levels in the striatum [32,34], while others do not [32,35]. We found that striatal dopamine levels were significantly decreased in the MPTP group compared to the control group after MPTP-induced degeneration, while no difference was found in the other groups in this research. It has been thought that the improvement in motor coordination may be related to the increased dopamine level with exercise.

There are also contradictions in the literature regarding the striatal levels of serotonin. Many scientific researches have reported that treadmill exercise elevates the level of serotonin in the striatum [36], while others have verified that there is no effect of exercise on the level of serotonin [37]. Also, other studies have stated that exercise reduces the level of serotonin [35,38]. Chaouloff et al. have done many studies examining the relationship between exercise and serotonin. These scientists gave rodents substances that affect dopamine activity and examined the relationship between exercise and serotonin levels in their study. As a result of this study, they found that dopamine metabolism increased in areas rich in serotonin [34]. In fact, except for one study [39], Chaouloff et al. reported that they could not find any change in serotonin levels in their other studies [32,40]. It has been reported that while physical exercise increases serotonin synthesis and metabolism in the midbrain, it does not change serotonin synthesis in the striatum [32]. We did not find a significant difference between the groups in the level of striatal serotonin in our study (Figure not seen). However, serum serotonin levels were significantly reduced in only the Parkinson's model group compared with the healthy control group. Again, no significant change was found in the exercise groups.

CONCLUSION

In conclusion, while moderate-forced treadmill exercise increased dopamine levels in the striatum in the Parkinson's mouse model, it did not cause a change in serotonin levels in the striatum. However, the decrease in serum serotonin level was determined only in the MPTP group. During exercise, different neurotransmitters are secreted in many parts of the brain, and these neurotransmitters exert different effects in different regions. Further studies at the molecular level are needed to present the activities of all neurotransmitters in different brain regions and their interactions with each other.

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REFERENCES

1- Damier P, Hirsch EC, Agid Y, & Graybiel AM (1999) The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain: a journal of neurology. 122 (Pt 8), 1437–1448. https://doi.org/10.1093/brain/122.8.1437

2- Ibraheem A, Ogeleyinbo I, Emmanuel K, Idar E, Oyewale J, Kunlere O, Olabiyi A.A., Adeniyi P.A (2019) Assessment of the Impacts of Selenocysteine on the Dopaminergic System in the Substantia Nigra and Striatum of 6-OHDA Parkinson's Disease Rat Model. IBRO Reports. 7:25. https://doi.org/10.1016/j.ibror.2019.09.053

3- Ito H (2015) Symptoms and signs of Parkinson's disease and other movement disorders. Deep Brain Stimulation for Neurological Disorders: Theoretical Background and Clinical Application. 21-37. ISBN: 978-3-319-08476-3

4- Gorton LM, Vuckovic MG, Vertelkina N, Petzinger GM, Jakowec MW, & Wood RI (2010) Exercise effects on motor and affective behavior and catecholamine neurochemistry in the MPTP-lesioned mouse. Behavioural brain research. 213(2):253–262. https://doi.org/10.1016/j.bbr.2010.05.009

5- Walsh,K, & Bennett G (2001) Parkinson's disease and anxiety. Postgraduate medical journal. 77(904), 89–93. https://doi.org/10.1136/pmj.77.904.89

6- Schuurman AG, van den Akker M, Ensinck KT, Metsemakers JF, Knottnerus JA, Leentjens AF, & Buntinx, F (2002) Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology. 58(10):1501–1504. https://doi.org/10.1212/WNL.58.10.1501

7- Chaudhuri KR, Healy DG, Schapira AH & National Institute for Clinical Excellence (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. The Lancet. 5(3):235–245. https://doi.org/10.1016/S1474-4422(06)70373-8

8- Laux G. (2022) Parkinson and depression: review and outlook. Journal of neural transmission. 129(5-6):601–608. https://doi.org/10.1007/s00702-021-02456-3

9- Frouni I, Kwan C, Belliveau S, Huot P (2022) Cognition and serotonin in Parkinson's disease. Progress in brain research. 269(1):373–403. https://doi.org/10.1016/bs.pbr.2022.01.013

10- Pedersen BK, Saltin B. (2006) Evidence for prescribing exercise as therapy in chronic disease. Scandinavian journal of medicine & science in sports. 16(Suppl 1):3–63. https://doi.org/10.1111/j.1600-0838.2006.00520.x

11- Pietrelli A, Lopez-Costa J, Goñi R, Brusco A, Basso N (2012) Aerobic exercise prevents age-dependent cognitive decline and reduces anxiety-related behaviors in middle-aged and old rats. Neuroscience. 202:252–266. https://doi.org/10.1016/j.neuroscience.2011.11.054

12- Jackson-Lewis V, Przedborski S (2007) Protocol for the MPTP mouse model of Parkinson's disease. Nature protocols. 2(1):141–151. https://doi.org/10.1038/nprot.2006.342

13- Duty S, Jenner P (2011) Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. British journal of pharmacology. 164(4):1357–1391. https://doi.org/10.1111/j.1476-5381.2011.01426.x

14- Tuon T, Valvassori SS, Lopes-Borges J, Luciano T, Trom CB, Silva LA, Quevedo J, Souza CT, Lira FS, Pinh, RA (2012) Physical training exerts neuroprotective effects in the regulation of neurochemical factors in an animal model of Parkinson's disease. Neuroscience. 227:305–312. https://doi.org/10.1016/j.neuroscience.2012.09.063

15- Lau YS, Patki G, Das-Panja K, Le WD, Ahmad SO (2011) Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. The European journal of neuroscience. 33(7):1264–1274. https://doi.org/10.1111/j.1460-9568.2011.07626.x

16- Kobayashi T, Araki T, Itoyama Y, Takeshita M, Ohta T, Oshima Y (1997) Effects of L-dopa and bromocriptine on haloperidol-induced motor deficits in mice. Life sciences. 61(26):2529–2538. https://doi.org/10.1016/s0024-3205(97)01007-2

17- Ogawa N, Mizukawa K, Hirose Y, Kajita S, Ohara S, Watanabe Y (1987) MPTP-induced parkinsonian model in mice: biochemistry, pharmacology and behavior. European neurology. 26(Suppl 1):16–23. https://doi.org/10.1159/000116351

18- Kayir H, Uzbay IT (2004) Evidence for the role of nitric oxide in caffeine-induced locomotor activity in mice. Psychopharmacology. 172(1):11–15. https://doi.org/10.1007/s00213-003-1625-5

19- Rozas G, Guerra MJ, Labandeira-García JL (1997) An automated rotarod method for quantitative drug-free evaluation of overall motor deficits in rat models of parkinsonism. Brain research. Brain research protocols. 2(1):75–84. https://doi.org/10.1016/s1385-299x(97)00034-2

20- Rozas G, López-Martín E, Guerra MJ, Labandeira-García JL (1998) The overall rod performance test in the MPTP-treated-mouse model of Parkinsonism. Journal of neuroscience methods. 83(2):165–175. https://doi.org/10.1016/s0165-0270(98)00078-8

21- Simon DK, Tanner CM, Brundin P (2020) Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. Clinics in geriatric medicine. 36(1):1–12. https://doi.org/10.1016/j.cger.2019.08.002

22- Doğru NÖ, Bal R (2019) Effects of Voluntary and forced exercise on anxiety-related behaviours and motor activity in Parkinson mouse model. Eur J Ther. 25(2):97-103. https://doi.org/10.5152/EurJTher.2018.18011

23- Dunn AL, Reigle TG, Youngstedt SD, Armstrong RB, Dishman RK (1996) Brain norepinephrine and metabolites after treadmill training and wheel running in rats. Medicine and science in sports and exercise. 28(2): 204–209. https://doi.org/10.1097/00005768-199602000-00008

24- Carek PJ, Laibstain SE, Carek SM (2011) Exercise for the treatment of depression and anxiety. International journal of psychiatry in medicine. 41(1):15–28. https://doi.org/10.2190/PM.41.1.c

25- Ozbeyli D, Gokalp AG, Koral T, Ocal OY, Dogan B, Akakin D, Yuksel M, Kasimay O (2015) Protective effect of exercise and sildenafil on acute stress and cognitive function. Physiology & behavior. 151:230–237. https://doi.org/10.1016/j.physbeh.2015.07.030

26- Motaghinejad M, Fatima S, Karimian M, Ganji S (2016) Protective effects of forced exercise against nicotine-

induced anxiety, depression and cognition impairment in rat. Journal of basic and clinical physiology and pharmacology. 27(1):19–27. https://doi.org/10.1515/jbcpp-2014-0128

27- Burghardt PR, Fulk LJ, Hand GA, Wilson MA (2004) The effects of chronic treadmill and wheel running on behavior in rats. Brain research. 1019(1-2):84–96. https://doi.org/10.1016/j.brainres.2004.05.086

28- Taylor TN, Greene JG, Miller GW (2010) Behavioral phenotyping of mouse models of Parkinson's disease. Behavioural brain research. 211(1):1–10. https://doi.org/10.1016/j.bbr.2010.03.004

29- Johnson RA (2016) Voluntary Running-Wheel Activity, Arterial Blood Gases, and Thermal Antinociception in Rats after 3 Buprenorphine Formulations. J Am Assoc Lab Anim Sci. 55(3):306–311.PMCID: 27177564

30- Erdogan F, Kucuk A, Gölgeli A, Liman N, Sagsoz H (2007) Assesment of The Effect of Pentylenetetrazole-induced Kindling on Behavior and Emotional Learning in Rats. EPILEPSI. 13(2):66-72.

31- Sasaki H, Hattori Y, Ikeda Y, Kamagata M, Iwami S, Yasuda S, Tahara Y, Shibata S (2016) Forced rather than voluntary exercise entrains peripheral clocks via a corticosterone/noradrenaline increase in PER2:LUC mice. Scientific reports. 6:27607. https://doi.org/10.1038/srep27607

32- Meeusen, R., & De Meirleir, K. (1995). Exercise and brain neurotransmission. Sports medicine (Auckland, N.Z.), 20(3), 160–188. https://doi.org/10.2165/00007256-199520030-00004

33- Tang C, Liu M, Zhou Z, Li H, Yang C, Yang L, Xiang J (2023) Treadmill Exercise Alleviates Cognition Disorder by Activating the FNDC5: Dual Role of Integrin αV/β5 in Parkinson's Disease. International journal of molecular sciences. 24(9):7830. https://doi.org/10.3390/ijms24097830

34- Chaouloff F, Laude D, Merino D, Serrurrier B, Guezennec Y, Elghozi JL (1987) Amphetamine and alpha-methyl-p-tyrosine affect the exercise-induced imbalance between the availability of tryptophan and synthesis of serotonin in the brain of the rat. Neuropharmacology. 26(8):1099–1106. https://doi.org/10.1016/0028-3908(87)90254-1

35- Lukaszyk A, Buczko W, Wiśniewski K (1983) The effect of strenuous exercise on the reactivity of the central dopaminergic system in the rat. Polish journal of pharmacology and pharmacy. 35(1):29–36. PMID: 6684280

36- Bailey SP, Davis JM, Ahlborn EN (1993) Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. Journal of applied physiology. 74(6):3006–3012. https://doi.org/10.1152/jappl.1993.74.6.3006

37- Chaouloff F, Laude D, Elghozi JL (1989) PHysical exercise: evidence for differential consequences of tryptophan on 5-HT synthesis and metabolism in central serotonergic cell bodies and terminals. Journal of neural transmission. 78(2):121–130. https://doi.org/10.1007/BF01252498

38- Hellhammer DH, Hingtgen JN, Wade SE, Shea PA, Aprison MH (1983) Serotonergic changes in specific areas of rat brain associated with activity--stress gastric lesions. Psychosomatic medicine. 45(2):115–122. https://doi.org/10.1097/00006842-198305000-00004

39- Cicardo VH, Carbone SE, de Rondina DC, Mastronardi IO (1986) Stress by forced swimming in the rat: effects of mianserin and moclobemide on GABAergic-monoaminergic systems in the brain. Comparative biochemistry and physiology. C, Comparative pharmacology and toxicology. 83(1):133–135. https://doi.org/10.1016/0742-8413(86)90025-3

40- Acworth I, Nicholass J, Morgan B, Newsholme EA (1986) Effect of sustained exercise on concentrations of plasma aromatic and branched-chain amino acids and brain amines. Biochemical and biophysical research communications. 137(1):149–153. https://doi.org/10.1016/0006-291x(86)91188-5

41- Kaplan DS, Bozkurt M (2018) Investigating the most commonly applied lactate recovery method according to the positions in football. Eur J Ther. 24(4):224-229. https://doi.org/10.5152/EurJTher.2018.463

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Original Research

Bibliometric Analysis of the Published Studies on the Kindling Model between 1980 and 2023

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ABSTRACT

Objective: Kindling is an animal model of epilepsy induced by electrical stimulation of the brain. The present study aimed to present a different perspective with a bibliometric approach by using the literature data on the "Kindling model" related keywords in the Web of Science (WoS) online database between 1980 and 2023.

Methods: The bibliometric data were obtained from the online database WoS and analyzed and visualized with the VoS Viewer Program. The bibliometric datasets were analyzed and visualized regarding article productivity numbers according to years, article productivity numbers according to countries, the most used keywords according to authors, and cross-country cooperation.

Results: Considering the results of the analysis of the published datasets, 2022 was determined as the year with the highest article productivity, and an acceleration was observed in the publication increase rate on the subject in general. When the order of the countries in the top three in the number of article productivity was examined, the USA, Germany, and Japan are the main countries, respectively. The most used keywords by the authors were determined as "Epilepsy", "Kindling", and "Hippocampus". In the cooperation among countries, it was found that the USA, Germany, and Japan had more cooperation with other countries, respectively.

Conclusion: This study will contribute to the literature by providing a detailed understanding of the research basis, relevant research results, current research boundaries and main research focus in the Kindling Model.

Keywords: kindling model, epilepsy, bibliometric

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures [1] as a common disease associated with chronic brain dysfunction [2]. More than 2/3 of epilepsy patients are not treated. More than a third of premature deaths can be attributed either directly or indirectly to epilepsy [3]. The course of epilepsy, its etiology, and the range of risk factors vary according to age and geographical distribution. Congenital, developmental, and genetic conditions are most often associated with the development of epilepsy during childhood, adolescence, and early adulthood. In underdeveloped countries, endemic infections are associated with epilepsy. The presence of epilepsy in the family's genetic history increases risk factors and might suggest that epilepsy has a very complex etiology [4]. A lot of research has been done in the last two decades to distinguish the mechanisms that cause the epilepsy disease process and to inhibit it [5]. Many different methods were used to better understand the complex mechanism of epilepsy and to develop treatments against it. One of these research methods is experimental animal models [6].

Kindling is an animal model of chronic epilepsy that has been extensively and thoroughly investigated to better understand the course of epileptogenesis and to uncover new anti-epileptic compounds as the most studied experimental animal model of epilepsy with complex processes [7]. The cellular and molecular changes that occur in Kindling-modeled experimental animals gradually provide extensive data on epilepsy [8]. A repeated and regular stimulus is applied to the brain regions of the experimental animals in which the Kindling Model will be created. As the time progresses, motor seizures are observed with the stimulus. As time progresses, the same stimulus results in intense limbic and clonic motor seizures. In 1961, Sevillano first discovered that repeated administration of this stimulus to the hippocampal region of the brain increases the intensity of seizures. The first stimulus occurs with little change in behavior or electrical brain activity. Additional stimulations result in an electrical seizure recorded after focal discharge or by electroencephalogram (EEG) [7]. This form of stimulation provides a very good opportunity to study the changes in neuronal networks. The cellular and

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molecular changes occurring in Kindling-modeled experimental animals gradually provide extensive data on epilepsy [8].

In the present study, the purpose was to examine the studies conducted on the Kindling Model with bibliometric analysis. The word bibliometrics is of Greek origin and entered the literature by Alan Pritchard in 1969 with his study Statistical Bibliography or Bibliometrics [9]. Bibliometric analysis is the quantitative analysis of publications to better understand research outputs using mathematical and statistical methods [10]. Bibliometric data analysis sets provide important data on determining the scientific effect and course of research through performance analyses and bibliometric networks [11]. Examinations made through online databases provide a great convenience for us to see the current state of academic studies, their scientific volumes, and their effects, including citations [12]. Bibliometrics is very useful for developing a broad overview of resources in study areas or trends in the country [13]. A scientific dataset analysis provides a holistic approach because it includes a broad scope of academic research providing an objective analysis [14]. The study was planned to visualize a quantitative analysis of the research areas made with the Kindling Model, countries, cross-country cooperation, and the most used keywords of the authors. This research aims to examine the literature on the kindling model, which has been widely used in modeling in recent years, by using bibliometric data analysis method.

METHODS

Bibliometrics is a field of study that applies mathematical and statistical techniques to examine publication patterns in the distribution of information and a set of tools that researchers might employ to analyze published data [15]. Bibliometric analysis includes a set of statistical methods applied to detect the changes in the framework of the subject in scientific studies, trends and originality of publications [16,17].

1. Database

An online WoS database was used to analyze bibliometric data in the present study. The WoS database was searched with the keyword "Kindling Model" between 1980 and 2023. Database coverage is an important component of a bibliometric study [18]. The WoS database was preferred in the study because it covers more research compared to other online databases.

2. Data Analysis

The datasets of the bibliometric analysis program "Bibliometric R-package" were analyzed. The ".bib" files were converted into "bibtex" files by using the Bibliometric R-package (or R Studio) Software. The data and descriptive analyzes were classified, collected one by one, and loaded into the Bibliometric R-package Program to create science maps and statistical graphs.

Main Points

- Epilepsy is a chronic neurological disorder characterized by re-current seizures.
- Kindling is an animal model of epilepsy induced by electrical stimulation of the brain.
- The bibliometric datasets were examined and the current data of the publications, the trends of research activities, and the changes in the literature in recent years were analyzed in the present study.

3. VOSviewer

The study presents a further graphical analysis of bibliographic data by using the VOSviewer Software. VOSviewer can analyze and visualize bibliometric network data such as citation relationships between publications, journals and countries, and collaborative relationships between researchers [19]. The VOSviewer (version 1.6.14) Software was preferred to visualize network maps of bibliometric datasets. Also, the most productive cooperation between countries on the subject and the relationships between the most frequently used keywords by the authors were analyzed and visualized by using this software.

4. Limitations

In the present study, the data analysis was made by using the Web of Science (WoS) Database, which is accepted as the most widely used and most comprehensive scientific database in the world, and a constraint was formed accordingly. Also, the editing dates of the datasets in the study covered the years between 1980 and 2023 (the date of accessing the WoS database: 03.02.2023).

RESULTS

In the present study, which was conducted with the bibliometric data analysis system, analyses were made under the headings such as the number of publications, cooperation between countries, and the most frequently used keywords by the authors, and the data obtained were visualized with graphics and tables. According to the Web of Science (WoS), online database results of the publications on the keywords "Kindling Model" between 1980 and 2023, 307 sources (Journals, Books, etc.), and 1053 documents were determined by bibliometric data analysis method. The distributions of these data sets are; 825 articles, 2 articles; book chapters, 45 Articles; proceedings paper, and 84 reviews.The results of 2855 Keywords Plus (ID) and 2142 Author's Keywords (DE) analyses appeared. The number of authors conducting studies on this subject was 3263, the number of studies with a single author was 54, and the number of studies with more than one author was 3209 (Table 1).

Table 1. Main statistical information of kindling model articles in WOS.

Description	WOS
Timespan	1980:2023
Sources (Journals, Books, etc)	307
Documents	1053
Average years from publication	15.7
Average citations per documents	30.85
Average citations per year per doc	1.931
Document Types	
Article	825
Article; book chapter	2
Article; proceedings paper	45

Review	84
Document Contents	
Keywords Plus (ID)	2855
Author's Keywords (DE)	2142
Authors	
Authors	3263
Author Appearances	4858
Authors of single-authored documents	54
Authors of multi-authored documents	3209
Authors Collaboration	
Documents per Author	0.323
Authors per Document	3.1
Co-Authors per Documents	4.61
Collaboration Index	3.27

The beginning year of the datasets of this study was 1980, and the number of publications related to the "Kindling Model" was determined as only 2. It was found that the highest number of articles was reached with 51 articles in 2022. The analysis of the dataset of the study was evaluated until 2023 (03.02.2023). When the datasets were analyzed, the acceleration in the increase in the number of articles published by years is given in Figure 1 (Fig. 1). According to WoS, the process that started with 2 studies in 1980, when the first study was conducted, appeared in double-digit numbers in 1991 (12 articles), but continued to increase in the following years, displaying a fluctuating graphic course. It reached the highest number of article publications in 2022 (51 articles). A slight decrease was observed in the number of articles (20 articles) in 2012. The number of articles published in the period until January 2023 (until 03.02.2023) was found to be 825 (Figure1).

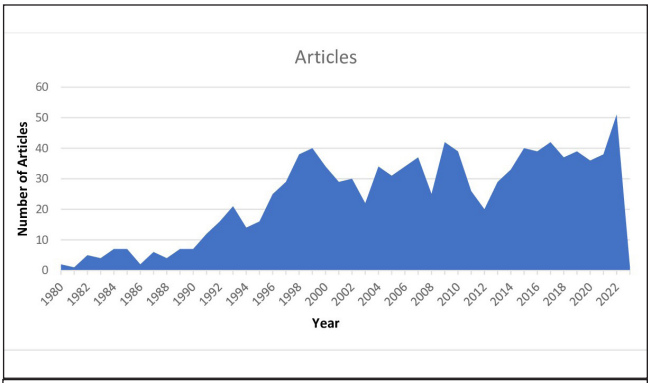

Figure 1. Illustration of the distribution of articles by year in WoS between 1980 and 2023 by years.

In this study, the analyzes of the most used keywords by the authors were made to follow the current data in the literature and the dynamics according to the years of the studies for which the Kindling Model was created. In the search results made with the term "Kindling Model" in the Web of Science (WoS) online database, where the bibliometric data set information was obtained, it was found that a total of 2142 different keywords were used by the authors. When Figure 2 is examined, it is seen that the word it represented was used more frequently as the size of the knots increased. The line thicknesses between the nodes show the interaction between the keywords. In this context, the interaction can be expressed more as the line thicknesses between the nodes increase. As a result of the analysis of this, the most used keywords were found to be; "epilepsy" (327), "Kindling" (268), and "hippocampus" (97). In Figure 2, each node represents a keyword, and the "epilepsy" node, which is visualized in green as the largest, appears in the center of the graph (Figure 2).

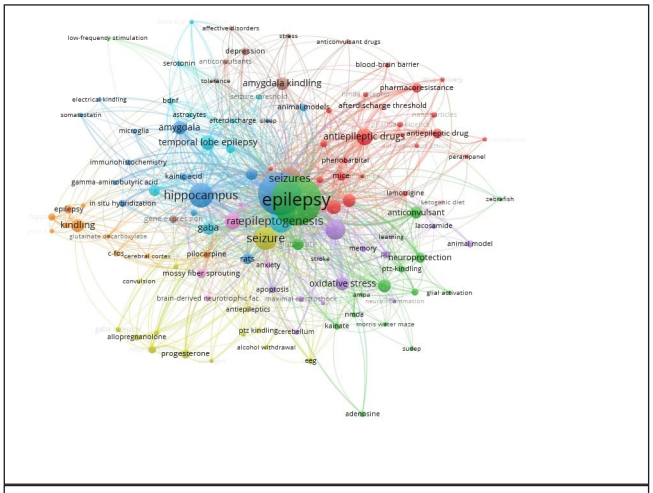

Figure 2. The Most Frequently Used Author's Keywords Between 1980 and 2023.

Keywords are important structures that constitute the contents and basis of publications. Keywords play important roles in the number of citations of articles, evaluating their effects, and increasing their availability. The most frequently used keywords by the authors were analyzed in the WoS Online Database in the present study. In this context, the most frequently used keywords by the authors were determined as "Epilepsy", "Kindling" and "Hippocampus", followed by the words "seizure" and "epileptogenesis", respectively. The first 10 words most frequently used by the authors are given in Figure 3 in order of frequency of use (Figure 3). The word cloud is one of the most used methods for the visualization of datasets. The purpose of the word cloud is to make the most used words in publications more visible. As a result of the analysis made with the term "Kindling Model" in the WoS database, the cloud of the most used words by the authors is given in Figure 4. The frequency of use of words increased as the size of the word grew according to its proximity to the central settlement. The word "Epilepsy", written in the largest font and located in the center, appeared in Figure 4. The word in second place in size is seen as "Kindling". The third word most commonly used by the authors was found to be "hippocampus" (Figure 4). Table 2 shows the order of the top 10 countries within the scope of the findings obtained according to the number of article publications and countries, the number of single article productivity, and the number of multiple articles. As well as the number of article productivity, the number of individual article productivity, and the number of multiple article productivity of the countries are also important compared to the countries. The

order of the countries in the first three ranks according to the number of articles were as follows; USA (196), Germany (111), and Japan (89). When the countries in the top three ranks according to the number of article productivity alone were evaluated, the same country ranking was seen, similar to the article productivity title. The first three countries in the article's productivity ranking alone were the USA (174), Germany (98), and Japan (89). In the multi-article productivity ranking, the USA (22) took first place, and Germany and Canada (13) took second place. It was also found that Japan and China [9] took third place. Also, when the ranking of the most cited countries was evaluated, the USA (10316) ranked first, Germany (4869) ranked second, and Canada (2146) ranked third (Table 2). The cooperation between countries according to publication production on the "Kindling Model", which is the subject of bibliometric research, is given in Figure 5. The clusters in which the countries are shown in different colors and sizes. The lines between clusters show the inter-country relationship, and the thickness of the line shows a higher level of cooperation. Clusters that depict countries around the map show poor cooperation with other clusters. When the countries towards the center of the map were examined, it was found that the USA was in a central place with the largest cluster image. After the USA, it was seen that the nodes of Germany and Canada were more prominent than other countries. The cooperation of these countries appears with thicker lines, which shows that they had a greater share in the cooperation between countries on the "Kindling Model" (Figure 5).

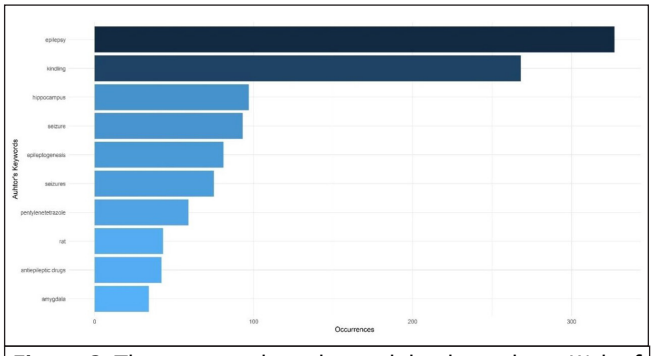

Figure 3. The most used words graph by the authors; Web of Science categorie from 1980 to 2023.

Figure 4. Cloud view of the most used words by the authors.

Table 2. Corresponding Author's Country.

No	Country	Articles	SCP	MCP	TC
1.	USA	196	174	22	10316
2.	GERMANY	111	98	13	4869
3.	JAPAN	89	80	9	2108
4.	CHINA	76	67	9	1170
5.	IRAN	64	63	1	760
6.	CANADA	55	42	13	2146
7.	INDIA	41	37	4	702
8.	POLAND	36	29	7	525
9.	TURKEY	35	31	4	357
10.	BRAZIL	28	24	4	312

SCP: Single Country Publications.
MCP: Multiple Country Publications.
TC: Total Citations.

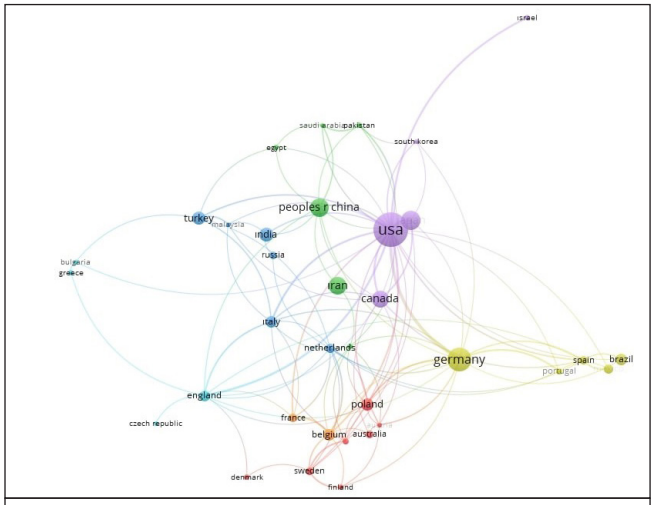

Figure 5. The cooperation among the countries.

DISCUSSION

Epilepsy is a brain disorder with a complex etiology, progressing with epileptic seizures [20]. Risk factors that accompany epilepsy are stroke, brain tumors, fever, and genetic epilepsy [21]. The Kindling Model in rats is the most reliable and widely used model. The positive characteristics of the model include ease of induction and spontaneous seizures that are easy to detect [22]. The purpose of using bibliometric dataset analysis are to reveal article productivity, publisher performance, cooperation networks among countries or authors, and the originality and trends of scientific studies [23]. The bibliometric datasets were examined and the current data of the publications, the trends of research activities, and the changes in the literature in recent years were analyzed in the present study. The results of the bibliometric analysis regarding the use of the concept of the "Kindling Model" in the scientific field and the methodological research trends in the last 43 years (1980; 2023) were determined in the study. In this study that used the Web of Science (WOS) database, the analyzes were made under the headings such as the number of publications, cooperation between countries, and

the most frequently used keywords by the authors, and the data obtained were visualized with graphics and tables. The place and changes of the 43-year (1980; 2023) Kindling Model concept in the literature were presented to the scientific platform with a comprehensive bibliometric data analysis. The "Kindling Model" keywords, which started publication life with two documents in 1980, increased significantly in the number of publications after 1996. It was found that the highest number of publications was reached in 2022 (50). According to the results of these datasets, it was observed that the number of publications on the subject accelerated in recent years and continues to increase. In the context of this result, it is seen that the studies conducted on the "Kindling Model" are a current issue in the scientific field literature and the tendency of the researchers to this subject is increasing.

Keywords are generally defined as important research themes for the analysis of datasets in bibliometric studies [24]. The number of keywords used by the authors in this study was presented as 2142 (Table 1). The most frequently used keywords by the most cited authors were found to be "epilepsy", "kindling" and "hippocampus" in the present study (Figure 3). The analysis of the keywords, trends, and themes identified within the scope of this study will serve as a guideline for future scientific research. The number of articles on productivity rises to high numbers with cross-country cooperation and close collaboration between authors in the Kindling Model area. The top three countries in article productivity were found to be the USA (196), Germany (111), and Japan (89), respectively. It was concluded that the cooperation network between countries is also very developed in the same countries. It is seen in these datasets that the countries with high cooperation also have a high number of article productivity. When the obtained datasets are reviewed, it can be argued that the number of articles can gain momentum in case of increased cooperation between countries in the field of "Kindling Model" keywords. A total of 1053 sources (documents) and analyses of 3263 authors' studies were included in the present study according to the Web of Science (Wos) online database datasets with the keywords "Kindling Model" between 1980 and 2023 (Table 1). Although there are few studies on the subject of epilepsy conducted with the literature review method on scientific platforms, no bibliometric research, which is a detailed analysis method that deals with the Kindling Model, was found.

CONCLUSION

The findings of the present study provide an overview of the current literature data and the trend of studies with Kindling Model keywords in the coming years. The purpose of the study was to provide a comprehensive perspective on the studies that were conducted in the past and will be conducted in the future with the analysis of the Kindling Model keywords with the datasets. These guidelines can be used in future studies (theses, projects, articles, etc.). In light of this, researchers can plan the course of their studies, their relationships to sub-branches, and critical situations such as not repeating some aspects in this field. This bibliometric study on the Kindling model may offer different perspectives to other studies in the same field. Considering the results of the study, it can be argued that the field of the Kindling Model is a current study area and academic interest is increasing in this field with each passing day. In this context, it is expected that this study will make important contributions in emphasizing the need for the interaction between countries and authors, keyword analysis, and evaluating different approaches to the subject in studies to be conducted in the field of the Kindling Model.

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REFERENCES

1. Samokhina E and Samokhin A (2018) Neuropathological profile of the pentylenetetrazol (PTZ) kindling model. International Journal of Neuroscience. 128(11):1086-1096. https://doi.org/10.1080/00207454.2018.1481064

2. Vinogradova LV and Van Rijn CM (2008) Anticonvulsive and antiepileptogenic effects of levetiracetam in the audiogenic kindling model. Epilepsia. 49(7):1160-1168. https://doi.org/10.1111/j.1528-1167.2008.01594.x

3. Thijs RD, Surges R, O'Brien TJ and Sander JW (2019) Epilepsy in adults. The lancet. 393(10172):689-701. https://doi.org/10.1016/S0140-6736(18)32596-0

4. Sander JW (2003) The epidemiology of epilepsy revisited. Current opinion in neurology. 16(2):165-170. https://doi.org/10.1097/00019052-200304000-00008

5. Singh N, Saha L, Kumari P, Singh J, Bhatia A, Banerjee D and Chakrabarti A (2009) Effect of dimethyl fumarate on neuroinflammation and apoptosis in pentylenetetrazol kindling model in rats', Brain Research Bulletin. 144:233-245. https://doi.org/10.1016/j.brainresbull.2018.11.013

6. Anissian D, Ghasemi-Kasman M, Khalili-Fomeshi M, Akbari A, Hashemian M, Kazemi S and Moghadamnia AA (2018) Piperine-loaded chitosan-STPP nanoparticles reduce neuronal loss and astrocytes activation in chemical kindling model of epilepsy. International journal of biological macromolecules. 107:973-983. https://doi.org/10.1016/j.ijbiomac.2017.09.073

7. Kraus JE (2000) Sensitization phenomena in psychiatric illness: lessons from the kindling model. The Journal of neuropsychiatry and clinical neurosciences. 12(3):328-343. https://doi.org/10.1176/jnp.12.3.328

8. Gorter JA, van Vliet EA, da Silva FHL (2016) Which insights have we gained from the kindling and post-status epilepticus models?. Journal of neuroscience methods. 260;96-108. https://doi.org/10.1016/j.jneumeth.2015.03.025

9. Adanır SS, Bahşi İ, Orhan M, Cihan ÖF (2020) Bibliometric analysis of articles published in Anatomy, the official publication of the Turkish Society of Anatomy and Clinical Anatomy between 2007-2018. Anatomy. 14(1):39-43. https://doi.org/10.2399/ana.20.019

10. Rubio C, Luna R, Ibarra-Velasco M, Lee Á (2021) Epilepsy: A bibliometric analysis (1968-2020) of the Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suarez" in Mexico. Epilepsy&Behavior. 115:107676. https://doi.org/10.1016/j.yebeh.2020.107676

11. Ni X-J, Zhong H, Liu Y-X, Lin H-W, Gu Z-C (2022) Current trends and hotspots in drug-resistant epilepsy research: Insights from a bibliometric analysis. Frontiers in Neurology. 13. https://doi.org/10.3389/fneur.2022.1023832

12. Morandi G, Guido D, Tagliabue A (2015) A bibliometric study of scientific literature on the dietary therapies for epilepsy in Scopus. Nutritional Neuroscience. 18(5):201-209. https://doi.org/10.1179/1476830514Y.0000000118

13. Hood WW, Wilson CS (2001) The literature of bibliometrics, scientometrics, and informetrics. Scientometrics. 52(2);291-314. https://doi.org/10.1023/A:1017919924342

14. Cardona JCD, Lobo RR, Mora VR (2002) La investigación regional en España: un análisis bibliométrico. Investigaciones Regionales Journal of Regional Research. 1:107-138.

15. Danvila-del-Valle I, Estévez-Mendoza, C, Lara FJ (2019) Human resources training: A bibliometric analysis. Journal of Business Research. 101; 627-636. https://doi.org/10.1016/j.jbusres.2019.02.026

16. Rey-Martí A, Ribeiro-Soriano D, Palacios-Marqués D (2016) A bibliometric analysis of social entrepreneurship. Journal of Business Research. 69(5):1651-1655. https://doi.org/10.1016/j.jbusres.2015.10.033

17. Bahşi İ, Adanır SS, Kervancıog P, Orhan M, Govsa F (2021) Bibliometric Analysis of Turkey's Research Activity in the Anatomy and Morphology Category from the Web of Science Database. Eur J Ther. 27(4):268-280. https://doi.org/10.5152/eurjther.2021.20108

18. Thompson DF (2018) Bibliometric Analysis of Pharmacology Publications in the United States: A State-Level Evaluation. J. Sci. Res. 7(3):167-172. https://doi.org/10.5530/jscires.7.3.27

19. Van Eck NJ, Waltman L (2014) Visualizing bibliometric networks' in Measuring scholarly impact. Springer. 285-320. https://doi.org/10.1007/978-3-319-10377-8_13

20. Cheng H, Wang Y, Chen J, Chen Z (2020) The piriform cortex in epilepsy: what we learn from the kindling model.Experimental neurology. 324;113137. https://doi.org/10.1016/j.expneurol.2019.113137

21. Guna V, Saha L, Bhatia A, Banerjee D, Chakrabarti A (2018) Anti-oxidant and anti-apoptotic effects of berberine in pentylenetetrazole-induced kindling model in rat. Journal of Epilepsy Research. 8(2):66. https://doi.org/10.14581/jer.18011

22. Meng X, Wang F, Li C (2014) Resveratrol is neuroprotective and improves cognition in pentylenetetrazole-kindling model of epilepsy in rats. Indian journal of pharmaceutical sciences. 76(2):125.

23. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM (2021) How to conduct a bibliometric analysis: An overview and guidelines. Journal of Business Research. 133:285-296. https://doi.org/10.1016/j.jbusres.2021.04.070

24. Chen G, Xiao L (2016) Selecting publication keywords for domain analysis in bibliometrics: A comparison of three methods. Journal of Informetrics. 10(1):212-223. https://doi.org/10.1016/j.joi.2016.01.006

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Original Research

The Impact of Using Technological Devices on Mental and Physical Health in Adolescents

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ABSTRACT

Objectives: In recent years, adolescents spend increasingly more time on technologic devices such as smartphones, televisions, computers, and tablets. The aim of the present study was to investigate the relationship between the usage of digital technology and health-related problems among adolescents.

Methods: A cross-sectional exploratory study was conducted by using a face-to-face survey administered to a sample of students studying at 4 randomly chosen public middle school and 4 randomly chosen public high school in the city of Istanbul. In this study recruited 1147 volunteer adolescents. All participants were answered a questionnaire regarding the demographic characteristics, technological devices useage patterns and health-related problems.

Results: Most of the adolescents had smartphones (99.4%) and the fewest had game consoles (18.2%). The rate of using television and smartphone for more than two hours a day among adolescents was 13.1% and 28.4%, respectively. A decrease in sleep duration, increase in falling asleep time, distraction, fatigue, eating disorders and psychological symptoms were significantly more present for individuals using smartphone more than two hours. A positive and very weak relationship was detected between the duration of smartphone use and neck (r=0.096; p=0.002), wrist (r=0.079; p=0.008) and shoulder (r=0.069; p=0.021) pain. Also, positive and very weak relationship was detected between the duration of computer use and upper back (r=0.102; p=0.001), lower back (r=0.078; p=0.011) and shoulder (r=0.069; p=0.041) pain.

Conclusion: This study showed the most widely used technological device among adolescents is smartphones and it was observed that the excessive use of this device among adolescents is more associated with many different health-related problems than other technological devices.

Keywords: technological devices; adolescents; adolescents health; screen time; musculoskeletal pain, health problems

INTRODUCTION

In the 21st century, increasingly popular digital technologies are the Internet of Things (IoT), artificial intelligence (AI), big data, blockchain technology and 5G telecommunications networks. These technologies are interconnected with each other and benefit human life. Digital technology devices take part in an important role in adolescents' social lives as well as entertainment. In recent years, both academics and the public have expressed concern about the rise of digital technology, focusing on smartphones and social media use [1]. It is observed that children start using technological devices at a very early age (during the kindergarten period) and the use of technological devices get more common by age. The transition to new digital technological devices has resulted in changes in device using habits. For example, in 1970s, children used to start watching television at the age of four, however, today they start to interact with digital technological devices when they are four months old [2]. Digital technology use is a general term that covers various devices, services, and types of use. Adolescents now spend more time on television, smartphones, tablets, and social media than they spend in school [3]. This became the most important activity for kids and adolescents while they are not sleeping. The largest growth in digital media usage has occurred when watching online videos, using social media, and browsing websites. Of these activities, both tweens (8- to 12-year-olds) and teens (13- to 18-year-olds) report that watching videos on YouTube is their favorite form of digital media activity, followed in order of preference by Snapchat, TikTok, Instagram, Discord, Facebook, Twitter, Pinterest, and Reddit. On average, teens spend close to an hour and a half a day on social media. In the context of daily interaction, most people in Malaysia use WhatsApp, Facebook, TikTok, Instagram, Zoom, and Hangout Meet. Facebook and WhatsApp applications have become the choice that dominates

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80% to 90% of social media usage among adolescents as these applications are able to speed up communication relationships and be able to reach other users at a time. Excessive use of digital technologic devices such as television, video games, and computers poses a danger on the body and mental health of kids and adolescents [4].

Effects of technological devices such as violence and aggression, sleep problems, fear, antisocial behaviours, eating disorders, obesity, attention problems and addiction are of particular concern to those who are interested [5-8]. In literature, more studies are found in recent years which indicates a relationship between the use of mobile technological devices (laptops, tablets) and musculoskeletal disorders among children and teenagers [9,10]. Using smartphones causes impaired joint position sense in flexion, decreased deep cervical flexors activity, and forward head posture [11]. A study conducted with children aged 6-17 has found that the risk of obesity is two times more for children who use technological devices for a long time and do less physical activity [12]. Despite the importance of sleep-in optimal adolescent health and development, sleep deficits are prevalent in this age group. In a study has shown that night-time use of at least one screen-based media devices, and specifically mobile phones or televisions, was associated with adverse sleep outcomes, particularly insufficient sleep duration, late midpoint of sleep, and poor sleep quality among adolescents [13]. A research conducted in Singapore, it was identified that headache is more common among smartphone users and as the daily talk time increases as minutes (>60 mins) and frequency of headache also increases which is considered as a dose-response relationship [14]. Studies report that spending a long time with mobile phones causes problems such as eye strain, eye irritation, blurred vision, rash, and diplopia [15, 16]. Moreover, excessive digital technologic device use might cause postural defects, musculoskeletal pain, anxiety, depression, and a decrease in proprioception [9, 17-19]. On the other hand, studies have shown that addiction to smartphones can be an obvious risk factor for poor academic performance [20, 21].

Considering the recent technological growth observed in Turkey and that concomitant to this fact, there has been an increase in access to these technologies, it is believed that today's adolescents are more exposed to these resources. It is important to determine the potential negative effects of technological device use on the mental and physical health of adolescents. To the knowledge of the authors, there are limited studies in the literature evaluating the use of technological devices, duration of use, preferences, and health-related problems among school-age students in Turkey. Therefore, the aim of this study is to examine the relationship between the use of digital technology and health-related problems in adolescents in Turkey.

METHODS

This was an epidemiological and cross-sectional study, which was conducted in the 2018-2019 academic year with the students studying at 4 randomly chosen public middle school and 4 randomly chosen public high school in the city of Istanbul, Turkey. According to data provided by Provincial Ministry of National Education there are 25 public middle schools and 32 public high schools in the city of Istanbul, Turkey. In the 2018-2019 academic year an estimated 65,048 adolescents were enrolled in these 57 public middle and high school. The sample size, estimated population was calculated as 1290 by using Epi-Info [22] program with a 95% confidence interval; sampling error of %3; estimated prevalence of 50%; sample loss of 20% and a two-fold design effect. Study inclusion criteria; attending one of the selected schools and age between 11 and 18 years. Students who do not have parental consent or parental consent form, do not use any technological device, have any known systemic disease, and fill the questionnaire insufficiently were excluded from the study. In each school, participant classes were chosen by a simple randomized sampling method. Two classes were chosen from each grade and 20±3 volunteer students were chosen from each class.

Data Collection

Data collection form was prepared by the researcher in the light of current literature and the form was finalized after performing pretest with 34 students. The form is divided into three parts; The first part of the data collection form aimed to assess socio-demographic characteristics of the participants such as age, gender, height, weight, body-mass index, type of education, type of school. In this study, ≥85 X <95 percentile BMI was considered as overweight and ≥95 percentile BMI was considered as obese [23]. The second part of the data collection form aimed to assess technological device usage habits (number of technological devices in the participants' house and time of daily use). The third part of the data collection form aimed to assess health-related symptoms such as sleep status, musculoskeletal pain, concentration, tiredness, stress, and nutrition [7, 9, 13]. The musculoskletal pain level of the participants was evaluated by the Numeric Pain Rating Scale. In this scale, the evaluation of pain level starts with 0 (no pain) and ends with 10 (severe pain) [24].

Data Analysis

Data analysis was performed using SPSS software version 21.0 (SPSS inc., Chicago, IL, USA). Shapiro-Wilk test was used to identify whether the data was normally distributed. The data obtained from the results of this test were found to be non-normally distributed and non-parametric tests were used for analysis. For statistical analysis, parameters were defined by average (mean), standard deviation (SD), frequency (n) and percentage (%) values. For comparing demographic and clinic characteristics of the groups, the Mann- Whitney U test was used for quantitative data and the Chi-Square test was used for qualitative data. Spearman Correlation test was used to analyze the relationship between the data obtained from the participants. Correlation values are rated as: r ≥ 0.81–1.0 is excellent; 0.61–0.80, very good; 0.41–0.60, good; 0.21–0.40, weak; and 0.00–0.20, very weak) [25]. In all tests, a p-value <0.05 was considered statistically significant.

RESULTS

At the end of the study, in total 1189 adolescents were included in the study. However, 42 individuals were excluded due to errors when completing the questionnaire and excluded from the

analysis. The final sample consisted of 1147 adolescents forms 572 public middle schools and 575 public high schools. The demographic characteristics are described in Table 1. Mean age and BMI of the participants was 13.5±2.3 years and 20.1±3.5 kg/m2, respectively. However, 52.1% of the participants were female. A statistically significant difference was found in every parameter except gender (p=0.409) in terms of the type of school (p=0.001).

It was found in the study rate of being overweight and obese was 19.9% among public middle school students and 13.5% among public high school students. By comparing in terms of the type of school, middle school students were found to be more overweight-obese than high school students (p=0.001) (Figure 1).

By investigating the technological devices that students have at home, it was found that smartphone (99.4%) and television (TV) (99.2%) were found the most and game consoles (18.2%) were found the least (Figure 2). Among participants 28.4% reported using smartphones for more than 2 hours on average per day, 13.1% of the individuals reported watching TV for more than 2 hours per day. In addition, 88.7% and 72.6% of the participants stated they do not use game consoles and tablets, respectively (Table 2).

The comparison of using different technological devices for more than two hours and various health-related problems is given in Table 3. A decrease in sleep duration, increase in falling asleep time, distraction, exhaustion, eating disorders and psychological symptoms were significantly more present for individuals using smartphones more than two hours (p<0.05). Psychological symptoms were significantly more present for individuals using computers for more than two hours compared to those using computers for less than two hours (p<0.05). Fatigue was significantly more present for individuals using game consoles for more than two hours compared to those using game consoles for less than two hours (p<0.05).

A positive and very weak relationship was detected between the duration of smartphone use and neck (r=0.096; p=0.002), wrist (r=0.079; p=0.008) and shoulder (r=0.069; p=0.021) pain. A positive and very weak relationship was detected between the duration of computer use and upper back (r=0.102; p=0.001), lower back (r=0.078; p=0.011) and shoulder (r=0.069; p=0.041) pain. A positive and very weak relationship was detected between the duration of watching television and neck (r=0.059; p=0.041) pain. A positive and very weak relationship was detected between the daily time of using all devices and all musculoskeletal pain complaints (p<0.05) (Table 4).

Table 1. Demographic characteristics of participants

		Total (n=1147) Mean±SD n (%)	Middle school (n=572) Mean±SD n (%)	High school (n=575) Mean±SD n (%)	p
Gender	**Male**	598 (52.1)	305 (53.3)	292 (50.9)	0.409[a]
	Female	549 (47.9)	267 (46.7)	282 (49.1)	
Age (years)		13.56±2.31	11.56±1.25	15.55±1.09	**0.001**[b]
Weight (kg)		52.33±14.05	44.78±12.04	59.87±11.67	**0.001**[b]
Height (cm)		160.30±12.75	152.07±10.95	168.38±8.53	**0.001**[b]
BMI (kg/m$^{2)}$)		20.10±3.56	19.15±3.61	21.06±3.25	**0.001**[b]
Duration of daily exposure to technological devices, hour		4.55±1.64	4.39±1.30	4.70±1.94	0.053[b]

BMI; body mass index
[a] Chi-square test, p<0.05
[b] Mann Whitney U-test, p<0.05

Table 2. Distribution of participants' average daily use time of technological devices

	Never used n (%)	<1 hour n (%)	1-2 hours n (%)	3-4 hours n (%)	>4 hours n (%)
Mobile phone	148 (13.0)	277 (24.4)	387 (34.1)	223 (19.6)	100 (8.8)
Computer	582 (52.0)	278 (24.8)	166 (14.8)	58 (5.2)	35 (3.1)
Television	206 (18.4)	402 (35.8)	367 (32.7)	112 (10.0)	35 (3.1)
Tablet	809 (72.6)	179 (16.1)	92 (8.3)	28 (2.5)	7 (0.6)
Game console	999 (88.7)	68 (6.0)	39 (3.5)	17 (1.5)	3 (0.3)

Table 3. Comparison of the use of technological devices over two hours and the presence of health problems

	Mobile phone %/p[a]	PC %/p[a]	TV %/p[a]	Tablet %/p[a]	Game console %/p[a]
Distractibility	**35.6/0.029**	25.8/0.263	29.2/0.632	37.1/0.437	20.0/0.279
Course activity	**56.8/0.001**	49.4/0.928	55.7/0.080	51.4/0.788	30.0/0.082
Sleep time	**57.5/0.001**	44.0/0.486	**34.6/0.001**	34.2/0.116	60.0/0.259
Sleep onset	**58.8/0.002**	55.9/0.391	59.1/0.053	60.0/0.316	60.0/0.448
Nutrition	**33.0/0.035**	46.2/0.093	33.5/0.286	38.2/0.965	40.0/0.835
Psychology	**41.6/0.001**	**48.3/0.018**	57.8/0.593	60.0/0.968	65.0/0.650
Failure of social activities	**15.4/0.001**	25.8/0.428	25.1/0.227	25.7/0.651	40.0/0.284
Fatigue	**6.8/0.005**	7.5/0.246	10.2/0.813	14.2/0.541	**30.0/0.006**

[a] Chi-square test; p<0.05

Table 4. The relationship between participants' duration of using technological devices and musculoskeletal pain complaints

Device usage	Upper Back		Lower Back		Neck		Hand		Wrist		Shoulder	
	r	p[c]	r	p[c]	r	p[c]	r	p[c]	r	p[c]	r	p[c]
Mobile phone, hour	0.057	0.051	0.043	0.141	0.096	**0.002**	0.056	0.052	0.079	**0.008**	0.069	**0.021**
Computer, hour	0.102	**0.001**	0.078	**0.011**	0.004	0.891	0.020	0.501	0.036	0.222	0.061	**0.041**
Television, hour	-0.018	0.552	0.009	0.773	0.059	**0.041**	0.029	0.335	0.023	0.444	-0.006	0.843
Tablet, hour	0.016	0.592	0.010	0.724	0.007	0.825	0.045	0.137	0.012	0.694	0.048	0.101
Game console, hour	-0.016	0.586	0.002	0.945	0.013	0.656	0.017	0.574	-0.003	0.916	-0.001	0.975
Total device usage, hour	0.093	**0.002**	0.094	**0.002**	0.109	**0.001**	0.088	**0.003**	0.114	**0.001**	0.101	**0.001**

[c] Spearman correlation; p<0.05

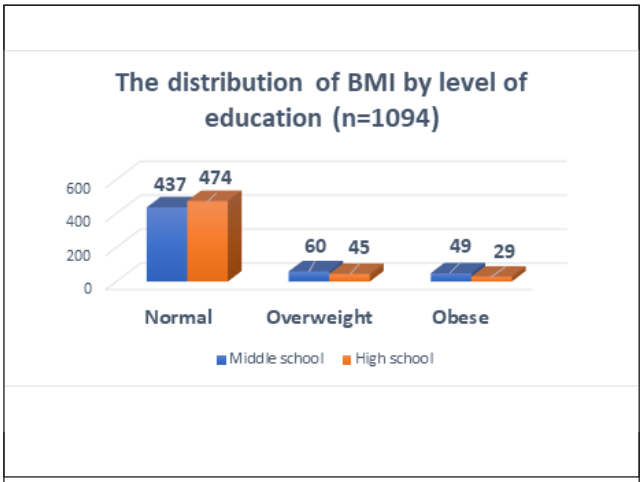

Figure 1. The distribution of participants BMI according to the educational level

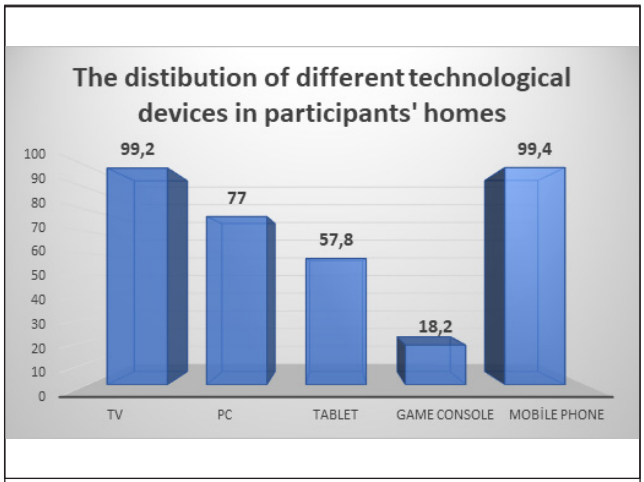

Figure 2. The distribution of different technological devices in participants' homes

DISCUSSION

As a result of the research, it was seen that the adolescents used smartphones the most and the game consoles the least. The rate of using television and smartphone for more than two hours a day among adolescents was 13.1% and 28.4%, respectively. A decrease in sleep duration, increase in falling asleep time, distraction, fatigue, eating disorders and psychological symptoms were more present for individuals using smartphone more than two hours. Moreover, there is an association between the smartphone use duration and presence of neck, shoulder, and wrist pain.

In the present study it is revealed that smartphone had the highest prevalence of use. Similar to recent large studies conducted in the Norway [7], United Kingdom [13], and Singapore [18] the smartphone was the most used device among the adolescents. Possible reasons for the high usage of smartphones included portability, convenience and multiple functions offered, such as ease of access to the internet, social media and messaging, and usage for daily functions. A study has proven that adolescents nowadays are more comfortable to interact through the Facebook than face to face. This is because the use of Facebook allows a person to interact with anyone around the world without being limited by time and geographical distance.

In literature investigating the effects of the use of digital technological devices on the musculoskeletal system of adolescents Harris et al. [26], states that there is a relationship between children's musculoskeletal complaints and using computer both at school and at home, musculoskeletal symptoms that start during youth due to the increased use of computers may cause an increase in discomfort and pain complaints during adulthood. A study conducted by Myrveit et al. [27], state that the teenagers who spend more time in front of the screen (console games, computer games, and other computer activities) experience more neck and shoulder pain. Moreover, it was stated in this study that the relationship between neck and shoulder pain and the time spent in front of the screen is partially related to depression. In another study Gustafsson et al. [28], reported that the greater amount of smartphone use was associated with a higher prevalence of musculoskeletal symptoms in neck/shoulders, upper back, arms and wrist/hand. Similarly in the Toh et al. [18] study, found that after adjusting for potential confounders, more hours/day of smartphone use was associated with increased risk of neck/shoulders, upper back, arms and wrist/hand discomfort to and visual symptoms. The results of our study are found to be in the same direction as literature. In another study, it was reported that, using smartphones causes impaired joint position sense in flexion, decreased deep and superficial cervical muscle activity, and forward head posture [11]. In the authors' opinion, smartphone users are unaware of their neck positions while using smartphones and learn an unhealthy flexion posture. This flexion posture has become a frequent and persistent habit among young individuals. The results of our study about the effects of daily total use of technological devices on pain complaints were different from the literature. Discomfort is likely associated with adolescent's unhealthy technological devices usage behaviours including frequent and long durations of devices use, adopting awkward postures because of inappropriate seating and furniture and workstation layout, inadequate forearm support during texting, gaming by keyboard and mouse use. However, the relationship between technological devices use and musculoskeletal symptoms is unknown, and prospective cohort or longitudinal studies are needed to provide more information on the nature of the relationship.

Besides, in our study, it was observed that the increase in fatigue status, psychological symptoms, neglecting house duties and eating disorders was significantly more frequent for the adolescents who use smartphones for more than two hours a day compared to those who use less than two hours a day. In a study conducted by Bickham et al. [29], it was reported that mobile phone use and television viewing were associated with depressive symptoms, while computer use, music listening, and video game play were unrelated. Nakamura et al. [30], it was found that frequency of breakfast decreased, duration of studying at home decreased, frequency of depression, anxiety and discomfort feelings increased for the children who play electronic games for more than one hour a day. It was also reported that, frequency of breakfast decreased and feeling of anxiety and discomfort increased for the children who watch television and using computer for more than one hour a day compared to those who watch less than one hour a day. As a result of the study, it was reported that multiple use of technological devices have a cumulative effect on subjective health. Orben et al. [31] found small negative between-person relations between social media use and life satisfaction in a large United Kingdom sample of adolescents over 7 years. In a sample of 1749 Australian adolescents, found overall low within-person relations between total screen time and depressive symptoms [32]. In literature, there are different results about the effects of technological devices on fatigue, neglecting house duties, psychological symptoms, and eating disorders. We believe that further study on this subject will be beneficial.

In the current study, it was found that the decrease in sleep duration and the increase in the duration of falling asleep was more frequent for the adolescents who use smartphone for more than two hours a day. Similarly, Parent et al. [33], reported that as the time spent in front of the screen increases, quality of sleep decreases, sleep duration decreases during puberty and sleep disorders occur in the group of age three. Hysing et al. [7], revealed that the extensive use of the technological devices was significantly and positively associated with sleep onset latency and sleep deficiency, with an inverse dose–response relationship between sleep duration and media use. Cain and Gradisar [34] reported that the frequency of use of a computer or electronic games is associated with longer falling asleep duration and shorter sleep duration. Possible mechanism might be in the compilation that technological device screens might increase physiological and mental stimulation which makes it difficult to fall asleep. It was also reported that the bright light of the television or computer screens might suppress the secretion of melatonin which might delay the onset of sleep. Similarly, Liu et al. [21], reported that excessive digital media use or screen time

may increase risk of sleep deprivation, sleep disturbance, mental and physical health problems, and daily functioning impairment.

Limitations and Recommendations

There is some limitation of the study. The first limitation is that the study only includes public school students. The fact that the participants were randomly selected from secondary and high school students studying in Bahçelievler district of Istanbul limits the generalizability of our results. Second, the reliability of the study is limited to the accuracy of the answers of the participants. Finally, the interpretation of the study results is based on the survey data and no objective evaluation method was used.

Nowadays, most digital activities can be accomplished with a single smartphone, and mobile phones will continue to increase in popularity and use. Adolescents should be advised to limit or reduce the time they spend on a mobile phone and take preventative measures against the harmful effects of screen time on sleep, mental health, and academic performance. So, parents need to take the efforts to guard, control and limit the screen time to avoid the risk of behaviour and psychological problems. Therefore, adolescents need more parental supported and direction as they gradually develop their own digital literacy skills. This is a valuable contribution to existing research in that significant increases in technological device use time may indicate that an adolescent health is deteriorating. Longitudinal research should be utilized to confirm our findings and provide evidence for directionality.

CONCLUSION

According to the results of our research, the increase in the time of using technological devices such as smartphones, computers, and television which have become indispensable parts of daily life for adolescents which is associated with various health problems. The smartphones were found to be the most used technological device among adolescents, and it was associated with various health problems such as decrease in sleep duration, increase in falling asleep duration, attention deficit, fatigue, eating disorders, psychological symptoms, neck, shoulder, and wrist pain. It is expected that the results of the study will contribute to raising awareness of the effects of intense technological device use on health.

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Ethics Committee Approval: The study was approved by the was approved by the Istanbul University, Faculty of Medicine Clinical Research Ethics Committee (IRB:2018/1094, Approval Date; August 10, 2018).

REFERENCES

1- Dienlin T, Johannes N (2020) The impact of digital technology use on adolescent well-being. Dialogues Clin Neurosci.22(2):135. https://doi.org/10.31887/DCNS.2020.22.2/tdienlin

2- Kulakci-Altintas H (2020) Technological device use among 0–3 year old children and attitudes and behaviors of their parents towards technological devices. J Child Fam Stud. 29(1):55-61. https://doi.org/10.1007/s10826-019-01457-x

3- Radovic A, Badawy SM (2020) Technology use for adolescent health and wellness. Pediatrics.145(Supplement 2):S186-S94. https://doi.org/10.1542/peds.2019-2056G

4- Scherr S, Wang K (2021) Explaining the success of social media with gratification niches: Motivations behind daytime, nighttime, and active use of TikTok in China. Comput Human Behav. 124:106893. https://doi.org/10.1016/j.chb.2021.106893

5- Ayandele O, Popoola OA, Oladiji TO (2020) Addictive use of smartphone, depression and anxiety among female undergraduates in Nigeria: a cross-sectional study. J Health Res. 34.5: 443-453. https://doi.org/10.1108/JHR-10-2019-0225

6- Gustafsson M-L, Laaksonen C, Salanterä S, Löyttyniemi E, Aromaa M (2019) Associations between daytime sleepiness, psychological symptoms, headache, and abdominal pain in schoolchildren. J Sch Nurs.35(4):279-86. https://doi.org/10.1177/1059840518774394

7- Hysing M, Pallesen S, Stormark KM, Jakobsen R, Lundervold AJ, Sivertsen B (2015) Sleep and use of electronic devices in adolescence: results from a large population-based study. BMJ open. 5(1):e006748. https://doi.org/10.1136/bmjopen-2014-006748

8- Mei X, Zhou Q, Li X, Jing P, Wang X, Hu Z (2018) Sleep problems in excessive technology use among adolescent: a systemic review and meta-analysis. Sleep Sci Pract.2(1):1-10. https://doi.org/10.1186/s41606-018-0028-9

9- Straker L, Coleman J, Skoss R, Maslen B, Burgess-Limerick R, Pollock C (2008) A comparison of posture and muscle activity during tablet computer, desktop computer and paper use by young children. Ergonomics.51(4):540-55. https://doi.org/10.1080/00140130701711000

10- Silva GRR, Pitangui ACR, Xavier MKA, Correia-Júnior MAV, Araújo RCD (2016) Prevalence of musculoskeletal pain in adolescents and association with computer and videogame use. J Pediatr (Rio J). 92(2):188-96. https://doi.org/10.1016/j.jped.2015.06.006

11- Cetin H, Turkmen C, Bal GA, Tekerlek H, Bilgin S, Köse N (2022) Factors affecting the performance of the deep cervical flexors in young people using smartphones. Cranio. 25;1-9. https://doi.org/10.1080/08869634.2022.2078944

12- Sisson SB, Broyles ST, Baker BL, Katzmarzyk PT (2010) Screen time, physical activity, and overweight in US youth: National Survey of Children's Health 2003. J Adolesc Health. 47(3):309-11. https://doi.org/10.1016/j.jadohealth.2010.02.016

13- Mireku MO, Barker MM, Mutz J, Dumontheil I, Thomas MS, Röösli M, et al. (2019) Night-time screen-based media device use and adolescents' sleep and health-related quality of life. Environ Int.124:66-78. https://doi.org/10.1016/j.envint.2018.11.069

14- Chia S-E, Chia H-P, Tan J-S (2000) Prevalence of headache among handheld cellular telephone users in Singapore: a community study. Environ Health Perspect. 108(11):1059-62. https://doi.org/10.1289/ehp.001081059

15- Falkenberg HK, Johansen TR, Thorud HMS (2020) Headache, eyestrain, and musculoskeletal symptoms in relation to smartphone and tablet use in healthy adolescents. SJOVS. 13(2), 8–14. https://doi.org/10.5384/sjovs.vol13i2p8-14

16- Ichhpujani P, Singh RB, Foulsham W, Thakur S, Lamba AS (2019) Visual implications of digital device usage in school children: a cross-sectional study. BMC ophthalmology. 19(1):1-8. https://doi.org/10.1186/s12886-019-1082-5

17- Zirek E, Mustafaoglu R, Yasaci Z, Griffiths MD (2020) A systematic review of musculoskeletal disorders related to mobile phone usage. Musculoskelet Sci Pract. 49:102196. https://doi.org/10.1016/j.msksp.2020.102196

18- Toh SH, Coenen P, Howie EK, Mukherjee S, Mackey DA, Straker LM (2019) Mobile touch screen device use and associations with musculoskeletal symptoms and visual health in a nationally representative sample of Singaporean adolescents. Ergonomics. 62(6):778-93. https://doi.org/10.1080/00140139.2018.1562107

19- Straker L, Harris C, Joosten J, Howie EK (2018) Mobile technology dominates school children's IT use in an advantaged school community and is associated with musculoskeletal and visual symptoms. Ergonomics. 61(5):658-69. https://doi.org/10.1080/00140139.2017.1401671

20- Domoff S, Foley R, Ferkel R (2020) Addictive phone use and academic performance in adolescents. Hum Behav & Emerg Tech. 2:33–38. https://doi.org/10.1002/hbe2.171

21- Liu X, Luo Y, Liu ZZ, Yang Y, Liu J, Jia CX (2020) Prolonged Mobile Phone Use Is Associated with Poor Academic Performance in Adolescents. Cyberpsychol Behav Soc Netw. 23(5):303-311. https://doi.org/10.1089/cyber.2019.0591

22- Kamangar F, Islami F (2013) Sample size calculation for epidemiologic studies: principles and methods. Arch Iran Med. 16(5):295-300

23- Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F (2015) Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 7(4):280-293. https://doi.org/10.4274/jcrpe.2183

24- Kahl C, Cleland JA (2005) Visual analogue scale, numeric pain rating scale and the McGill pain Questionnaire: an overview of psychometric properties. Physical therapy reviews. 10(2):123-8. https://doi.org/10.1179/108331905X55776

25- Cohen J (1992) Statistical power analysis. Current directions in psychological science. 1(3):98-101. https://doi.org/10.1111/1467-8721.ep1076878

26- Harris C, Straker L, Pollock C, Smith A (2015) Children, computer exposure and musculoskeletal outcomes: the development of pathway models for school and home computer-related musculoskeletal outcomes. Ergonomics. 58(10):1611-23. https://doi.org/10.1080/00140139.2015.1035762

27- Myrtveit SM, Sivertsen B, Skogen JC, Frostholm L, Stormark KM, Hysing M (2014) Adolescent neck and shoulder pain—the association with depression, physical activity, screen-based activities, and use of health care services. J Adolesc Health. 55(3):366-372. https://doi.org/10.1016/j.jadohealth.2014.02.016

28- Gustafsson E, Coenen P, Campbell A, Straker L (2018) Texting with touchscreen and keypad phones-A comparison of thumb kinematics, upper limb muscle activity, exertion, discomfort, and performance. Appl Ergon. 70:232-239. https://doi.org/10.1016/j.apergo.2018.03.003

29- Bickham DS, Hswen Y, Rich M (2015) Media use and depression: exposure, household rules, and symptoms among young adolescents in the USA. Int J Public Health. 60(2):147-155. https://doi.org/10.1007/s00038-014-0647-6

30- Nakamura H, Ohara K, Kouda K, Fujita Y, Mase T, Miyawaki C, et al. (2012) Combined influence of media use on subjective health in elementary school children in Japan: a population-based study. BMC Public Health. 12:432. https://doi.org/10.1186/1471-2458-12-432

31- Orben A, Dienlin T, Przybylski AK (2019) Social media's enduring effect on adolescent life satisfaction. Proc Natl Acad Sci. 21;116(21):10226-10228. https://doi.org/10.1073/pnas.1902058116

32- Houghton S, Lawrence D, Hunter SC, Rosenberg M, Zadow C, Wood L, et al. (2018) Reciprocal relationships between trajectories of depressive symptoms and screen media use during adolescence. J Youth Adolesc. 47(11):2453-2467. https://doi.org/10.1007/s10964-018-0901-y

33- Parent J, Sanders W, Forehand R (2016) Youth screen time and behavioral health problems: The role of sleep duration and disturbances. Journal of developmental and behavioral pediatrics: J Dev Behav Pediatr. 37(4):277-284. https://doi.org/10.1097/DBP.0000000000000272

34- Cain N, Gradisar M (2010) Electronic media use and sleep in school-aged children and adolescents: A review. Sleep Med. 11(8):735-742. https://doi.org/10.1016/j.sleep.2010.02.006

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Original Research

The Preventative Knowledge and Experience of Anesthesiology Students with C-arm Fluoroscopy

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ABSTRACT

Objective: Long-term C-arm fluoroscopy exposes medical personnel to substantial radiation doses. Preventing this exposure requires protective equipment and radiation safety. This study examined anesthesia students' using fluoroscopy and preventive knowledge.

Methods: This descriptive and cross-sectional study included 139 Vocational High School Anesthesia students. The "Healthcare Professional Knowledge of Radiation Protection" scale and a 13-question survey collected data. The scale was designed with a Likert scale and three sub-factors. If the total and sub-dimension item average score of the scale is below 5, it indicates that the level of knowledge of radiation protection among medical personnel is low, and if it is above 5, it indicates that the level of knowledge is high.

Results: More than half of the students (59.8%) heard the radiation from the fluoroscopy device, the vast majority (82.7%) did not receive radiation protection training, 58.3% stayed away from the device while it was operating, and 70.5% stated that it is crucial to stay away from the device while it was operating. It was determined that there was a statistically significant difference ($p<0.05$) in the "Radiation Physics, Biology, and Radiation Usage Principles" sub-dimension of students who were male, in their second year of education, received radiation protection training, and offered reliable answers to a number of questions measuring their level of radiation knowledge. In addition, the research revealed a positive and highly significant correlation between the scale and its subdimensions.

Conclusion: Although the scale scores of the students who received radiation protection training and had a high level of radiation knowledge were substantially higher than those of the other students, the average score of the students was less than 5. This indicates that students have an inadequate understanding of radiation protection. To prevent the negative biological effects of radiation on the human body, it is necessary to conduct epidemiological research, educate health care professionals and anesthesiology students about the effects and processes of this radiation on human cells, and provide frequent training. Radiation, radiation's biological effects, and radiation protection should be included in health students' curricula.

Keywords: Scopy, Radiation hazards, Radiation exposure

INTRODUCTION

Radiation, which is defined as the emission and transfer of energy from atoms, exposes humans to various forms and doses due to its expanding use in medical and industrial settings [1]. Radiation types are classified as either ionizing or non-ionizing [2]. Since the discovery of ionizing radiation in 1895, its usage in medicine has steadily increased. However, its ever-increasing use increases the population's exposure to radiation and poses a significant threat to public health [3, 4]. In addition, epidemiological research indicates that the ionizing radiation utilized in surgical operations and diagnostic imaging causes cancer [5]. Non-ionizing radiation is radiation that does not produce ions in the materials with which it interacts. This type of radiation includes microwaves, radio waves, ultraviolet light, and visible light as examples [6]. While modern diagnostic and treatment procedures facilitate the early detection and treatment of disease, they also increase radiation exposure and have irreversible biological impacts on patients, healthcare professionals, and students in the area of medicine [7]. Moreover, ionizing radiation might have negative impacts on cells. Ionizing radiation can cause chromosomes to splinter, clump, and twist. Chromosomes that have been broken may remain unchanged or unite with another chromosome. Resulting from these processes, mutation or cell death may ensue [8]. Fluoroscopy devices utilized in medical applications pose a danger of ionizing radiation exposure. C-arm fluoroscopy, which is extensively utilized in invasive surgery nowadays, is frequently employed in orthopedic surgery because it provides a clear image of the skeletal system [9]. Because of this, the use

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of long-term C-arm fluoroscopy systems exposes healthcare professionals and patients to excessive radiation doses [10]. To prevent this exposure, it is essential to employ protective gear and adhere to radiation safety regulations [11, 12]. Numerous strategies have been described to reduce the negative effects of radiation during medical procedures. Some of these were determined to be a lead apron, safety jacket, thyroid neck collar, and spectacles [7, 9]. It is crucial to take the risk of radiation seriously and to be knowledgeable about radiation [13]. There are three types of radiation exposure: medical, social, and occupational [14]. Radiation areas are defined as places where exposure to radiation is predicted to exceed 1 mSv for one year. Areas where the annual dose of radiation exposure is projected to surpass 1 mSv are referred to as "Radiation Fields." Examining the scientific literature, 1 mSv is a high equivalent dosage value and is typically stated as milliSv or microSv [3]. The maximum annual radiation rate indicated by the International Radiation Protection Association and the American National Radiation Measurement and Protection Association is between 20 and 50 mSv. These readings have decreased over time due to the radiation's long-term harmful effects [9]. In addition, according to the regulations of the Turkish Energy, Nuclear and Mining Research Institute (TENMAK, formerly the Turkish Atomic Energy Agency-TAEK), the effective dose for students aged 16 to 18 who are trained in the use of radiation sources should not exceed 6 mSv per year [3]. It is vital to determine whether the students take the required steps to prevent the anesthesia department students who will practice in this field as health care professionals in the future from the negative effects of radiation exposure. This topic, which is significant in terms of public health, requires research so that those who work or will work in the field of radiation can safeguard themselves and those around them. It is crucial that students who will become the future health care workforce do not put their health at danger during medical practices and are aware of the detrimental effects of radiation. This study aims to assess the fluoroscopy utilization and preventive knowledge of anesthesia department students.

METHODS

This study is descriptive and cross-sectional in design. The event took place during the spring semester of the academic year 2021-2022 at the Vocational School of a foundation university in Gaziantep.

The Sample Size of the Study

The study group was made up of 165 students at a Gaziantep foundation university who were in the Department of Anesthesia. The sample includes 139 students who volunteered to participate in the investigation.

Research Ethical and Legal Aspects

The Health Sciences Non-Interventional Ethics Committee at a foundation university accepted our study on February 28, 2022, with Decision No. 2022/016. The research was conducted in conformity with the Declaration of Helsinki, and participants were given verbal information and consent forms. Permission to use the scale was secured by email from the scale's owner.

Data Collection Tools

The data was collected between 1 March and 30 April 2022 using a 13-question questionnaire that included questions about the students' introduction, radiation, and fluoroscopy safety. In addition, the students were administered the "Healthcare Professional Knowledge of Radiation Protection (HPKRP)" in person during 45 min. Ay evaluated the validity and reliability of this scale in 2021 [15]. Schroderus-Salo et al. (2019) created the scale with 33 components and three sub-dimensions [16]. The universe and sample group for the development of the scale consisted of nursing professionals working in various clinics. The first, second, and third subdimensions of the Explanatory Factor Analysis (EFA) model of the scale had Cronbach's alpha coefficients of 0.96, 0.95, and 0.95, respectively. It was determined that the whole Cronbach's alpha coefficient of the scale was 0.93 and that the overall Cronbach's alpha coefficient was 0.97. The Cronbach's alpha coefficient was found to be 0.95 in our investigation. It is a 10-point Likert-type scale with 1 = I do not know and 10 = I have complete knowledge for each item. Calculation of scale score, scale It is calculated using the weighted average of the total and subdimension scores. A score between 1 and 10 is obtained from the scale. The scale's cutoff point was determined to be 5 If the total and sub-dimension item average score of the scale is less than 5 points, then the degree of knowledge of radiation protection among health workers is poor, and if it is greater than 5 points, then it is high. The scale has three subdimensions;

- Radiation physics, biology, and radiation usage principles (RPBP): It consists of 12 items (1-12) that assess the level of knowledge of healthcare professionals regarding the fundamental properties of radiation.
- Radiation protection sub-dimension (RPS): It consists of a total of 13 items (13-25) that assess the level of radiation protection knowledge among healthcare professionals.
- Guide to safe use of ionizing radiation (GSU): It consists of eight questions (26-33) that assess the level of knowledge of healthcare professionals regarding the radiation use guide.

Statistical Analysis

The application SPSS 23.0 was used to evaluate the data. Standard deviation, frequency, and percentage values were calculated during the data analysis. In descriptive statistics, the number (n) and percentage value (%) are used to describe categorical variables, whereas the mean standard deviation is used to express numerical values. Using the Kolmogrov-Smirnov test, the histogram, Q-Q plot, P-P plot, skewness and kurtosis values, the normality of quantitative data was determined. Independent Samples t-test and Single Factor Analysis of Variance were done on normally distributed independent groups. In groups that did not exhibit a normal distribution, the Mann Whitney U and Kruskal-Wallis H tests were conducted. The association between the "Healthcare Professional Knowledge of Radiation Protection (HPKRP)" and its sub-dimensions was determined using a simple correlation analysis. All outcomes of the study fell within the 95% confidence interval, and a p value of 0.05 was considered statistically significant.

RESULTS

It was found that 40.3% of the students in the study were between the ages of 19 and 20, and their average age was (21.101.90) (from 19 to 35). It was discovered that 78.4% of the students were female and 52.5% were in the first school year. More than half of the students (59.8%) heard the radiation connected to the fluoroscopy device, the majority (82.7%) did not receive radiation protection training, 58.3% stayed away from the device while the C-arm fluoroscopy device was operating, and 70.5% stayed away from the device while the C-arm fluoroscopy device was operating. Due to the fact that 61.2% of the students emit radiation, care should be taken when storing radiation protection equipment. Additionally, 51.8% of the students reported that there was a radiation hazard warning sign in the rooms where the C-arm fluoroscopy operates in the hospitals where they practice, and 62.6% of them pay attention to air exchange in the operating room where the C-arm fluoroscopy is used. stated that it should be the case. Table 1 reveals that 61.9% of the students stated that they ate a well-balanced diet to safeguard themselves from radiation harm, while 46.8% of them stated that they had never been in the room where the C-arm fluoroscopy was used in the previous year (Table 1).

When the scores of the Health Professionals' Radiation Protection Knowledge Scale and its sub-dimensions were compared with the gender, educational year, and radiation knowledge level of the students, it was found that male students, second-year students, and students with a higher level of radiation knowledge had significantly higher RPBP sub-dimension scores. In addition, it was determined that individuals who received radiation protection training had substantially higher scores in all subgroups and on the total scale. Table 1 provides a comprehensive breakdown of the questions indicating radiation knowledge levels and the significance values of the scale scores (Table 1).

The cumulative mean score on the HPKRP Scale was determined to be 3.95±1.68. When examining the sub-dimensions of the scale, "Radiation Physics, Biology, and Radiation Usage Principles" sub-dimension mean score was3.02±1.50, "Radiation Protection" sub-dimension mean score was 4.65±2.03, and "Safe Ionizing Radiation Use Guide" sub-dimension mean score was 4.20±2.12 (Table 2).

In our study, we also evaluated the relationship between the HPKRP and its subscales. A moderately positive correlation was

Table 1. Comparison of the Socio-demographic Characteristics of the Students and the Mean Scores of the Health Professionals' Radiation Protection Knowledge Scale and its Sub-Dimensions

	%	n	RPBP	RPS	GSU	Total Score of Scale
			Mean±SD	Mean±SD	Mean±SD	Mean±SD
Gender						
Female	78.4	109	2.85 ± 1.38	4.58 ± 2.01	4.08 ± 2.04	3.83 ± 1.63
Male	21.6	30	3.64 ± 1.79	4.91 ± 2.10	4.63 ± 2.37	4.38 ± 1.83
Statistical significance			t=2.621, **p=0.010***	t=0,777, p=0.439	t=1.255, p=0.212	t=1.594, p=0.113
Education Status						
First Year	52.5	73	2.76 ± 1.40	4.38 ± 2.14	3.91 ± 2.09	3.68 ± 1.71
Second Year	47.5	66	3.30 ± 1.57	4.95 ± 1.87	4.53 ± 2.12	4.25 ± 1.61
Statistical significance			t=2.166, **p=0.032***	t=1.660, p=0.099	t=1.739, p=0.084	t=2.026, **p=0.045***
Hearing the radiation associated with the fluoroscopy instrument						
Yes	59.8	79	3.29 ± 1.53	4.89 ± 1.87	4.39 ± 2.03	4.19 ± 1.59
No	43.2	60	2.66 ± 1.40	4.34 ± 2.20	3.95 ± 2.22	3.64 ± 1.76
Statistical significance			t=2.458 **p=0.015***	t=1.592 p=0.114	t=1.228 p=0.221	t=1.928 p=0.056
Status of receiving education about radiation protection						
Yes*	17.3	24	3.67 ± 1.60	5.58 ± 2.15	5.38 ± 2.80	4.84 ± 1.86
No	82.7	113	2.88 ± 1.45	4.46 ± 1.96	3.95 ± 2.01	3.76 ± 1.59
Statistical significance			t=2.389 **p=0.018***	t=2.518 **p=0.013***	t=3.093 **p=0.002***	t=2.928 **p=0.004***
Situation of staying away from the C-arm fluoroscopy device while it is operating						
Yes	58.3	81	3.30 ± 1.54	5.01 ± 1.90	4.46 ± 2.10	4.26 ± 1.60
No	41.7	58	2.62 ± 1.37	4.16 ± 2.12	3.84 ± 2.11	3.52 ± 1.71

Statistical significance			t=2.720 **p=0.007***	t=2.484 **p=0.014***	t=1.708 p=0.090	t=2.590 **p=0.011***
The necessity of maintaining a safe distance from the C-arm fluoroscopy while it is in operation.						
Yes	70.5	98	3.25 ± 1.56	5.00 ± 1.93	4.53 ± 2.12	4.25 ± 1.64
No	29.5	41	2.46 ± 1.22	3.81 ± 2.04	3.42 ± 1.93	3.23 ± 1.58
Statistical significance			t=2.881 **p=0.005***	t=3.258 **p=0.001***	t=2.894 **p=0.004***	t=3.389 **p=0.001***
Presence of a radiation hazard warning sign in the rooms where the C-arm fluoroscopy works in the hospitals where you practice.						
Yes	51.8	72	3.61 ± 1.64	5.38 ± 1.92	4.88 ± 2.18	4.61 ± 1.67
No	48.2	67	2.39 ± 1.02	3.87 ± 1.86	3.48 ± 1.80	3.24 ± 1.39
Statistical significance			Z=4.529 **p=0.000****	t=4.676 **p=0.000***	Z=3.572 **p=0.000****	Z=4.578 **p=0.000****
The necessity of paying close attention to air exchange in the operating room chambers in which the C-arm fluoroscopy operates.						
Yes	62.6	87	3.24 ± 1.58	4.86 ± 1.20	4.38 ± 2.20	4.16 ± 1.70
No	37.4	52	2.64 ± 1.29	4.30 ± 2.05	3.90 ± 1.96	118.85±53.49
Statistical significance			t=2.296 **p=0.023***	t=1.577 p=0.117	t=1.312 p=0.192	t=1.895 p=0.060
The state of paying attention to adequate and balanced nutrition in order to be protected from the harms of radiation.						
Yes	61.9	86	3.24 ± 1.62	4.87 ± 2.10	4.47 ± 2.28	4.18 ± 1.80
No	38.1	53	2.65 ± 1.23	4.30 ± 1.88	3.77 ± 1.75	3.57 ± 1.41
Statistical significance			Z=2.057 **p=0.040****	t=1.635, p=0.104	Z=1.527 p=0.127	Z=1.871 p=0.061
Frequency of C-arm scopy room visits over the past year.						
More than once a week	14.3	20	3.85±2.01	5.20±2.09	4.45±2.14	4.53±1.88
Once a week	18.0	25	2.83±1.26	3.94±1.42	3.79±1.85	3.50±1.42
Rarely	20.9	29	3.35±1.52	5.96±1.59	5.50±2.10	4.90±1.49
None	46.8	65	2.68±1.29	4.17±2.10	3.70±2.00	3.52±1.62
Statistical significance			F= 3.990 **p= 0.009*****	KW=16.373 **p= 0.001 ********	F= 5.836, **p= 0.001*****	F= 6.620, **p= 0.000*****

* Independent Samples t- test, ** Mann Whitney U test, *** One Way Anova test, **** Kruskal Wallis H test,SD;Standart Deviation

Table 2. Total Score Averages of the HPKRP and its Sub-Dimensions of Healthcare Professionals

Scale and Sub-Dimensions	Number of items	Min-Max	Mean±SD
Radiation Physics, Biology and Radiation Usage Principles	12 (1-12)	12-112	3.02±1.50
Radiation Protection	13 (13-25)	13-121	4.65±2.03
Guide to Safe Ionizing Radiation Use	8 (25-33)	8-74	4.20±2.12
Healthcare Professional Knowledge of Radiation Protection Scale (Total)	33 (1-33)	33-267	3.95±1.68

SD; Standart Deviation

found between the sub-dimensions of "Radiation Physics, Biology, and Radiation Usage Principles" and "Radiation Protection" and "Safe Ionizing Radiation User Guide" (respectively; r=0.691, p<0.01; r=0.676 p<0.01).

The relationship between "Radiation Protection" and "Safe Ionizer Radiation User Guide" is positive and highly significant (r=0.841, p<0.01). Positive and highly significant relationships were discovered between the sub-dimensions of the HPKRP Scale and "Radiation Physics, Biology, and Radiation Use Principles", "Radiation Protection", and "Guidelines for Safe Ionizing Radiation Use" (respectively; r=0.840, p<0.01, r=0.950, p0.01, r=0.914, p<0.01).

DISCUSSION

During fluoroscopic operations, professionals and students in this area may be exposed to ionizing radiation. It is advised that protective equipment be worn throughout radiation-causing processes, that the duration of the procedures be kept to a minimum, and that only required radiation-causing applications be performed [5]. In addition, according to the Radiology Services Regulation drafted by the Ministry of Health, the effective dosage for people who operate with ionizing radiation sources should not exceed 100 mSv for five consecutive years, 20 mSv yearly, and 2 mSv monthly [11]. Fluoroscopy-assisted medical operations are one of the most important parts of the success of modern medical practices. Nonetheless, the frequency of radiation exposure during fluoroscopy operations poses a concern to the public health of healthcare workers and anesthesia department students studying in this department. As a result, the amount of radiation protection knowledge the anesthesia students who will work in radiation sectors in the future possess and the education they get in this subject are strongly tied to their health. In our study, the majority of students heard the radiation emanating from the fluoroscopy, however 82.7% of students did not get radiation protection training. In research involving intensive care nurses, it was concluded that 37.3% had intermediate understanding and 62.7% had limited awareness about radiation safety [17]. Examining the literature, there are research indicating that employees in occupational categories including physicians and radiology technicians have inadequate awareness of radiation safety [18, 19]. It is evident that the findings of our study are comparable to those of previous research. In addition, our research revealed a strong correlation between students' understanding of radiation safety and their radiation protection practices. In this regard, we believe it is essential for students to establish appropriate radiation safety behavior and get instruction on this topic. The average overall score on the HPKRP scale for the students in our research was 3.95 ± 1.68 (Table 2). It was established that the "Radiation Physics, Biology, and Radiation Usage Principles" subdimension average score of 3.02±1.50 was the lowest among the other subdimension averages. Rahimi et al. revealed that the sub-dimension "Radiation Physics and Biology and the Principles of Radiation Use" had the lowest documented degree of knowledge, with a mean score of 4.69±2.49 [20]. When our study is analyzed in conjunction with other current studies, it is evident that the knowledge of the individuals who will work in the field of radiation about the notion of radiation safety as low as may be realistically achieved is crucial. In our study and in the literature, it was shown that students who practice in the health sector and health professionals who operate in this field are not well-informed about the unknown consequences of a given radiation dose on medical radiation [21, 22].

In our study, the socio-demographic features of the students and the mean scores on the HPKRP scale and its subdimensions were compared. Consequently, Those who study in the second year of education, learn about radiation protection, stay away from the device when the C-arm scanner is working, and say that it is important to stay away from the device when the C-arm fluoroscopy is working, and those who say that there are radiation hazard warning signs in the rooms where the C-arm fluoroscopy works in the hospitals where they work, their average score on the scale was statistically higher than others. Also, there was a statistically significant difference between the average results of the sub-dimensions of the scale and some sociodemographic characteristics of the students. Despite the significant differences indicated above, it was decided that the students' radiation safety knowledge level was inadequate, as the students' average score was less than 5. According to the findings of this study, radiation protection training is highly beneficial. Although they have understanding of the topic, they are not adequately aware of the radiation hazards in the units in which they practice. In addition, it was deemed beneficial that no other study in the literature investigated the usage of fluoroscopy and radiation protection knowledge among anesthesia department students using the HPKRP.

When the relationship between the HPKRP and its sub-dimensions was examined in the students who participated in our study, it was determined that there was a moderate, high, very high, and significant positive relationship between all of the scale's sub-dimensions. Based on these data, it was determined that the scale in our investigation was very accurate.

CONCLUSION

It was established that the understanding of the research participants regarding the usage of a fluoroscopy device and the radiation it generates was inadequate. Therefore, these students' ignorance of ionizing radiation may prevent them from protecting themselves and their patients efficiently. One of the primary responsibilities of public health is to reduce the impact of risk factors and boost protective ones. The use of ionizing radiation in medicine is one of the primary goals of public health; it is the most important factor in maintaining health, reducing the morbidity and mortality of individual diseases, and extending life, but irresponsible use and a lack of knowledge about the effects and mechanisms of radiation on human cells can result in serious health issues. To avoid the negative biological effects of radiation on the human body, it is necessary to conduct epidemiological research, teach health care professionals and anesthetic department students about the effects and processes of this radiation on human cells, and provide frequent training. Radiation, radiation's biological impacts, and radiation protection should be included in the curriculum of health students. On the basis of the data presented here, it suggests that these students

require advanced educational preparation for safety precautions connected to ionizing radiation. To develop a culture of radiation protection, to adhere to national and international standards, to ensure their awareness, and to include them in their education courses on radiation and the biological effects of radiation, it is necessary to increase their education among anesthesia department students.

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REFERENCES

1. Yavaş MC, Çelik MS (2019) The effects of some phytotherapeutic plants on Escherichia coli spp. that are exposed to different doses of gamma radiation. Eur J Ther. 25(4):279-84. https://doi.org/10.5152/EurJTher.2019.18060
2. Taysi S, Alafandi N, Demir E, Çınar K (2021) Propolis attenuates nitrosative stress in the brain tissue of rats exposed to total head irradiation. Eur J Ther. 27(4):281-5. https://doi.org/10.5152/eurjther.2021.21096
3. Parlak Y, Uysal B, Kıraç FS, Kovan B, Demir M, Ayan A, et al. (2020) Radyasyon Güvenliği Kılavuzu: Genel Tanımlar ve Nükleer Tıp Uygulamalarında Radyasyondan Korunma Kuralları. Nucl Med Semin. 6(2):71-89. https://doi.org/10.4274/nts.galenos.2020.0009
4. Huhn A, Vargas MAdO, Melo JACd, Gelbcke FL, Ferreira ML, Lança L (2017) Implementation of a radiation protection program: opinion of the health team working in a radiology service. Texto contexto-Enferm. 26. https://doi.org/10.1590/0104-07072017005370015
5. Özçöllü E, Taş A, Çapacı B, Kalkan A, Kiraz EDE, Okyay P (2019) Bir Üniversite Hastanesinde Ameliyathane Radyasyon Güvenliği: Çalışanların Maruz Kalma Durumu, Farkındalıkları, Korunma ile ilgili Bilgi ve Davranışları. GMJ. 30:237-40. https://doi.org/10.12996/gmj.2019.61
6. Gökharman DF, Aydın S, Koşar PN (2016) Radyasyon güvenliğinde mesleki olarak bilmemiz gerekenler. SDÜ Sağ. Bil. Der. 7(2):35-40. https://doi.org/10.22312/sdusbed.261237
7. Andsoy İl, Asiye G, Görücü R, Bayram Ö (2019) Ameliyathane çalişanlarinin skopi kullanimi ve güvenliğine yönelik uygulamalarinin incelenmesi. Balıkesir Sağ. Bil. Der. 8(1):1-6.
8. Kuruş M, Hülya E, Taşlidere E, Uğraş M, Ali O (2014) Düşük doz x işinlarinin siçan midesinde oluşturduğu hasara karşi prunus armeniaca l.(kayisi)'nin koruyucu ve tedavi edici etkisi. Balıkesir Sağ. Bil. Der. 3(2):108-13. https://doi.org/10.5505/bsbd.2014.97268
9. Çeçen GS, Gülabi D, Pehlivanoğlu G, Bulut G, Bekler H, Asil K (2015) Radiation in the orthopedic operating theatre. Acta Orthop Traumatol Turc. 49(3):297-301. https://doi.org/10.3944/AOTT.2015.14.0250
10. Badawy MK, Henely-Smith E, Hasmat S (2023) Radiation exposure to staff during fluoroscopic endoscopic procedures. DEN open. 3(1):e234. https://doi.org/10.1002/deo2.234
11. Park IW, Kim SJ, Shin D, Shim SR, Chang HK, Kim CH (2021) Radiation exposure to the urology surgeon during retrograde intrarenal surgery. PloS one. 16(3):e0247833. https://doi.org/10.1371/journal.pone.0247833
12. Şahiner T, Gül SS, İlçe HT, Deveci EK, Erdem AF, Kurt M, et al. (2014) C-Kollu skopi cihazları için radyasyon yönetimi. Gaziosmanpaşa Üni Tıp F Der. 6(2):101-9.
13. Ramanathan S, Ryan J (2015) Radiation awareness among radiology residents, technologists, fellows and staff: where do we stand? Insights Imaging. 6(1):133-9. https://doi.org/10.1007/s13244-014-0365-x
14. Zeyrek C (2013) İyonize radyasyon uygulamaları için güvenlik ve korunmaya yönelik genel kavramlar. SDÜ Fen Bil. Enst. Der. 17(3):1-9.
15. Ay M. Sağlık çalışanlarının Radyasyondan Korunma Bilgisi Ölçeği›nin Türkçeye uyarlanması: Geçerlik ve güvenirlik çalışması: NEÜ Sağlık Bilimleri Enstitüsü; Yüksek Lisans Tezi 2021.
16. Schroderus-Salo T, Hirvonen L, Henner A, Ahonen S, Kääriäinen M, Miettunen J, et al. (2019) Development and validation of a psychometric scale for assessing healthcare professionals' knowledge in radiation protection. Radiography. 25(2):136-42. https://doi.org/10.1016/j.radi.2018.12.010
17. Azimi H, Majd Teimouri Z, Mousavi S, Kazem Nezhad Leyli E, Jafaraghaee F (2018) Individual protection adopted by ICU nurses against radiation and its related factors. J Holist Nurs Midwifery. 28(1):18-25. https://doi.org/10.18869/acadpub.hnmj.28.1.18

18. Faj D, Edyvean S, Lajunen A, Katukhov A, Vassileva J (2023) Establishment and utilization of diagnostic reference levels in medical imaging: Results from a survey and consultation under the IAEA technical cooperation programme in Europe and Central Asia. Physica medica. 108:102565. https://doi.org/10.1016/j.ejmp.2023.102565

19. Ng CG, Manan HA, Mohd Zaki F, Zakaria R (2022) Awareness of Medical Doctors in Pusat Perubatan Universiti Kebangsaan Malaysia on Diagnostic Radiological Examination Related Radiation Exposure in the Pediatric Population. IJERPH. 19(10). https://doi.org/10.3390/ijerph19106260

20. Rahimi AM, Nurdin I, Ismail S, Khalil A (2021) Malaysian nurses' knowledge of radiation protection: a cross-sectional study. Radiology research and practice. 2021. https://doi.org/10.1155/2021/5566654

21. Cole P, Hallard R, Broughton J, Coates R, Croft J, Davies K, et al. (2014) Developing the radiation protection safety culture in the UK. J Radiol Prot. 34(2):469. https://doi.org/10.1088/0952-4746/34/2/469

22. Alotaibi M, Saeed R (2006) Radiology nurses' awareness of radiation. Journal of Radiology Nursing. 25(1):7-12. https://doi.org/10.1016/j.jradnu.2005.12.001

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Original Research

The Predictive Effect of Anxiety and Burnout Levels Related to the COVID-19 Pandemic and Organizational Commitment on their Intention to Leave the Organization of the Healthcare Professionals

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ABSTRACT

Objective: The study was conducted to determine predictive effect of anxiety and burnout levels related to the COVID-19 Pandemic and organizational commitment on their ıntention to leave the organization of the healthcare professionals.

Methods: The sample of study consisted of 251 healthcare professionals who actively worked during the pandemic process. Data were collected by applying the "Coronavirus Anxiety Scale", "COVID-19 Burnout Scale", "Organizational Commitment Scale", and "Intention to Leave the Organization Scale".

Results: 66.5% of all participants worked in the pandemic units during the pandemic process, 57.4% of them had COVID-19, 75.3% of them had COVID-19 vaccine, and 32.3% of them lost a relative due to COVID-19. 42.2% of the healthcare professionals had dysfunctional anxiety and they experienced a very high level of burnout, their continuance commitment, which is one of the subscales of organizational commitment, was high, their affective and normative commitment was moderate, and their intention to leave the organization was moderate. The anxiety level of healthcare professionals explained 7.7% of the change in their intention to leave the organization. The anxiety ($p<0.05$) and burnout levels ($p>0.05$) together explained 8.5% o the change in intention to leave the organization. The Anxiety and burnout levels and organizational commitment levels together explained 25.9% of the change in intention to leave the organization ($p<0.05$).

Conclusions: The anxiety levels and the levels of affective organizational commitment of healthcare professionals during the pandemic process are significant predictors of intention to leave the organization. It is recommended that decision makers make arrangements that will improve health workers' intention to leave the organization, reduce anxiety and burnout levels, and increase organizational commitment levels.

Keywords: Anxiety, Burnout, Covid-19 Pandemic, Healthcare Professionals, Organizational Commitment

INTRODUCTION

Coronaviruses (CoVs) are a large family of viruses that can cause anything from the commoncold to more serious infections. A new infectious disease outbreak called COVID-19 was reported in December 2019 [1].

The highest risk occupational group against this virus, which has a high contagious rate, is the health field [2]. From past to present, healthcare professionals have been affected by many contagious diseases and are considered among the groups that are most likely to be affected by possible future pandemics [3]. Working in all health institutions and organizations, nurses, physicians, and all other allied healthcare professionals are exposed to the stress of pandemics at the highest level. As a result, pandemics endanger the physical and psychosocial health of these people [4]. At the beginning of the COVID-19 pandemic, it was predicted that healthcare professionals all over the world would face an unprecedented situation that they would have to make difficult decisions and would have to work under extreme pressure [5].

Healthcare professionals working with sick individuals during the pandemic are at high risk for mental problems in the short and long term. These mental problems can be especially psychological distress, insomnia, higher perceived stress, anxiety, burnout, anger, and depression. These mental problems, which may also affect the quality of patient care, may be related to personal, social, psychological, and organizational factors [6].

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When these factors, which can be effective during the pandemic period, are examined, the risks of being infected and ill, the risk of transmitting the disease to their closecircles, uncertainties about the pandemic, constantly changing protocols, increasing workload, and working hours, deprivation of social support resources, discourses, and approaches that devalue the efforts of healthcare professionals and the stigmatization of them cause mental burden and burnout in healthcare professionals [7-10]. While the burnout rates were high among health workers before the pandemic period, factors such as the anxiety of getting sick during the pandemic period increase burnout in healthcare professionals even more [10].

In addition, demoralization and reluctance to work are frequently observed in healthcare professionals as a result of increased hygiene practices, social distance, and isolation practices [11]. All these situations experienced during the COVID-19 pandemic period may cause reluctance in healthcare professionals to go to work and even leave the profession [8].

Job satisfaction is one of important variables that affect burnout [12]. Healthcare professionals may feel powerless, inadequate, and useless due to burnout, and as a result of these feelings, they may want to leave the organization they work for. The result of this request, which can also be called the intention to leave the job, may result in the employee leaving the organization or starting a new job search process [13]. The survival of an organization depends on the fact that the employees of that organization do not leave the organization. The more committed the employees are to the organization, the stronger the organization becomes. The strength of the bond that the employee feels towards the organization she/he works for is expressed as organizational commitment [14]. There are many factors that affect organizational commitment, such as the safety of the work environment, workload, stress, perceived support, attitudes of managers, rewards, punishments, and attention given to employees [12,15]. All negative behaviors experienced in the organization deeply affect the organizational commitment of the employees towards their work. The sense of organizational commitment reduces the negative consequences such as leaving the job that may occur in individuals [15].

According to the existing literature, studies with healthcare professionals during the COVID19 pandemic period have focused on variables such as fear of COVID-19, anxiety, burnout, hopelessness, depression, psychological well-being, and deterioration in sleep patterns [12,16-21].

In the literature, studies on the impact of the pandemic on organizational commitment and job satisfaction of healthcare professionals have been conducted [22-25]. There are studies examining the predictive effect of factors such as fear of COVID-19, perceived threat of COVID-19, and job stress in healthcare professionals [26-28].

When the current literature is examined, there is no study that examines the predictive effects of the levels of anxiety and burnout due to COVID-19 pandemic and organizational commitment in healthcare professionals on their intention to leave the organization. For this reason, the present study was conducted to determine (I) anxiety and burnout levels, organizational commitment and intention to leave the organization of healthcare professionals due to the COVID-19 pandemic; (II) identify the influential variables; and (III) the anxiety, burnout levels and organizational commitment to determine predictive effects of intentions to leave the organization.

METHODS

Design

This study was a descriptive survey to investigate the factors that influence predictive effect of anxiety and burnout levels related to the COVID-19 pandemic and organizational commitment on their ıntention to leave the organization of the healthcare professionals.

Setting and study participants

The descriptive study was carried out in a state hospital and two training and research hospitals located in two cities in the southeast of Turkey. Healthcare professionals working in these institutions formed population of the research. Sample of study consisted of 251 healthcare professionals who voluntarily accepted to participate in study and worked actively during pandemic process.

Data collection

The data was collected between the dates of June 2021 and October 2021 with an online survey due to the physical distance rules for the healthcare professionals participating in the study. Data were obtained, after their consent was obtained, and by applying the "Personal Information Form", "Coronavirus Anxiety Scale", "COVID-19 Burnout Scale", "Organizational Commitment Scale" and "Intention to Leave the Organization Scale".

Measurements Tools

Personal Information Form: Considering the aims of the study, this form was developed by the researchers, and it includes 14 questions to determine the socio-demographic characteristics, working conditions, and characteristics of the participants regarding the pandemic.

Coronavirus Anxiety Scale (CAS): The scale was developed by Lee (2020) to measure anxiety levels of individuals during the pandemic process (α=.93); additionally, Evren et al. (2020) carried out its validity and reliability study in Turkish. The scale consists of 5 items based on experiences in the last two weeks. The score range varies between 0- 20. A high score from the scale indicates a higher level of coronavirus-related anxiety in the individuals, and a total score of ≥ 9 indicates coronavirus-related dysfunctional anxiety [29,30]. In the present study, Cronbach's alpha value of the scale was determined to be 0.90.

COVID-19 Burnout Scale (COVID-19-BS): This scale was adapted from the Burnout Measure, Short Version developed by Malach-Pines in 2005. Turkish adaptation of scale was done by Yıldırım and Solmaz (2020). To adapt the COVID-19-BS, the wording and

response format of the original items were changed, such as first replacing "your business" with "COVID-19". The scale is a one-dimensional, 5-point Likert-type (1=never, 5=always) scale consisting of 10 items. A total score is obtained by summing all the answers on the scale, and the score range varies between 10-50, and the high score obtained from the scale indicates that the level of burnout related to COVID-19 has increased [31,32]. In the present study, Cronbach's alpha value of scale was determined to be 0.93.

Organizational Commitment Scale (OCS): The scale was developed by Allen and Meyer (1991), and it was translated into Turkish by Özkan (2010), and its validity and reliability studies were done by him. The scale has 3 subscales which are "Affective Commitment", "Continuance Commitment", and "Normative Commitment". The scale consists of 22 items, including 7 items on the affective commitments ubscale, 8 items on the continuance commitment subscale, and 7 items on the normative commitment subscale. It is a 5-point Likert type scale and the score range varies between 22-110. The highest and lowest values to be taken from the subscales of the scale are as follows; Affective Commitment 7-35, Continuance Commitment 8-40, Normative Commitment 7-35. An increase in the score obtained from the subscales of the scale indicates that the commitment to the institution increases [33,34]. In the current study, Cronbach's alpha value for the whole scale was detected to be. 86.

Intention to Leave the Organization Scale (ILOS): The scale was developed by Scott et al. in 1999 to determine the intentions to leave the organization of the employees. The Turkish validity and reliability study of the scale was done by Tanrıöver (2005). The scale is a one- dimensional, 5-point Likert-type scale consisting of 4 items. The score range varies between 10-50. High scores obtained from the scale indicate that individuals have a high intention to leave their organization [35,36]. The Cronbach's alpha value of the scale in the present study was .78.

Statistical Analysis

The data was analysed in the SPSS 22 package program. In the evaluation of the data, descriptive statistical methods, t-test, One Way Anova, Kruskal Wallis, Mann Whitney-U, correlation, and regression analyzes were used. The p-value was accepted as significant at the $p<0.05$ level.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the Clinical Research Ethics Committee of Gaziantep University (2021/215) and from the head of the university hospital in which the study was conducted. The purpose and process of this study was explained by the researchers to the participants. Before collecting the research data, after informing about the study, the participants' consents were obtained, and after that, the data was collected. The study participants were guranteed confidentiality and voluntary participation and provided their written informed consent.

RESULTS

172 (68.5%) of the 251 healthcare professionals participating in the study were female, the age range was mostly between 26-35 (62.5%). Of the participants, 93 (37.1%) were single. 28 were doctors (11.2%), 153 were nurses (61%), 17 were midwives (6.8%). The majority of the participants (35.1%) had a term of employment of 6-10 years in the healthcare sector, and the majority (59.8%) had been working in their current institutions for 0-5 years. 121 (48.2%) of the participants were currently working in internal/surgical units, 21 (8.4%) were working in the pandemic units, and 167 (66.5%) of all participants had the experience of working in the pandemic units during the pandemic process.

In terms of working patterns in the institution, the majority of the participants (39.4%) were working both during the day shifts and night shifts. The number of participants who experienced COVID-19 was 144 (57.4%), the number of those who had COVID-19 vaccine was 189 (75.3%), and the number of those who lost any relatives due to COVID-19 was 81 (32.3%) (Table 1).

When the scales' score of the healthcare professionals participating in the research were examined, the mean score of CAS was 7.49±5.53, the mean score of COVID-19-BS was 35.04±9.49, the mean score of the subscale of affective commitment OCS was 19.69±7.72, the mean of the subscale of continuance commitment from OCS was 26.97±7.92, and the mean score of the subscale of normative commitment from OCS was 20.10±5.86, and the mean score ILOS was 12.06±5.75 (Table 2).

A positive moderate correlation between CAS and the COVID-19-BS and a weak positive correlation between CAS and ILOS were found.

No correlation was found between CAS and the subscales of OCS ($p>0.05$). A weak positive correlation between Covid19-BS and ILOS, positive correlation between Covid-19-BS and subscales of ILOS were found.

A weak negative correlation was found between the affective and normative commitment subscales of OCS and ILOS (p=.000) (Table 3).

Three different models were developed in the multiple regression analysis to reveal whether the anxiety and participants during the pandemic process and their organizational commitment predict intention to leave the organization.

A significant correlation was found in regression analysis performed to reveal how the anxiety level predicted the intention to leave the organization in Model 1 ($F=20.642$, $p<0.001$). According to Model 1, the level of anxiety explained 7.7% of the change in the intention to leave the organization of healthcare professionals ($R=.277$, $R^2=.077$). While there was significant correlation for the anxiety ($F=11.448$, $p<0.05$), no significant correlation was found for the burnout in Model 2, which was conducted to reveal how the anxiety and burnout

levels together predicted the intention to leave the organization. The anxiety and burnlevels together explained 8.5% of the change in intention to leave the organization (R=.291, R^2=.085). A significant correlation was found in Model 3, which was conducted to reveal how the level of anxiety and burnout and organizational commitment (Affective commitment) predicted the intention to leave the organization (F=21,461, p<0.001). The anxiety and burnout levels and organizational commitment levels together explained 25.9% of the change in the intention to leave the organization (R=.509, R^2=.259). It was observed that anxiety levels and affective commitment levels of healthcare professionals during the pandemic were significant predictors of their intention to leave the organization (p<0.05) (Table 4).

Table 1. The Distribution of Socio-Demographic Characteristics of the Healthcare Professionals (n=251)

Socio-Demographical Characteristics		Number (%)
Gender		
Female		172 (68.5)
Male		79 (31.5)
Age		
18-25		34 (13.5)
26-35		156 (62.5)
36-45		54 (21.5)
46 and more		7 (2.8)
Marital status		
Single		93 (37.1)
Married		158 (62.9)
Occupation		
Doctor		28 (11.2)
Nurse		153 (61.0)
Midwife		17 (6.8)
Laborant/Radiology technician		11 (4.4)
Paramedic/Emergency medical technician		3 (1.2)
Other		39 (15.5)
Term of employment in the healthcare industry		
0-5 years		87 (34.7)
6-10 years		88 (35.1)
11-15 years		45 (17.9)
16 years and more		31 (12.4)
Term of employment at current institution		
0-5 years		150 (59.8)
6-10 years		63 (25.1)
11-15 years		23 (9.2)
16 years and more		15 (6.0)
Current unit of work		
Emergency Service		27 (10.8)
Internal Units/Surgical Units		121 (48.2)
Pandemic Services/Intensive Care for the Pandemic		21 (8.4)
Intensive Care		30 (12.0)
Management and Other		52 (20.7)
The experience of working in the pandemic units during the pandemic process		
Present		167 (66.5)
Not present		84 (33.5)

Working pattern in the institution		
Day shift		83 (33.1)
Both day shift and night shift		99 (39.4)
Night shift		69 (27.5)
History of having COVID-19		
Present		107 (42.6)
Not present		144 (57.4)
The status of being vaccinated against COVID-19		
Present		189 (75.3)
Not present		62 (24.7)
History of losing any relatives due to COVID-19		
Present		81 (32.3)
Not present		170 (67.7)
The thoughts on the adequacy of protective equipment in the institution during the COVID-19 pandemic process		
Adequate		188 (74.9)
Inadequate		63 (25.1)
The thoughts on the adequacy of the number of healthcare professionals in the institution during the COVID-19 pandemic process		
Adequate		116 (46.2)
Inadequate		135 (53.8)

Table 2. The Mean Scores of Healthcare Professionals on the Coronavirus Anxiety Scale, Covid-19 Burnout Scale, Organizational Commitment Scale, and Intention to Leave the Organization Scale

Scales	X±SD	Min.	Max.
Coronavirus Anxiety Scale	7.49±5.53	0.00	20.00
COVID-19 Burnout Scale	35.04±9.49	10.00	50.00
Organizational Commitment Scale			
Affective Commitment	19.69±7.72	7.00	35.00
Continuance Commitment	26.97±7.92	8.00	40.00
Normative Commitment	20.10± 5.86	7.00	35.00
Intention to Leave the Organization Scale	12.06±5.75	4.00	24.00

Table 3. The Correlation Between the Mean Scores of Healthcare Professionals from the Coronavirus Anxiety Scale, Covid-19 Burnout Scale, Organizational Commitment Scale, and Intention to Leave the Organization Scale

	CAS	COVID-19-BS	Affective Commitment Subscale	Continuance Commitment Subscale	Normative Commitment Subscale	ILOS
Coronavirus Anxiety Scale (CAS)	1					
The COVID-19 Burnout Scale (COVID-19-BS)	**r**=0.536 p=0.000**	1				
Affective Commitment Subscale	r=0.116 p=0.068	r=-.103 p=0.104	1			
Continuance Commitment Subscale	r=0.052 p=0.412	**r**=0.222 p=0.000**	r=0.065 p=0.304	1		
Normative Commitment Subscale	r=0.099 p=0.118	r=-.077 p=0.226	r**=0.554 p=0.000	r=0.210 p=0.001	1	
Intention to Leave the Organization Scale (ILOS)	r**=0.277 p=0.000	r**=0.224 p=0.000	**r**=-,381 p=0.000**	r=-,027 p=0.672	r=-,280 p=0.000	1

****0.01**

Table 4. Determination of the Anxiety and Burnout Levels and Organizational Commitment of Healthcare Professionals in the COVID-19 Pandemic Process to Predict their Intention to Leave the Organization

Models	Variables	R	R^2	B	SD	β	F	t	p
Model 1	Constant	0.277	0.077	90.906	0.590		200.642	160.795	0.000
	Coronavirus Anxiety Scale			0.288	0.063	0.277		40.543	0.000
Model 2	Constant	0.291	0.085	80.102	10.362		110.448	50.949	0.000
	Coronavirus Anxiety Scale			0.229	0.075	0.220		30.056	0.002
	COVID-19 Burnout Scale			00.640	0.044	0.106		10.469	0.143
Model 3	Constant	0.509	0.259	160.934	10.787		210.461	90.478	0.000
	Coronavirus Anxiety Scale			0.341	0.069	0.328		40.921	0.000
	COVID-19 Burnout Scale			0.002	0.040	0.003		0.041	0.967
	The Subscale of Affective Commitment			-0.264	0.050	-0.355		-0.50.133	0.000
	The Subscale of Normative Commitment			-0.113	0.065	-0.116		-0.10.750	0.081

a. Dependent Variable: Intention to Leave the Organization

b. Predictors: (Constant), Coronavirus Anxiety Scale, COVID-19 Burnout Scale, The Subscale of Affective Commitment, The Subscale of Normative Commitment

Table 5. The Comparison of the mean scores of the scales on the Coronavirus Anxiety Scale, Covid-19 Burnout Scale, Organizational Commitment Scale, and the Intention to Leave the Organization Scale according to the descriptive characteristics of the participants

Characteristics	n	CAS	COVID-19-BS	Affective Commitment	Continuance Commitment	Normative Commitment	ILOS
		X±SD	X±SD	X±SD	X±SD	X±SD	X±SD
Gender							
Female	172	7.98±5.47	36.05±9.52	19.71±7.61	26.84±7.91	20.18±6.03	11.99±5.87
Male	79	6.43±5.54	32.86±9.11	19.65±8.01	27.26±8.00	19.93±5.53	12.21±5.52
P		0.977	0.422	0.138	0.771	0.167	0.364
Age							
18-25	34	7.32±5.41	34.94±9.10	18.47±5.96	28.85±7.27	19.02±5.38	12.11±4.37
26-35	156	7.40±5.54	35.85±9.37	18.84±7.73	26.82±7.80	19.93±6.03	12.88±6.04
36-45	54	7.72±5.80	33.00±10.00	21.64±7.83	26.74±8.40	21.11±5.57	10.07±5.11
46 and more	7	8.57±4.54	33.14±9.33	29.57±5.28	23.00±9.36	21.28±6.44	8.85±6.03
p		0.914	0.312	0.001**	0.330	0.225	0.008*
Occupation							
Doctor	28	6.17±5.47	30.89±11.14	19.25±7.34	24.96±8.69	18.07±6.17	12.32±6.03
Nurse	153	7.58±5.67	35.16±9.66	18.85±7.65	26.76±7.66	19.87±5.78	12.64±5.72
Midwife	17	8.70±5.00	35±7.43	21.35±5.91	27.35±8.10	20±6.07	12.17±5.44
Laborant	11	7.54±4.00	35.27±7.44	23.27±8.68	31.54±7.67	21.18±5.86	11±4.00
Paramedic	3	4.33±3.05	43.33±3.51	18±4.35	35.66±4.04	25±5.19	9.33±2.51
Other	39	7.79±5.73	36.8±8.44	21.71±8.50	27.12±8.08	21.82±5.57	10.07±6.13
p		0.622	0.103	0.164	0.099	0.093	0.199

Term of employment at current institution							
0-5 years	150	7.40±5.55	34.96±9.52	18.51±7.23	27.13±7.86	19.98±5.45	12.64±5.62
6-10 years	63	6.93±5.54	35.20±10.18	19.47±7.83	27.03±8.20	19.88±6.40	11.77±6.27
11-15 years	23	8.21±5.86	35.08±8.53	24.60±7.89	26.43±8.33	22.13±7.72	9.43±5.36
16 years and more	15	9.66±4.49	35.20±8.42	24.93±7.43	26.00±7.33	19.06±3.88	11.53±4.40
p		.250	.963	.000**	.892	.272	.059
Current unit of work							
Emergency Service	27	7.81±5.85	32.96±10.81	19.48±8.82	26.92±8.52	20.25±5.29	12.37±5.69
Internal Units/ Surgical Units	121	6.58±5.10	34.28±9.46	19.26±7.32	26.95±7.60	20.21±5.86	12.18±5.68
Pandemic Services/Intensive Care for the Pandemic	21	10.95±5.12	37.47±9.02	20.38±6.65	28.42±6.32	19.76±4.38	12.23±5.45
Intensive Care	30	6.70±5.89	35.56±10.30	17.53±6.31	26.43±8.09	18.03±5.93	12.33±5.09
Management and Other	52	8.50±5.73	36.61±8.40	21.78±8.83	26.76±8.99	21.09±6.52	11.40±6.55
p		.010**	.437	.166	.934	.318	.772
The experience of working in the pandemic units during the pandemic process							
Present	167	7.54±5.58	35.25±9.81	18.59±7.36	26.78±7.95	19.34±5.61	12.41±5.77
Not present	84	7.39±5.46	34.64±8.87	21.89±8.00	27.35±7.90	21.61±6.09	11.35±5.69
p		.843	.433	.002	.584	.008*	.150
History of having COVID-19							
Present	107	7.49±5.55	35.22±9.73	19.92±7.69	26.40±8.24	20.6±6.11	11.86±5.74
Not present	144	7.49±5.53	34.91±9.35	19.52±7.77	27.40±7.68	19.68±5.66	12.20±5.78
p		.866	.313	.983	.430	.320	.741
The status of being vaccinated against COVID-19							
Present	189	7.81±5.72	32.22±9.74	20.12±7.89	27.16±7.91	20.35±6.08	12.11±5.82
Not present	62	6.51±4.82	34.5±8.75	18.40±7.10	26.38±7.98	19.30±5.12	11.91±5.58
p		.018*	.237	.384	.910	.144	.588
History of losing any relatives due to COVID-19							
Present	81	9.20±5.48	36.70±7.98	20.41±7.91	27.53±8.27	20.59±5.71	12.80±5.70
Not present	170	6.67±5.38	34.25±10.06	19.35±7.63	26.71±7.76	19.87±5.94	11.71±5.76
p		.944	.018*	.976	.874	.629	.969
The thoughts on the adequacy of protective equipment in the institution during the COVID-19 pandemic process							
Adequate	63	8.85±5.55	36.46±10.12	18.92±6.95	26.12±8.54	19.26±5.91	13.58±5.90
Inadequate	188	7.03±5.46	34.57±9.25	19.95±7.96	27.26±7.71	20.38±5.84	11.55±5.63
p		.990	.194	.118	.208	.965	.784
The thoughts on the adequacy of the number of healthcare professionals in the institution during the COVID-19 pandemic							
Adequate	135	8.15±5.64	36.18±9.67	19.06±6.80	26.54±7.96	19.63±5.53	12.94±5.65
Inadequate	116	6.72±5.32	33.72±9.14	20.43±8.64	27.48±7.87	20.64±6.21	11.03±5.72
p		.545	.336	.000**	.836	.188	.877

**p<0.05, **p<0.001*

In Table 5, the scales' averages of the participants were compared according to some sociodemographic and employment characteristics. There was no difference in the scores of the scales according to the gender and occupation of the participants (p>0.05).

When evaluated in terms of the age variable, if there was no difference in the anxiety and burnout levels in terms of age groups ($p>0.05$), the average score of the subscale of the Affective Commitment from the Organizational Commitment Scale of the participants aged 46 and over was significantly higher than the other age groups of the participants ($p<0.001$). The Intention to Leave the Organization Scale's mean scores were found to be significantly lower ($p<0.01$) compared to other age groups. When examined in terms of the term of employment in the current institution, the score average of the subscale of the Affective Commitment from the Organizational Commitment Scale of the participants who worked in their current institutions for 16 years or more was found to be higher than the other groups ($p<0.001$).

When effects of the units that the participants were currently working on the anxiety levels of the participants were examined, the score of CAS of participants working in the pandemic units was found to be higher than score of the participants working in the other units ($p<0.01$). The score average of the subscale of the Normative Commitment from the OCS of the participants who had working experience in the pandemic units was found to be significantly lower than the average score of those who did not have the experience of working in the pandemic units ($p<0.005$). There was no significant difference in the mean score of the scale for history of having COVID-19 ($p>0.05$).

When the participants were examined in terms of the variable of being vaccinated against COVID-19, it was seen that score of CAS was higher in the participants who were vaccinated against COVID-19 than those who did not ($p<0.05$). The score of COVID-19-BS was found to be higher for the people who lost their relatives due to COVID-19 than those who did not ($p<0.05$).

It was detected that score of subscale of the Emotional Commitment from the OCS of the participants who thought that the number of healthcare professionals in their institutions was sufficient during the pandemic process was lower than the other group ($p<0.001$).

DISCUSSION

Considering the working conditions during the pandemic process, it is possible to say that the most difficult and risky professions are those who work in the health sector. The risk of transmission of the disease is higher in healthcare professionals than in others due to their direct and prolonged contact with patients. The unpredictable nature of the COVID-19 pandemic and the alarming incidence of infected professionals have significant impact on psychological health of healthcare professionals [37].

In this case, it becomes more important to know the anxiety, burnout perceptions, organizational commitment levels, intentions to leave the organization, and the variables that affect healthcare professionals. It is important to examine healthcare professionals in terms of these elements in order to manage the health system as it should be during pandemic periods.

In the current study, the majority of the participants were nurses, and doctors and other healthcare professionals were in the minority. 66.5% of all participants worked in the pandemic units during the pandemic process, 57.4% of them had COVID-19, 75.3% of them had COVID19 vaccine, and 32.3% of them lost a relative due to COVID-19.

When the anxiety levels of healthcare professionals participating in the study due to coronavirus were evaluated, the mean CAS score was found to be 7.49±5.53. In the evaluation of the scale, it was stated that higher scores indicated higher levels of anxiety, while scores of 9 and above indicated dysfunctional anxiety. In the light of this information, it was detected that although the anxiety level of healthcare professionals was relatively low, a substantial proportion of 42.2% had dysfunctional anxiety. In the meta-analysis study of Pappa et al., in which they examined prevalence of anxiety among healthcare professionals during the pandemic, the combined prevalence of anxiety among 12 studies was reported as 24.06% [19]. In the study of Şahin et al. (2020), in which they examined prevalence of anxiety among healthcare professionals during the COVID-19 process in our country, it was revealed that 60.2% of participants had anxiety symptoms [21]. These rates indicated that the anxiety problem experienced by healthcare professionals during the pandemic is a situation that needs to be addressed in terms of employee health. In this process, it has been reported that the frequency of anxiety disorders, post-traumatic stress, and health anxiety symptoms have increased in the general population [38].

It is possible to say that the levels of burnout due to COVID-19 of participants in the present study were quite high. Similar results were seen in studies carried out in different countries. For example, in the study of Orrù et al., 56% of healthcare professionals experienced emotional exhaustion [18], in addition, in the study of Denning et al. (2021) with 3573 healthcare professionals from the UK, Poland, and Singapore, it was revealed that 67% of healthcare professionals experienced burnout [17]. Before the pandemic, healthcare professionals' burnout levels were increasingly noticed as public health crisis in many countries. As COVID-19 spreads around the world, doctors, assistants, nurses, and other healthcare professionals are putting their own health at risk like never before. Excessive workload, lack of information about the mechanism of the virus, lack of treatment for the disease, difficult decisions to make, insufficient supply of personal protective equipment, fear of being infected and transmitting the disease to their families and close circle, witnessing the death of their patients caused healthcare professionals to be under extraordinary stress. All these negativities of the pandemic can cause to burnout in healthcare professionals. In this process, there is concern that burnout and posttraumatic stress disorder may become a 'parallel epidemic'. Concrete actions towards modifiable factors are critical in the management of the pandemic to prevent burnout in healthcare professionals, which is higher than previously reported rates [37].

In the present study, among the subscales of organizational commitment of healthcare professionals participating in the

research, it can be said that their continuance commitment was high, and their affective and normative commitment were at moderate levels. While affective commitment is related to emotional reactions of individuals towards the institution they work for and the satisfaction they get through the institution, continuance commitment is related to the thoughts of the individuals about the losses they will encounter as a result of leaving the institution they work for, and normative commitment is related to the individuals' feeling that they have to always stay connected to the organization they work for [39,34]. It was detected that the continuance commitment of healthcare professionals who participated in the present study was higher than their affective and normative commitments. No matter how high the difficulties experienced during the pandemic process are, it is thought that the deep feeling of the importance and indispensableness of the work they do for human health is effective in this high level of commitment.

Organizational commitment is one of the important factors affecting the performance of healthcare professionals during the COVID-19 period. Yáñez-Araque et al. revealed that healthcare professionals showed excellent commitment during the pandemic [40]. In the study of Sevinç Altaş during the COVID-19 period, it was determined that the organizational commitment of healthcare professionals was high [41]. In the comprehensive study of Gürcüoğlu et al., in which they collected data from 7 regions in our country during the COVID-19 process, it was revealed that score of subscale of the affective commitment from the organizational commitment scale of healthcare professionals was the highest, while score of normative commitment was at the lowest level among the other subscales [25]. In the study of Aminizadeh et al., in which they examined organizational commitment of paramedics during the pandemic process, it was revealed that normative commitment had the highest average among the other subscales and the affective commitment had the lowest average among the other subscales [24].

It can be said that intention to leave the organization of participants in the study was at moderate level. In the study conducted by Uçar et al. in a private hospital during the pandemic, it was revealed that intention to leave the organization was higher in nurses than in other healthcare professionals [42]. In their study, Çini et al. revealed that job stress experienced by healthcare professionals during the pandemic negatively affected thei rintention to stay at the organization through job satisfaction [26].

COVID-19 pandemic affects not only physical health but also mental health and working life [11]. The Covid-19 crisis caused increase in level of anxiety and burnout in individuals [43]. Increasing anxiety and burnout reduced the organizational commitment of individuals. As a result, the intention to leave the organization of the individuals increased because their burnout levels increased and their organizational commitment decreased [44]. No study has been found in the literature examining the relationship between the level of burnout and organizational commitment of healthcare professionals during the pandemic. According to the results of Esen's study with the participation of 182 healthcare professionals before the pandemic in 2019, it was determined that level of professional burnout is a full mediator in relationship between job stress and organizational commitment [45].

In a study by Irshad et al., it was concluded that the perceived threat of COVID-19 increased anxiety and intention to leave the organization among the nurses [28]. In their meta-analysis studies, in which Meyer et al. explained the three components of the organizational commitment scale, it was revealed that affective commitment, continuance commitment, and normative commitment were related to intention to leave the organization [47]. As a result of the situations where three components of organizational commitment scale decrease, that is, the decrease in the organizational commitment of the employees, and the increase in the intention to leave the job, results in leaving the organization and labor turnover [34,47]. It has been revealed that an increase in the affective and normative commitments and a decrease in the continuance commitment increase the health and well-being of employees. In addition, it has been revealed that organizational commitment is related to job satisfaction, job participation, and professional commitment [47]. In the literature, it is emphasized that the stronger institutional commitment of health professionals during the pandemic process is a very important factor affecting the intention of these individuals to stay in their jobs [23].

In addition, the socio-demographic and the variables of employment characteristics that may affect the anxiety and burnout levels, organizational commitment, and intention to leave the organization of healthcare professionals due to the pandemic were investigated in the present study. As a results, it was detected that the employees aged 46 and over have higher Affective Commitment and lower intention to leave the organization compared to the others. The participants who have worked in their current institutions for 16 years or more had higher Affective Commitment than those who have worked less. The age and term of employment were among the important factors affecting organizational commitment in the literature. According to the literature, older individuals tend to be more committed to their organizations compared to young people, and it is claimed that older employees were more likely to be satisfied with their professions and their positions in their organizations as the reason for this commitment [46,47]. According to the results of another study, it was revealed that the older employees in the organization and the individuals who work longer in the organization had higher organizational commitment because they had higher autonomy [48]. Örs et al. (2003) showed that there was no significant correlation between the age and organizational commitment [49].

When the effect of the current units of the participants on anxiety was examined, it was found that anxiety level of professionals working in the pandemic units was significantly higher than professionals working in other units. In the literature, results consistent with the present study findings were obtained [20,50,51].

The levels of Normative Commitment, one of the subscales of the Organizational Commitment Scale, were found to be lower than those who did not have the experience of working in the pandemic units. These organizational commitment levels can be increased by rotating the employees in the pandemic units. According to the present study's literature review, it has been observed that no study has yet been conducted between this variable and the organizational commitment.

When evaluated according to the status of having COVID-19 vaccination, the anxiety level of the participants with vaccination was significantly higher than the participants who were not vaccinated ($p<0.05$). Bayülgen et al. (2021), in their study to determine the anxiety and hopelessness levels of nurses in the pandemic process before the COVID-19 vaccine was developed, revealed that the high anxiety levels of nurses may be related to the fact that an effective vaccine has not been developed yet [20].

When evaluated in terms of the history of losing a relative due to COVID-19, it has been shown that the burnout level of people who lost a relative was significantly higher. During the pandemic, people's fear of losing one of their relatives due to this disease is one of the factors that negatively affect psychological health of individuals [16]. This higher level of burnout may be due to reasons such as working at the forefront of the COVID-19 process, providing one-on-one care to patients with COVID-19, and fear of transmitting this disease to their relatives.

Limitations

The main limitation of this study the fact that it only included health workers working in a certain region. Another limitation of the study is that the variables of the study were evaluated only with self-report scales.

CONCLUSION

In the present study, correlation between levels of anxiety and burnout, organizationalcommitment, and intention to leave the organization of healthcare professionals due to the pandemic was examined. According to results of current study, as anxiety levels of healthcare professionals increased during the pandemic process, their burnout levels and intention to leave organization also increased. As burnout levels of healthcare professionals increased, level of organizational commitment (continuance commitment) decreased, and their intention to leave organization increased. As normative commitment and affective commitment levels of participants decreased, their intention to leave organization increased.

It has been observed that anxiety levels and affective commitment levels of participants during the pandemic process are significant predictors of intention to leave the organization. Individuals' intention to leave organization increases, if their anxiety and burnout levels increase, and their organizational commitment decreases. The results of the study presented scientific data that decision-makers should make arrangements to reduce the intention to leave the organization of the healthcare professionals, reduce anxiety and burnout levels, and increase organizational commitment levels during the pandemic periods.

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REFERENCES

1- T.R. Ministry of Health General Directorate of Public Health. (2020). COVID-19 (SARSCoV-2 Infection) general ınformation, epidemiology and diagnosis. T.R. Ministry of Health. Available from: https://covid19.saglik.gov.tr/Eklenti/39551/0/covid19rehberigenelbilgilerepidemiyolojivetanipdf.pdf. Accessed 26 December 2021.

2- Çetintepe SP, İlhan MN (2020) Risk Reduction in Healthcare Workers in the Covid-19 Outbreak. J Biotechnol and Strategic Health Res. 1:50-54. https://doi.org/10.34084/bshr.712539

3- Çalışkan Pala S, Metintaş S (2020) Healthcare Professionals in the Covid-19 Pandemic Estüdam Halk Sağlığı Dergisi. 5(COVID-19 Special Issue):156-68. https://doi.org/10.35232/estudamhsd.789806

4- Enli Tuncay F, Koyuncu E, Özel Ş (2020) A Review of Protective and Risk Factors Affecting Psychosocial Health of Healthcare Workers in Pandemics. Ankara Med J. 2:488-501. https://doi.org/10.5505/amj.2020.02418

5- Greenberg N, Docherty M, Gnanapragasam S, Wessely S (2020) Managing Mental Health Challenges Faced by Healthcare Workers During Covid-19 Pandemic. BMJ. 368:m1211. https://doi.org/10.1136/bmj.m1211

6- Stuijfzand S, Deforges C, Sandoz V, Sajin CT, Jaques C, Elmers J, et al (2020) Psychological Impact of an Epidemic/Pandemic on the Mental Health of Healthcare Professionals: A Rapid Review. BMC Public Health. 20:1230. https://doi.org/10.1186/s12889- 020-09322-z

7- Yılmaz Karaman İG, Yastıbaş C (2021) The Relationship of Depression, Anxiety and Posttraumatic Stress Symptoms with Sociodemographic and Vocational Variables in Healthcare Professionals Who Work in COVID-19 Pandemia. Van Tıp Derg. 28(2):249-257. https://dx.doi.org/10.5505/vtd.2021.55453

8- Ataç Ö, Sezerol MA, Taşçı Y, Hayran O (2020) Anxiety and İnsomnia Among Healthcare Workers During the COVID-19 Pandemic. Turk J Public Health. 18:47-57. https://doi.org/10.20518/tjph.767187

9- Gomez Salgado J, Domínguez-Salas S, Romero-Martín M, Ortega-Moreno M, García- Iglesias JJ, Ruiz-Frutos J (2020) Sense of Coherence and Psychological Distress Among Healthcare Workers During the COVID-19 Pandemic in Spain. Sustainability. 12:6855. https://doi.org/10.3390/su12176855

10- Yumru M (2020) COVID-19 and Burnout in Health Workers. Klin Psikiyatr. 23(Ek 1):5-6. https://doi.org/10.5505/kpd.2020.18942

11- Restubog SLD, Ocampo ACG, Wang L (2020) Taking Control Amidst the Chaos: Emotion Regulation During the COVID-19 Pandemic. J Vocat Behav. 119:Article 103440. https://doi.org/10.1016/j.jvb.2020.103440

12- Arpacıoğlu MS, Baltacı S, Ünübol B (2021) Burnout, Fear of Covid, Depression, Occupationalsatisfaction Levels and Related Factors in Healthcare Professionals in the COVID-19 Pandemic. Cukurova Med J. 46(1):88-100. https://doi.org/10.17826/cumj.785609.

13- Aytaç S, Çetin Aydın G. (2020) The Relationship Between Psychological Health, Burnout and Intention to Leave: A Study on Health Workers. In: Akar S (ed). Health with its socio-economic dimension. [Uluslararası Farklı Boyutlarıyla Sağlık Konferansı]. Select papers. E-book, pp. 79-94.

14- Özata M (2015) The Determination of Organizational Commitment Levels of Health Staffs in Hospitals. Sosyal Bilimler Meslek Yüksekokulu Dergisi. 18(1):155-166.

15- Eren H, Demirgöz Bal M (2015) Organizational Commitment in Nursing. SHYD. 1(2):44-50. https://doi.org/10.5222/SHYD.2015.044

16- Alper Ay F, İçen BT (2021) Evaluation of Covid-19 Anxiety and Burnout Levels of Health Workers in the 3rd Peak Period of the Covid-19 Pandemic in Turkey. J Int Soc Res. 14(80):1-17.

17- Denning M, Goh ET, Tan B, Kanneganti A, Almonte M, Scott A, et al (2021) Determinants of Burnout and Other Aspects of Psychological Well-Being in Healthcare Workers During the COVID-19 Pandemic: A Multinational Cross-Sectional Study. Plos One. 16(4):e0238666. https://doi.org/10.1371/journal.pone.0238666

18- Orrù G, Marzetti F, Conversano C, Vagheggini G, Miccoli M, Ciacchini R, et al (2021) Secondary Traumatic Stress and Burnout in Healthcare Workers During COVID-19 Outbreak. Int J Environ Res Public Health. 18(1):337. https://doi.org/10.3390/ijerph18010337

19- Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P (2020) Prevalence of Depression, Anxiety, and Insomnia Among Healthcare Workers During the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. Brain Behav Immun. 88:901-907. https://doi.org/10.1016/j.bbi.2020.05.026

20- Yeşil Bayülgen M, Bayülgen A, Yeşil FH, Türksever HA (2021) Determination of Anxiety and Hopelessness Levels of Nurses Working During the COVID-19 Pandemic Process. SBÜ Hemşirelik Dergisi, 3(1):1-6. https://doi.org/10.48071/sbuhemsirelik.839229.

21- Şahin MK, Aker S, Şahin G, Karabekiroğlu A (2020) Prevalence of Depression, Anxiety, Distress and Insomnia and Related Factors in Healthcare Workers During COVID-19 Pandemic in Turkey. J Community Health. 45(6):1168-1177. https://doi.org/10.1007/s10900-020-00921-w

22- Chanana N (2021) The Impact of COVID-19 Pandemic on Employees Organizational Commitment and Job Satisfaction in Reference to Gender Differences. J Public Affairs. e2695:1. https://doi.org/10.1002/pa.2695

23- Sharif Nia H, Arslan G, Naghavi N, Sivarajan Froelicher E, Kaveh O, Pahlevan Sharif S, et al (2021) A Model of Nurses' Intention to Care of Patients with COVID-19: Mediating Roles of Job Satisfaction and Organisational Commitment. J Clin Nurs. 30(11- 12):1684-1693. https://doi.org/10.1111/jocn.15723

24- Aminizadeh M, Saberinia A, Salahi S, Sarhadi M, Jangipour Afshar P, et al (2021) Quality of Working Life and Organizational Commitment of Iranian Pre-Hospital Paramedic Employees During the 2019 Novel Coronavirus Outbreak. Int J Healthc Manag. 1-9. https://doi.org/10.1080/20479700.2020.1836734

25- Gürcüoğlu S, Hürmet Çetinel M, Karagöz A (2020) Job Satisfaction Organizational Commitment Relationship: A Research on Airline Employees. J Hum Sci. 17(4):1204-21. https://doi.org/10.14687/jhs.v17i4.6096

26- Çini MA, Erdirençelebi M, Ertürk E (2021) The Effect of Work Stress with Mediation Effect of Job Satisfaction on Intention to Stay at Work in the Covıd-19 Pandemic Period. İAD. 13(3):2356-2375. https://doi.org/10.20491/isarder.2021.1266

27- Yiğitol B, Büyükmumcu S (2021) Analysis of the Relationships Between Fear of Covid-19, Personality Traits, Job Performance and Turnover Intention. OPUS Int J Soc Res (Pandemic Special Issue). 17:3414-3447. https://doi.org/10.26466/opus.890502

28- Irshad M, Khattak SA, Hassan MM, Majeed M, Bashir S (2020) How Perceived Threat of Covid-19 Causes Turnover Intention Among Pakistani Nurses: A Moderation and Mediation Analysis. Int J Ment Health Nurs. 30(1):350. https://dx.doi.org/10.1111%2Finm.12775.

29- Lee SA (2020) Coronavirus Anxiety Scale: A Brief Mental Health Screener for COVID-19 Related Anxiety. Death Stud. 44(7):393-401. https://doi.org/10.1080/07481187.2020.1748481

30- Evren C, Evren B, Dalbudak E, Topcu M, Kutlu N (2020) Measuring Anxiety Related to COVID-19: A Turkish Validation Study of the Coronavirus Anxiety Scale. Death Stud. 3:1-7. https://doi.org/10.1080/07481187.2020.1774969

31- Yıldırım M, Solmaz F (2022) COVID-19 Burnout, COVID-19 Stress and Resilience: Initial Psychometric Properties of COVID-19 Burnout Scale. Death Stud. 46(3):524- 532. https://doi.org/10.1080/07481187.2020.1818885

32- Malach Pines A (2005) The Burnout Measure Short Version (BMS). Int J Stress Manag. 12(1):78-88. https://psycnet.apa.org/doi/10.1037/1072-5245.12.1.78

33- Meyer JP, Allen NJ (1991) A Three Component Conceptualization of Organizational Commitment. Hum Resour Manag Rev. 1:61-89. https://doi.org/10.1016/1053-4822(91)90011-Z

34- Özkan S (2010) The Organizational Commitment And Work Values of Primary School Teachers. Mersin University, Social Sciences Enstitüte, Master Thesis.

35- Tanrıöver U (2005) The Effects of Learning Organization Climate and Self Directed Learning on Job Satisfaction, Affective Commitment and Intention to Turnover. Marmara University, Social Sciences Enstitüte, Master Thesis.

36- Scott CR, Connaughton SL, Diaz-Saenz HR, Maguire K, Ramirez R, Richardson B, et al (1999) The İmpacts of Communication and Multiple Identifications on Intent to Leave: A Multimethodological Exploration. Manag Commun Q. 12(3):400-435. https://doi.org/10.1177%2F0893318999123002

37- Özışık L. (2020). Burnout Among Healthcare Professionals During COVID-19 Pandemic. In: Sain Güven G, Uyaroğlu OA (ed). İç Hastalıkları ve COVID-19. 1st Edn. Ankara: Türkiye Klinikleri. pp.103-8.

38- Çakır Kardeş V. (2020). Anxiety Disorders and Depression During Pandemics with the Updates on COVID-19. In: Coşar B (ed) Psikiyatri ve COVID-19. 1st Edn. Ankara: Türkiye Klinikleri. pp. 23-9.

39- Demir F, Yıldırım G (2020) The Role of Internal Communication on Institutional Commitment in the Context of the System Theory in Public Relations: Comparative Analysis in the Transportation Sector. SBAD. 3(2):170-194. https://doi.org/10.38004/sobad.773966

40- Yáñez-Araque B, Gómez-Cantarino S, Gutiérrez-Broncano S, López-Ruiz VR (2021) Examining the Determinants of Healthcare Workers' Performance: A Configurational Analysis During COVID-19 Times. IJERPH. 18(11):5671. https://doi.org/10.3390/ijerph18115671

41- Altaş SS (2021) The Relationships Between Health Workers' Organizational Identification, Organizational Commitment, Organizational Trust and Perceived Organizational Support. İAD. 13(1):875-891. https://doi.org/10.20491/isarder.2021.1171

42- Uçar MZ, Akbolat M, Özer A (2021) Transformation of Business Management in the Covid-19 Pandemic. In: Akbolat M, Ünal Ö (ed) Investigation of the Relationship Between Alturistic Leadership and Intention to Leave the Work in Health Care Workers in the Covid-19 Period. Ankara. pp. 1-12.

43- Yáñez JA, Jahanshahi AA, Alvarez-Risco A, Li J, Zhang SX (2020) Anxiety, Distress, and Turnover Intention of Healthcare Workers in Peru by Their Distance to the Epicenter During the COVID-19 Crisis. ASTMH. 103(4):1614. https://dx.doi.org/10.4269%2Fajtmh.20-0800

44- Aydın AU, Akgemci T (2020) The Effects of Burnout Syndrome on The Intention of Quitting Job: The Case of Banking Sector Employees. SPMJ. 6(11):103-114. https://doi.org/10.25069/spmj.634829.

45- Esen M (2019) The Relationship Between Job Stress, Burnout and Organizational Commitment: A Research on Health Employees. Ekonomik ve Sosyal Araştırmalar Dergisi. 15(1):1-13.

46- Özkaya MO, Kocakoç İD, Karaa E (2016) Examining the Relations Between Demographic Factors and Managers' Organizational Commitment: A Field Study. CBÜ İİBF Yönetim ve Ekonomi Dergisi. 13(2):77-96.

47- Meyer JP, Stanley DJ, Herscovitch L, Topolnytsky L (2002) Affective, Continuance, and Normative Commitment to the Organization: A Meta-Analysis of Antecedents, Correlates, and Consequences. J Vocat Behav. 61:20–52. https://doi.org/10.1006/jvbe.2001.1842

48- Brimeyer TM, Perrucci R, Wadsworth SM (2010) Age, Tenure, Resources for Control, and Organizational Commitment. Soc Sci Q. 91(2):511-530.

49- Örs M, Acuner AM, Sarp N, Önder ÖR (2003) Evaluation of the Views of the Medical Doctors and Nurses Working in the Hospitals Concerning Their Loyalties to Their Organizations. Ankara Üniversitesi Tıp Fakültesi Mecmuası. 56(4).

50- Arnetz J, Goetz CM, Sudan S, Arble E, Janisse J, Arnetz BB (2020) Personal Protective Equipment and Mental Health Symptoms Among Nurses During the COVID-19 Pandemic. JOEM. 62(11):892-897. https://doi.org/10.1097/JOM.0000000000001999

51- Naushad VA, Bierens JJ, Nishan KP, Firjeeth CP, Mohammad UH, Maliyakkal AM, et al (2019) A Systematic Review of the Impact of Disaster on the Mental Health of Medical Responders. PMD. 34(6):632-643. https://doi.org/10.1017/s1049023x19004874

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Original Research

Relationship Between Ostiomeatal Complex Variations and Maxillary Sinus Pathologies in Children and Adolescents Using CBCT

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ABSTRACT

Objective: The aim of this study is to evaluate relationship between ostiomeatal complex variations (OMC) and maxillary sinus pathologies in children and adolescents using cone-beam computed tomography (CBCT).

Methods: CBCT images of 72 patients (44 males and 28 females) aged 7-18 years were evaluated retrospectively. Presence of nasal septal deviation (NSD), nasal septal pneumatization (NSP), concha bullosa (CB), accessory maxillary ostium (AMO), agger nasi cell (ANC), Haller cell (HC), Onodi cell (OC), ethmoid sinusitis and maxillary sinus pathologies were investigated. Maxillary sinus pathologies were classified. Correlations of OMC variations with each other, maxillary sinus pathologies and ethmoid sinusitis were investigated. Chi-square test was used to analyze relationships among variables and distribution of parameters.

Results: NSD was determined in 70.8%, NSP in 40.3%, ethmoid sinusitis in 75%, maxillary sinus pathology in 34.8% of images. OMC variations rates were detected as CB 31.3%, AMO 16%, ANC 16%, HC 24.3% and OC 18.8%. The most common maxillary sinus pathology was localized mucosal thickening, with a rate of 15.3% on right and 22.2% on left. Statistically significant differences were determined between almost all OMC variations with each other, and between anatomical variations in OMC with maxillary sinus pathologies except for NSP and AMO ($p < 0.05$). The presence of ethmoid sinusitis was more common in males ($p = 0.026$).

Conclusion: Anatomical variations in OMC had no significant effect on maxillary sinus pathology except for NSP and AMO. Besides, most of anatomical variations in OMC were statistically significantly correlated with each other. CBCT visualization of these variations is important for sinonasal surgery and is an effective method in children and adolescents with low radiation dose and high image quality compared to computed tomography.

Keywords: Ostiomeatal complex, anatomical variations, maxillary sinus pathologies, children and adolescents, cone-beam computed tomography

INTRODUCTION

Ostiomeatal complex (OMC) is formed by the maxillary sinus ostium, hiatus semilunaris, infundibulum, frontal recess, ethmoid bulla, uncinate process, frontal sinus ostium and middle turbinate [1]. Anatomical variations of the OMC predispose to infection and cause focal symptoms in some patients thus ethmoid sinusitis and maxillary sinus pathologies may occur [2]. The most common anatomical variations in the OMC were nasal septum deviation, nasal septal pneumatization, concha bullosa, agger nasi cell, Haller cell, and Onodi cell [3]. The structure, size, and location of paranasal sinuses differ in children from adults, and anatomical variations are more common [4]. Allergy, odontogenic infections, anatomical variations and ostiomeatal occlusions are the most important causes of chronic sinusitis and maxillary sinus pathologies in children and adolescents cases [5, 6].

Nasal septal deviation (NSD) may be developmental or acquired. Intrauterine, perinatal and post-natal traumas, developmental defects, congenital deformities, mouth breathing and finger sucking may cause NSD [7]. Nasal septal pneumatization (NSP) occurs when air cells extend from the sphenoid sinus or crista galli to the nasal septum and can narrow the sphenoethmoidal recess [8].

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Concha bullosa (CB) is the pneumatized structure of the middle concha that does not normally contain air [9].

Agger nasi cell (ANC) is formed by the pneumatization of the anterior ethmoid cells into the frontal process of the maxilla [3, 10].

Haller cells (HC), which are formed by the migration of posterior ethmoid cells to the maxillary sinus, are air cells above and adjacent to the maxillary sinus ostium [3, 10].

Onodi cells (OC), also called sphenoethmoid cells, are posterior ethmoid air cells localized in the upper anterior region of the sphenoid sinus [10].

Primary maxillary ostium is an essential structure in the drainage of maxillary sinuses [11]. The accessory maxillary ostium (AMO), located between the uncinate process and the inferior concha and originating from the membranous area of the medial wall of the maxilla, is an anatomical variant that may play a role in the development of maxillary sinusitis [12].

CBCT is one of the most preferred imaging systems to evaluate the anatomical structure of the head and neck region in three dimensions. It is recommended to use CBCT in determination of pathological conditions, developmental anomalies, traumatic injuries, impacted and supernumerary teeth in children and adolescents [13]. It has advantages such as lower radiation dose, less scattered radiation and high image quality compared to CT [14]. Besides, shorter exposure time prevents cooperation difficulties and movement artifacts that may occur in children and adolescents [15]. Maxillary sinus pathologies, ethmoid sinuses and surrounding anatomical structures can be examined in detail with CBCT [16].

There are several studies to determine the prevalence of chronic sinusitis by examining the frequency of anatomical variations of OMC using paranasal CT images in the child and adolescent population [3, 8, 17, 18]. However, as far as we know, in only one study conducted by Shokri et al. [19], this subject was investigated on CBCT scans, although their study sample included not only pediatric patients but also adults. Therefore, the aim of this study is to retrospectively evaluate the relationship of OMC variations with each other and with maxillary sinus pathologies using CBCT in pediatric patients.

Main Points:

- Most of anatomical variations of the ostiomeatal complex in children and adolescents were not associated with maxillary sinus pathology, however, there was a statistically significant relationship between nasal septal pneumatization, accessory maxillary ostium and maxillary sinus pathology.
- Most of anatomical variations in ostiomeatal complex were significantly associated with each other.
- These variations can be visualized with the use of cone-beam computed tomography in children and adolescents with low radiation dose and high image quality compared to computed tomography.

METHODS

Before the study, the ethical approval was obtained from Clinical Researches Ethics Committee of Gaziantep University (Protocol No: 2020/358). In this study, the images taken with Planmeca Promax 3D (Helsinki, Oy, Finland) CBCT device between 2017-2020 in the Gaziantep University Faculty of Dentistry, Department of Dentomaxillofacial Radiology tomography archive with asymptomatic children and adolescents who underwent CBCT for any dental reason were used. Before the study, "Power Analysis" was carried out so that the data to be obtained from the study could be used and evaluated. The minimum sample size to be examined (number of images) was found to be 68 when α=0.05 and test power 1-ß=0.80. Multiplanar images were obtained from 16×9, 16×16 FOV (field of view) with 0.4 mm3 voxel size and 1 mm slice thickness. Inclusion criteria were CBCT images in which the paranasal sinuses could be examined in the study area and no distortion, magnification, artifact, and foreign bodies were seen. Exclusion criteria; syndrome and facial growth disorder, presence of metabolic disease involving the bone, presence of cyst, tumor and fracture line in the examination area, presence of cyst affecting the maxillary sinuses, tumor and trauma in the maxillofacial region, odontogenic infection. CBCT scans of 72 patients (44 males and 28 females) aged 7-18 (mean age: 14.65±2.88 years) were evaluated retrospectively.

Image Analysis

Romexis software **version 11.5** (Helsinki, Oy, Finland) was used to analyze the images. On CBCT images, the presence of AMO (Figure 1), NSD (Figure 2), CB (Figure 2), NSP (Figure 3), OC (Figure 3), HC (Figure 4) and ANC (Figure 5) were investigated. Inflammation of the paranasal sinus membranes is called 'sinusitis' [20]. The accumulation of secretions accompanying ethmoid sinusitis narrows the air space, causing it to appear radiopaque. Inability to distinguish the thin outer walls of ethmoid air cells is an important symptom of ethmoid sinusitis (Figure 6a, 6c) [21]. Mucosal thickening is inflammatory changes in the mucosal inner surface of the paranasal sinuses. It is usually asymptomatic and is the most common pathology in the maxillary sinus. If the membrane thickness is between 2-3 mm, it is thought that there is mucosal thickening, if it is more, other pathologies. When mucosal thickening is seen in one or several walls of the maxillary sinus, localized mucosal thickening (Figure 6a), generalized mucosal thickening (Figure 6a) when it is present in all of its walls, and mucosal thickening that occurs in the form of a dome in the maxillary sinus wall is called polypoidal mucosal thickening (Figure 6b) [22, 23]. Sinus opacification is used to describe the unilateral or bilateral partial (Figure 6c) or total opacification (Figure 6d) of the maxillary sinus. In inflammatory diseases, fungal infections, mucoceles, mucosal retention cysts and benign neoplasms in the maxillary sinus are replaced by air with a complete radiopaque appearance [24].

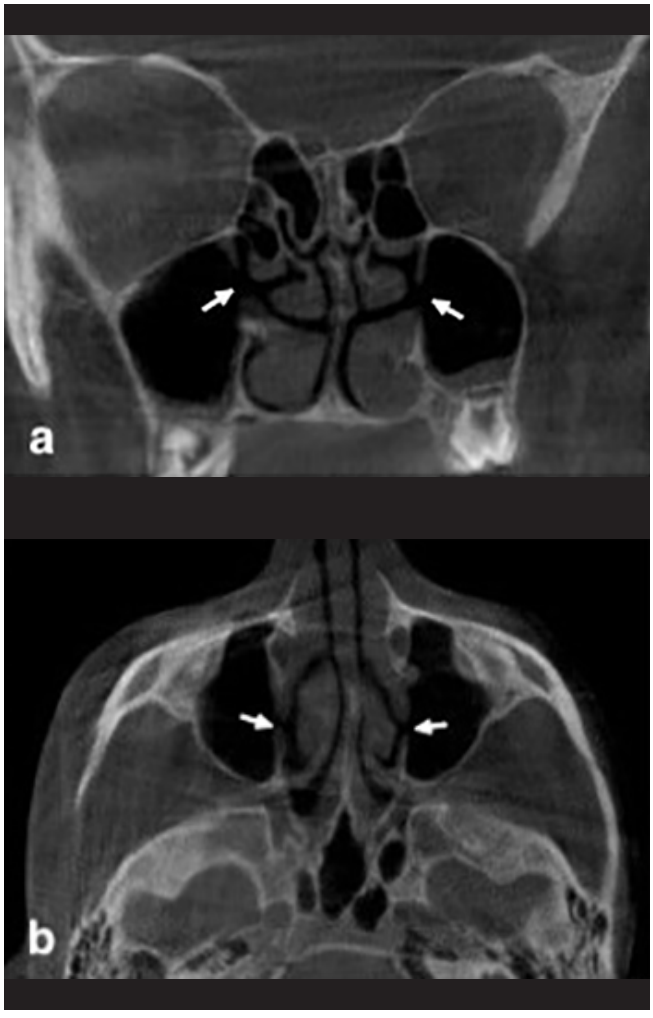

Figure 1. Coronal (a) and axial (b) CBCT images show right and left accessory maxillary ostium (white arrows). Coronal CBCT image demonstrates mucosal thickening localized in the left maxillary sinus.

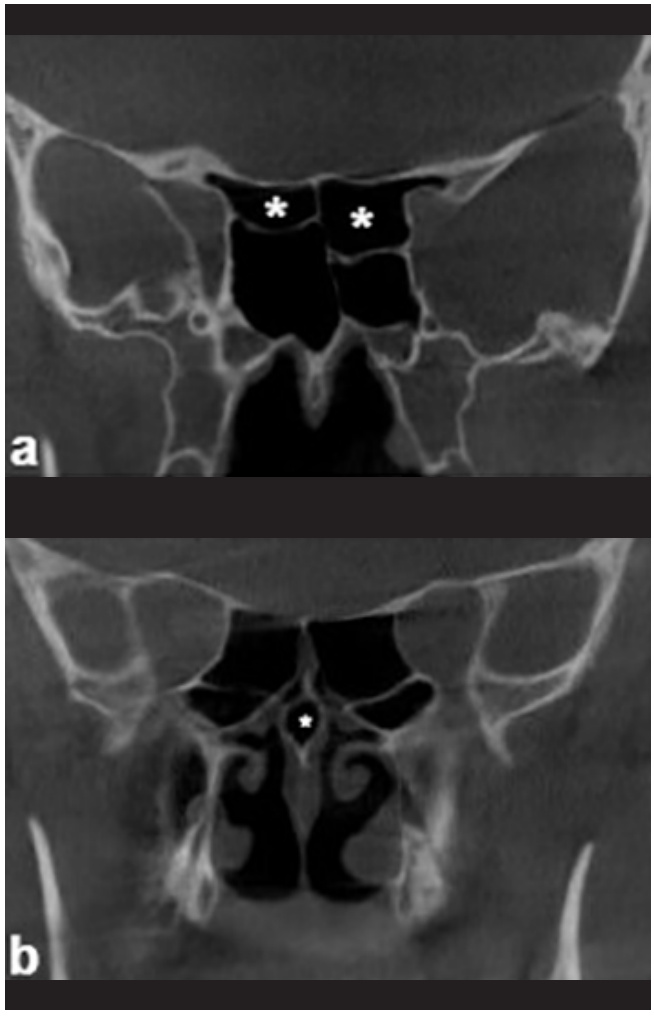

Figure 3. On coronal CBCT images: a) right and left Onodi cells (asteriks); b) nasal septal pneumatization (star).

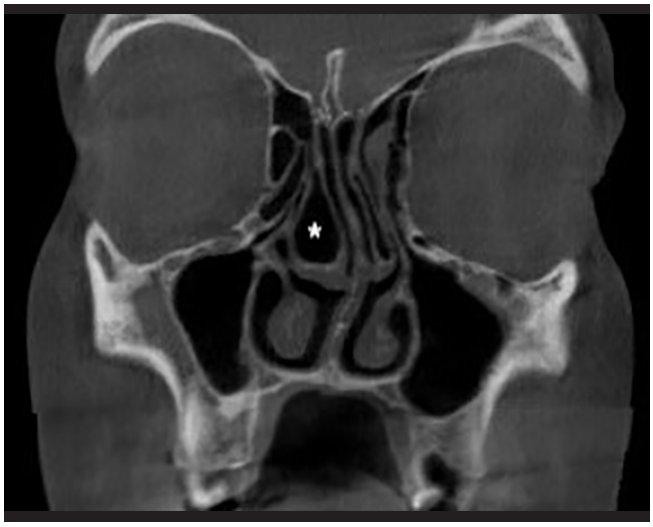

Figure 2. Coronal CBCT image shows a large concha bullosa (asteriks) on the right and nasal septal deviation to the left.

Figure 4. Coronal CBCT image demonstrates the right Haller cell (white arrow) and localized mucosal thickening in the left maxillary sinus.

Figure 5. Coronal (a) and sagittal (b) CBCT images indicate right agger nasi cell (white arrows).

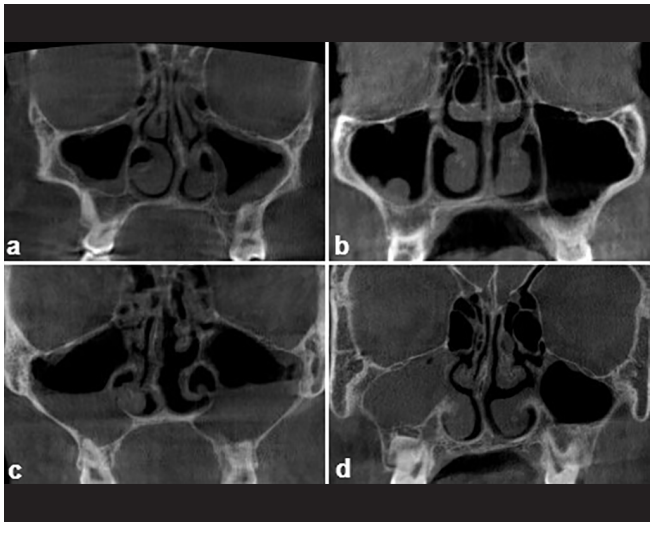

Figure 6. Maxillary sinus pathologies on coronal CBCT images: a) ethmoid sinusitis and mucosal thickening localized in the right maxillary sinus, generalized mucosal thickening in the left maxillary sinus; b) polypoidal mucosal thickening in the right maxillary sinus; c) ethmoid sinusitis and partial opacification in the right and left maxillary sinuses; d) total opacification in the right maxillary sinus.

The existence of ethmoid sinusitis and maxillary sinus pathologies were analyzed. Maxillary sinus pathologies were classified as localized mucosal thickening, generalized mucosal thickening, polypoidal mucosal thickening, partial opacification and total opacification (Figure 6). All evaluations were performed by two dentomaxillofacial radiologists, one is research assistant (EMAO), the other with nine year experience (EDY). When disagreement existed among the observers, consensus was reached by discussion. For intra-examiner calibration and reliability of the evaluations, the images were reviewed by the same observers two weeks after the first evaluation.

Statistical Analysis

The kappa statistics was applied to calculate the inter-observer and intra-observer agreement. The Chi-square test was used to examine the relationships among the categorical variables. SPSS software version 22.0 (IBM Corp, Armonk, NY) was used to analyze the data. Statistical significance was accepted as $p < 0.05$.

RESULTS

The coefficient of intra and inter-observer reliability for all assessments was found to be excellent (0.93 and 0.88, respectively). A total of 72 CBCT images of 44 (61.1%) males and 28 (38.9%) females (with a mean age of 14.23±3.17 and 15.32±2.25, respectively) were investigated. NSD was observed in 70.8%, NSP in 40.3%, and ethmoid sinusitis in 75% of the images examined. The direction of the NSD was 33.3% on the right and 37.5% on the left. The frequency of OMC variations and pathologies are shown in Table 1.

Table 1. The frequency of anatomical variations and sinus pathologies.

Variables	Right		Left	
	Present N (%)	Absent N (%)	Present N (%)	Absent N (%)
Concha Bullosa	24 (33.3)	48 (66.7)	21 (29.2)	51 (70.8)
Accessory Maxillary Ostium	13 (18.1)	59 (81.9)	10 (13.9)	62 (86.1)
Agger Nasi Cell	13 (18.1)	59 (81.9)	10 (13.9)	62 (86.1)
Haller Cell	23 (31.9)	49 (68.1)	12 (16.7)	60 (83.3)
Onodi Cell	10 (13.9)	62 (86.1)	17 (23.6)	55 (76.4)
	Present N (%)		Absent N (%)	
Nasal Septum Deviation	51 (70.8)		21 (29.2)	
Nasal Septum Pneumatization	29 (40.3)		43 (59.7)	
Ethmoid Sinusitis	54 (75.0)		18 (25.0)	
Maxillary Sinus Pathology	50 (34.8)		94 (65.3)	

When the OMC variations were examined according to sex, a statistically significant difference was found between the presence of ethmoid sinusitis (p=0.026) and maxillary sinus pathology on the left side with sex (p=0.041). The existence of ethmoid sinusitis and on the left side, the absence of maxillary sinus pathology were significantly higher in males than in females. Distribution of OMC variations by sex is demonstrated in Table 2. The distribution of the classification of maxillary sinus pathologies on the right and left is shown in Table 3. The most common maxillary sinus pathology was localized mucosal thickening with a rate of 15.3% on the right and 22.2% on the left. This is followed by polypoidal mucosal thickening and partial opacification.

In the assessment of the relationship between OMC variations with each other, there was no statistically significant difference between NSD with NSP, ethmoid sinusitis, CB, AMO, ANC, HC and maxillary sinus pathology (p>0.05), while a significant difference was found between NSD and OC (p=0.028). In the absence of left OC, the rightward orientation of the NSD was observed significantly more. There was no statistically significant difference between NSP with NSD, ethmoid sinusitis, ANC and HC (p>0.05). However, in the absence of NSP, significant difference was determined between the absence of left CB (p=0.018), the absence of right AMO (p=0.043), and the absence of right maxillary sinus pathology (p=0.044). There was no statistically significant difference between ethmoid sinusitis and ANC with all other parameters (p>0.05). No statistically significant difference was found between CB with NSD, ethmoid sinusitis, AMO, ANC, HC and maxillary sinus pathology (p>0.05). There was no statistically significant difference between AMO with NSD, ethmoid sinusitis, CB, ANC and HC (p>0.05). A statistically significant difference was determined between the absence of left AMO, absence of left OC (p=0.034) and absence of left maxillary sinus pathology (p=0.030).

Table 2. Distribution of osteomeatal complex (OMC) variations by gender.

Right		Female		Male		
		Present N (%)	Absent N (%)	Present N (%)	Absent N (%)	P
	Concha Bulloza	11 (15.3)	17 (23.6)	13 (18.1)	31 (43.1)	0.393
	Accessory Maxillary Ostium	3 (4.2)	25 (34.7)	10 (13.9)	34 (47.2)	0.196
	Agger Nasi Cell	4 (5.6)	24 (33.3)	5 (6.9)	39 (54.2)	0.715
	Haller Cell	9 (12.5)	19 (26.4)	16 (22.2)	28 (38.9)	0.714
	Onodi Cell	6 (8.3)	22 (30.6)	10 (13.9)	34 (47.2)	0.897
	Maxillary Sinus Pathology	7 (9.7)	21 (29.2)	15 (20.8)	29 (40.3)	0.414
Left		Present N (%)	Absent N (%)	Present N (%)	Absent N (%)	P
	Concha Bulloza	8 (11.1)	20 (27.8)	13 (18.1)	31 (43.1)	0.929
	Accessory Maxillary Ostium	4 (5.6)	24 (33.3)	6 (8.3)	38 (52.8)	0.938
	Agger Nasi Cell	2 (2.8)	26 (36.1)	5 (6.9)	39 (54.2)	0.556
	Haller Cell	8 (11.1)	20 (27.8)	12 (16.7)	32 (44.4)	0.905
	Onodi Cell	8 (11.1)	20 (27.8)	9 (12.5)	35 (48.6)	0.429
	Maxillary Sinus Pathology	15 (20.8)	13 (18.1)	13 (18.1)	31 (43.1)	0.041*
		Female		Male		
		Present N (%)	Absent N (%)	Present N (%)	Absent N (%)	P
	Nasal Septal Deviation	17 (23.6)	11 (15.3)	34 (47.2)	10 (13.9)	0.132
	Nasal Septal Pneumatization	12 (16.7)	16 (22.2)	17 (23.6)	27 (37.5)	0.722
	Ethmoid Sinusitis	17 (23.6)	11 (15.3)	37 (51.4)	7 (9.4)	0.026*

Chi-square test; *p < 0.05

Table 3. Distribution of maxillary sinus pathologies.

Classification of Maxillary Sinus Pathology	Right N (%)	Left N (%)
Generalized Mucosal Thickening	0 (0.0)	2 (2.8)
Localized Mucosal Thickening	11 (15.3)	16 (22.2)
Polypoidal Mucosal Thickening	5 (6.9)	5 (6.9)
Partial Opacification	3 (4.2)	5 (6.9)
Total Opacification	3 (4.2)	0 (0.0)
Absent	50 (69.4)	44 (61.1)
Total	72 (100)	72 (100)

There was no statistically significant difference between HC with NSD, NSP, ethmoid sinusitis, CB, AMO, ANC and maxillary sinus pathology (p>0.05). There was only a significant difference between the absence of left HC and absence of left OC (p=0.035). There was no statistically significant relationship between OC with NSP, ethmoid sinusitis, CB, ANC and maxillary sinus pathology (p>0.05). There was no statistically significant relationship between maxillary sinus pathology with NSD, ethmoid sinusitis, CB, ANC, HC and OC (p>0.05). Correlations between anatomical variations are indicated in Table 4 and Table 5. Considering the relationship between the classification of maxillary sinus pathologies and anatomical variations, a significant relationship was observed between left AMO and maxillary sinus pathologies (p=0.002).

When the anatomical variations of OMC were compared on the right and left sides, a significant difference was found between two sides in the CB (p < 0.001), AMO (p < 0.05), OC (p < 0.001), and maxillary sinus pathologies (p=0.025). The difference in all these relationships is that in the absence of the parameter on the right, there is absence of the parameter on the left.

Table 5. Correlations between anatomical variations of ostiomeatal complex (OMC) and maxillary sinus pathologies.

		Right Maxillary Sinus Pathology		P			Left Maxillary Sinus Pathology		P
		Present N (%)	Absent N (%)				Present N (%)	Absent N (%)	
Right					**Left**				
Concha Bullosa	**Present N (%)**	7 (9.7)	17 (23.6)	0.856	**Concha Bullosa**	**Present N (%)**	10 (13.9)	11 (15.3)	0.330
	Absent N (%)	15 (20.8)	33 (45.8)			**Absent N (%)**	18 (25.0)	33 (45.8)	
Accessory Maxillary Ostium	**Present N (%)**	6 (8.3)	7 (9.7)	0.177	**Accessory Maxillary Ostium**	**Present N (%)**	7 (9.7)	3 (4.2)	0.030*
	Absent N (%)	16 (22.2)	43 (59.7)			**Absent N (%)**	21 (29.2)	41 (56.9)	
Agger Nasi Cell	**Present N (%)**	3 (4.2)	10 (13.9)	0.518	**Agger Nasi Cell**	**Present N (%)**	5 (6.9)	5 (6.9)	0.437
	Absent N (%)	19 (26.4)	40 (55.6)			**Absent N (%)**	23 (31.9)	39 (54.2)	
Haller Cell	**Present N (%)**	6 (8.3)	17 (23.6)	0.573	**Haller Cell**	**Present N (%)**	4 (5.6)	8 (11.1)	0.665
	Absent N (%)	16 (22.2)	33 (45.8)			**Absent N (%)**	24 (33.3)	36 (50.0)	
Onodi Cell	**Present N (%)**	4 (5.6)	6 (8.3)	0.485	**Onodi Cell**	**Present N (%)**	7 (9.7)	10 (13.9)	0.825
	Absent N (%)	18 (25.0)	44 (61.1)			**Absent N (%)**	21 (29.2)	34 (47.2)	

Chi-square test; *p < 0.05

Table 4. Correlations between anatomical variations of ostiomeatal complex (OMC).

	RIGHT						LEFT					
	Concha Bullosa	Accessory Maxillary Ostium	Agger Nasi Cell	Haller Cell	Onodi Cell	Maxillary Sinus Pathology	Concha Bullosa	Accessory Maxillary Ostium	Agger Nasi Cell	Haller Cell	Onodi Cell	Maxillary Sinus Pathology
	P	P	P	P	P	P	P	P	P	P	P	P
Concha Bullosa	******	0.386	0.665	0.074	0.335	0.856	******	0.151	0.417	0.297	0.980	0.330
Accessory Maxillary Ostium	0.386	******	0.062	0.225	0.475	0.177	0.151	******	0.702	0.128	0.034*	0.030*
Agger Nasi Cell	0.665	0.062	******	0.920	0.110	0.518	0.417	0.702	******	0.761	0.608	0.437
Haller Cell	0.074	0.225	0.920	******	0.887	0.573	0.297	0.128	0.761	******	0.035*	0.665
Onodi Cell	0.335	0.475	0.110	0.887	******	0.485	0.980	0.034*	0.608	0.035*	******	0.825
Maxillary Sinus Pathology	0.856	0.177	0.518	0.573	0.485	******	0.330	0.030*	0.437	0.665	0.825	******

Chi-square test; *$p < 0.05$

DISCUSSION

In this study, the presence of OMC variations and maxillary sinus pathologies in children and adolescents were examined and the relationships of the variations with maxillary sinus pathologies were investigated using CBCT images. Although there are many studies in the literature on anatomical variations and chronic sinusitis in pediatric patients, [3,8,17,25,26] as far as we know, our study is the first CBCT study to classify maxillary sinus pathologies and examine their relationship with OMC in the children. In this study, the most common observed pathologies in the OMC were maxillary sinus pathologies and ethmoid sinusitis which are also the most common pathologies in males, and the most common variation was CB in this region. Significant relationship was found between AMO and maxillary sinus pathologies.

CBCT is preferred as an alternative to CT in the examination of craniofacial anomalies and pathologies. Compared to CT, the presence of isotropic voxels in CBCT prevents distortion in multi-plane reconstruction images, and the lower radiation dose compared to CT is an important advantage [27]. The use of CBCT in children is controversial due to the radiation dose and immature anatomical and biological structures and their greater susceptibility to radiation damage [28,29]. Dentists should adhere to the principles of ALARA (as low as reasonably achievable) and ALARP (as low as reasonably feasible), an appropriately sized imaging field should be used, and the radiation dose should be kept at the optimum level to solve clinical problems. The dosage should be adjusted and limited according to the age and body weight of the child. CBCT should not be used routinely for children and adolescents, but rather for undiagnosed complex cases such as bone disorders of the temporomandibular joint, presence of oral and maxillofacial pathology, evaluation of impacted teeth, and orthodontic problems [30]. This study was conducted by retrospectively evaluating the available images of patients aged 7-18 years, who applied to our clinic and were requested CBCT according to the SEDENTEX-CT [31] guidelines and CBCT indications.

The reported prevalence of NSD in children ranges from 28.9% to 70.8%[19, 32]. There are differences in the prevalence of NSD between studies as various classifications are used and different age groups may show different results [32]. NSD can cause recurrent rhinosinusitis, upper airway infections, and middle ear problems. Aramani et al. [25] detected NSD at a rate of 74.1% in their study on CT images of 54 patients with chronic sinusitis aged 13-70 years. Kim et al. [17] found NSD in 44.3% of the cases in their study with CT images of 113 pediatric patients with chronic sinusitis who underwent endoscopic sinus surgery, and observed that the prevalence of NSD increased with age. Fadda et al. [26] found NSD in 58.5% of the cases on CT images of 140 patients with chronic sinusitis aged 13-77 years. Al-Qudah et al. [8] detected NSD larger than 3 mm in 18% of the cases on CT images of 65 pediatric patients with chronic sinusitis. In the study conducted by Shokri et al. [19] on CBCT images of 250 patients between the ages of 10-55 years, NSD was determined with a rate of 70.8% in patients aged 10-25 years. In our study, similar to the literature, the frequency of NSD was 70.8%, and no significant relationship was found between sex and NSD.

Sivaslı et al. [3] found NSP in 6% of the cases in their study with CT images of 47 pediatric patients with chronic sinusitis. NSP was determined at a rate of 38% in the study of Al-Qudah et al. [8]. In the study of Shokri et al. [19], NSP was detected at a rate of 64.7%, and a statistically significant relationship was observed between NSD and NSP. In the present study, NSP was detected in 40.7% of the cases. This difference in the literature may be due to the limited number of studies on this subject, differences in ethnic origin, imaging method, and the number of cases. Shokri et al. [19] examined the correlation between NSP and anatomical variations and did not find statistically significant results, and in our study, different from the literature, a significant relationship was followed between NSP with AMO and CB.

When the pathologies in the paranasal sinuses were examined, Kim et al. [17] found the rate of maxillary sinusitis as 95.5%, divided ethmoid sinusitis as anterior ethmoid and posterior ethmoid sinusitis, and they observed it as 91.1% and 68.1%, respectively. They found no statistically significant difference between maxillary sinusitis with NSD and between CB with maxillary and ethmoid sinusitis. In the studies of Sivaslı et al. [3], maxillary sinusitis were observed in 51% of the cases, anterior ethmoid sinusitis in 15% of the cases, posterior ethmoid sinusitis in 16% of the cases. Also, an inverse correlation was found between maxillary sinusitis and the presence of ANC. In the study of Al-Qudah et al. [8], maxillary and anterior ethmoid sinusitis were determined in 46% of the cases, maxillary and posterior ethmoid sinusitis in 29% of the cases, and maxillary sinusitis in only 17% of the cases. Fadda et al. [26] detected maxillary sinusitis in 67.1% of the cases, anterior ethmoid sinusitis in 54.3%, and posterior ethmoid sinusitis in 10% of the cases. In the present study, ethmoid sinusitis was observed in 75% of the cases, maxillary sinus pathologies in 34.7% of the cases, and significant relationship was found between left NSD and left maxillary sinus pathology. Unlike other studies, we examined the presence of sinusitis without separating the ethmoid sinus as anterior ethmoid and posterior ethmoid sinus. This may explained that the frequency of ethmoid sinusitis in our study was more than the other study results. In addition, a significant relationship was detected between NSP with right maxillary sinus pathology. It may be though that the maxillary sinus pathologies may be a factor triggering the formation of NSP due to anatomical proximity.

Kim et al. [17] observed CB at a rate of 32.7% and did not find a significant relationship between CB and ipsilateral ethmoid and maxillary sinusitis. Sivaslı et al. [3] found the rate of CB as 58.0% and Al Qudah et al. [8] remarked it as 51.0%. Sivaslı et al. [3] found a significant relationship between CB and ANC. Al Qudah et al. [8] did not observe a significant relationship between CB and maxillary sinusitis. Köse et al. [33] did not find a statistically significant relationship between CB and NSD and maxillary sinus mucosal thickening. Fadda et al. [26] stated CB with a rate of 49.3% and found a significant relationship between bilateral CB

and bilateral maxillary sinusitis. In our study, CB was observed as 31.3%. Besides, a significant relationship was found between left CB and NSP.

In the study of Ali et al. [34] examining the CBCT images of 201 patients between the ages of 16-85, AMO was detected at a rate of 28.4%. Both AMO and maxillary sinusitis were observed in 71.9% of these patients, and a significant relationship was found between the presence of AMO and maxillary sinusitis. Shokri et al. [19] stated the presence of AMO at a rate of 58.5%, and no significant relationship was found between AMO and sex. In the current study, unlike the other study results, a lower rate of AMO (16%) was found, however, consistent with the literature, no significant relationship was determined between sex. AMO is an anatomical variation associated with the development of maxillary sinusitis in several studies [35-37], and in our study, similar to the literature, a significant relationship was found between left AMO and left maxillary sinus pathologies.

In the study of Kim et al. [17], HC was detected in 34.5% of the cases and 3.5% were on the right, 5.3% were on the left, and 25.7% were bilateral. Also, no significant relationship was observed between HC with maxillary and ethmoid sinusitis. Sivaslı et al. [3] determined HC in 30.0% of the cases, and they concluded that although most patients with HC had maxillary sinus involvement, this relationship was not statistically significant. Al Qudah et al. [8] found HC at a rate of 20.0%, and no significant correlation indicated between HC and maxillary sinusitis. Shokri et al. [19] detected HC at a rate of 69.4% in the group under the age of 25 in their study, and found a significant relationship between HC and NSD. Shpilberg et al. [38] determined HC in 39.1% of the cases and did not remark a significant relationship between HC and sinonasal disease. In the study of Fadda et al. [26], HC was determined at a rate of 22.8%, and found a significant association between HC and maxillary sinusitis. In the present study, HC was observed as 24.3%, and there was no significant correlation between the presence of HC and sex. Since HC is adjacent to the maxillary sinus ostium, it is considered a factor in narrowing of the infundibulum, in this case, recurrent maxillary sinusitis can be occur [39, 40]. However, in this study, a significant relationship between HC with maxillary sinus pathology and ethmoid sinusitis was not determined.

The reported prevalence of ANC varies widely among researchers. In the study conducted by Al Quadah and Mardini [41], on CT images of 50 children aged 4-15 years, ANC was detected bilaterally in 94.0% of the cases. Kim et al. [17] observed ANC in 69.0% of the cases and found that the relationship between ANC with frontal sinusitis was not significant. In the study of Sivaslı et al. [3], ANC was detected bilaterally at a rate of 15.0%, and a significant relationship was found between ANC and CB. In addition, an inverse correlation was determined between the presence of ANC and maxillary sinusitis. Al Qudah et al. [8] found ANC at a rate of 63.0% and observed that the relationship between ANC with frontal sinusitis was not significant. Shokri et al. [42] determined ANC in 62.7% of patients under the age of 25, and stated a significant relationship between ANC and HC.

Although the prevalence of OC is uncertain, it is thought to range from 1.3% to 42% [43]. Kim et al. [17] observed OC in 9.8% of the cases and found that the relationship between OC with sphenoid sinusitis was not significant. Sivaslı et al. [3] detected it as 6.0%, and Fadda et al. [26] as 8.5%. Cohen et al. [18] remarked OC in 15.7% of the cases, and did not find a significant relationship between OC with age groups. However, they found a significant relationship between OC and HC. Shokri et al. [19] determined OC in 57.0% of patients under the age of 25, and observed that there was no significant relationship between OC with other anatomical variations. In the current study, the OC rate was found as 18.8%, and no significant relationship was determined between OC with maxillary sinus pathologies and ethmoid sinusitis.

Anatomical variations in the nose and paranasal sinuses are common in children, and the structure of the paranasal sinuses is also quite different from those in adults. Anatomical variations of the nasal cavity and paranasal sinuses are factors that may contribute to occlusion of the ostiomeatal unit [8]. Obstruction of the OMC can lead to the development of pediatric chronic sinusitis with many reasons such as infection, allergies, immune disorders and mucociliary transport disorders [17]. During endoscopic sinus surgery, which is one of the chronic sinusitis treatments, the optic nerve, orbit, tear drainage system and brain tissues are at greater risk of injury due to the narrow intranasal space and thin bone anatomy in children. Anatomical variation is typically eliminated during surgery in adults, but the risk of abnormal facial bone growth in children may prevent the surgeon from doing this [8, 17]. For this reason, in the diagnosis and treatment phase, knowing and the imaging of anatomical variations of OMC is of great importance in terms of affecting the growth and development of the child, quality of life and preventing surgical complications.

In this study, we revealed that most of the anatomical variations of OMC in children and adolescents were not associated with maxillary sinus pathology and ethmoid sinusitis. This may be due to the anatomical variations not being large enough to cause mechanical occlusion. In addition, age, ethnicity, presence of systemic disease, genetic factors and the imaging method used may cause this. The difference results in the literature may be due to the reasons we mentioned above.

The limitation of this study was that the medical history and systemic diseases of the patients were not known since the study was retrospective. Besides, the sample size in this study is limited because the use of CBCT indication in children and adolescents is limited. In the future studies, the number of subjects can be increased and the cases can be divided into age groups.

CONCLUSION

In this study, anatomical variations in OMC had no significant effect on maxillary sinus pathology except for NSP and AMO. However, most of these variations were statistically significantly correlated with each other. This may be due to the anatomical variations not being large enough to cause mechanical occlusion. OMC variations are of great importance in endoscopic sinus surgery due to their proximity to the surrounding anatomical

structures. CBCT is a successful imaging method for examining sinonasal region anatomy in children and adolescents with its low radiation dose, high image quality and low cost compared to medical CT.

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Ethical approval: This retrospective study was approved by the Ethical Committee of Gaziantep University (Decision No: 2020/358) and conducted in the Dentomaxillofacial Radiology Department of Gaziantep University, Faculty of Dentistry.

REFERENCES

1- Ritter L, Lutz J, Neugebauer J, Scheer M, Dreiseidler T, Zinser MJ (2011) Prevalence of pathologic findings in the maxillary sinus in cone-beam computerized tomography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 111(5):634-640. https://doi.org/10.1016/j.tripleo.2010.12.007

2- Mamatha H, Shamasundar N, Bharathi M, Prasanna L (2010) Variations of ostiomeatal complex and its applied anatomy: a CT scan study. Indian J Sci Technol. 3(8):904-907.

3- Sivaslı E, Şirikçi A, Bayazıt Y, Gümüsburun E, Erbagci H, Bayram M (2002) Anatomic variations of the paranasal sinus area in pediatric patients with chronic sinusitis. Surg Radiol Anat. 24(6):399-404. https://doi.org/10.1007/s00276-002-0074-x

4- Medina J, Hernandez H, Tom LW, Bilaniuk L (1997) Development of the paranasal sinuses in children. Am J Rhinol. 11(3):203-210. https://doi.org/10.2500/105065897781751857

5- Kennedy DW, Zinreich SJ, Rosenbaum AE, Johns ME (1985) Functional endoscopic sinus surgery: theory and diagnostic evaluation. Arch Otolaryngol. 111(9):576-582. https://doi.org/10.1001/archotol.1985.00800110054002

6- Kretzschmar DP, Kretzschmar CJL (2003) Rhinosinusitis: review from a dental perspective. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 96(2):128-135. https://doi.org/10.1016/S1079-2104(03)00306-8

7- Beale TJ, Madani G, Morley SJ (2009) Imaging of the paranasal sinuses and nasal cavity: normal anatomy and clinically relevant anatomical variants. Seminars in Ultrasound, CT and MRI; WB Saunders. 30(1):2-16. https://doi.org/10.1053/j.sult.2008.10.011

8- Al-Qudah M (2008) The relationship between anatomical variations of the sino-nasal region and chronic sinusitis extension in children. Int J Pediatr Otorhinolaryngol. 72(6):817-821. https://doi.org/10.1016/j.ijporl.2008.02.006

9- Tomomatsu N, Uzawa N, Aragaki T, Harada K (2014) Aperture width of the osteomeatal complex as a predictor of successful treatment of odontogenic maxillary sinusitis. Int J Oral Maxillofac Surg. 43(11):1386-1390. https://doi.org/10.1016/j.ijom.2014.06.007

10- Kantarci M, Karasen RM, Alper F, Onbas O, Okur A, Karaman A (2004) Remarkable anatomic variations in paranasal sinus region and their clinical importance. Eur J Radiol. 50(3):296-302. https://doi.org/10.1016/j.ejrad.2003.08.012

11- Kumar H, Choudhry R, Kakar S (2001) Accessory maxillary ostia: topography and clinical application. J Anat Soc India. 50(1):3-5.

12- Sarna A, Hayman LA, Laine FJ, Taber KH (2002) Coronal imaging of the osteomeatal unit: anatomy of 24 variants. J Comput Assist Tomogr. 26(1):153-157.

13- Kang B-C, Yoon S-J, Lee J-S, Al-Rawi W, Palomo JM (2011) The use of cone beam computed tomography for the evaluation of pathology, developmental anomalies and traumatic injuries relevant to orthodontics. Seminars in Orthodontics; WB Saunders. 17:20-33. https://doi.org/10.1053/j.sodo.2010.08.005

14- Katheria BC, Kau CH, Tate R, Chen J-W, English J, Bouquot J (2010) Effectiveness of impacted and supernumerary tooth diagnosis from traditional radiography versus cone beam computed tomography. Pediatr Dent. 32(4):304-309. PMID: 20836949

15- Korbmacher H, Kahl-Nieke B, Schöllchen M, Heiland M (2007) Value of two cone-beam computed tomography systems from an orthodontic point of view. J Orofac Orthop. 68(4):278-289. PMID: 17639276

16- Naitoh M, Suenaga Y, Kondo S, Gotoh K, Ariji E (2009) Assessment of maxillary sinus septa using cone-beam computed tomography: etiological consideration. Clin Implant Dent Relat Res. 11:52-58. https://doi.org/10.1111/j.1708-8208.2009.00194.x

17- 17. Jun Kim H, Jung Cho M, Lee J-W, Tae Kim Y, Kahng H, Sung Kim (2006) The relationship between anatomic variations of paranasal sinuses and chronic sinusitis in children. Acta Otolaryngol. 126(10):1067-1072. https://doi.org/10.1080/00016480600606681

18- Cohen O, Adi M, Shapira-Galitz Y, Halperin D, Warman M (2019) Anatomic variations of the paranasal sinuses in the general pediatric population. Rhinology. 57(3):206-212. PMID: 30778427

19- Shokri A, Faradmal MJ, Hekmat B (2019) Correlations between anatomical variations of the nasal cavity and

ethmoidal sinuses on cone-beam computed tomography scans. Imaging Sci Dent. 49(2):103. https://doi.org/10.5624/isd.2019.49.2.103

20- Fokkens WJ, Lund VJ, Mullol J (2012) European position paper on rhinosinusitis and nasal polyps, A summary for otorhinolaryngologists. Rhinology. 50(1):1-12. https://doi.org/10.4193/rhino12.000

21- White SC, Pharoah MJ (2014) Oral radiology-E-Book: Principles and interpretation, Elsevier Health Sciences.

22- Pelinsari Lana J, Moura Rodrigues Carneiro P, de Carvalho Machado V (2012) Anatomic variations and lesions of the maxillary sinus detected in cone beam computed tomography for dental implants. Clin Oral Implants Res. 23(12):1398-1403. https://doi.org/10.1111/j.1600-0501.2011.02321.x

23- Rege ICC, Sousa TO, Leles CR (2012) Occurrence of maxillary sinus abnormalities detected by cone beam CT in asymptomatic patients. BMC Oral Health. 12:1-7. https://doi.org/10.1186/1472-6831-12-30

24- Dave M, Loughlin A, Walker E (2020) Challenges in plain film radiographic diagnosis for the dental team: a review of the maxillary sinus. Br Dent J. 228(8):587-594. https://doi.org/10.1038/s41415-020-1524-8

25- Aramani A, Karadi R, Kumar S (2014) A study of anatomical variations of osteomeatal complex in chronic rhinosinusitis patients-CT findings. J Clin Diagn Res. 8(10):KC01. https://doi.org/10.7860/JCDR/2014/9323.4923

26- Fadda G, Rosso S, Aversa S, Petrelli A, Ondolo C, Succo G (2012) Multiparametric statistical correlations between paranasal sinus anatomic variations and chronic rhinosinusitis. Acta Otorhinolaryngol Ital. 32(4):244. PMID: 23093814

27- Farman AG, Scarfe WC (2009) The basics of maxillofacial cone beam computed tomography. Seminars in Orthodontics, Elsevier. https://doi.org/10.1053/j.sodo.2008.09.001

28- Scarfe WC, Farman AG, Sukovic P (2006) Clinical applications of cone-beam computed tomography in dental practice. J Can Dent Assoc. 72(1):75-80.

29- Scarfe WC (2012) Radiation risk in low-dose maxillofacial radiography. Oral Surg Oral Med Oral Pathol Oral Radiol. 114(3):277-280. https://doi.org/10.1016/j.oooo.2012.07.001

30- Affairs ADACoS (2012) The use of cone-beam computed tomography in dentistry: an advisory statement from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 143(8):899-902. https://doi.org/10.14219/jada.archive.2012.0295

31- Theodorakou C, Walker A, Horner K, Pauwels R, Bogaerts R, Jacobs Dds R (2012) Estimation of paediatric organ and effective doses from dental cone beam CT using anthropomorphic phantoms. Br J Radiol. 85(1010):153-160. https://doi.org/10.1259/bjr/19389412

32- Šubarić M, Mladina R (2002) Nasal septum deformities in children and adolescents: a cross sectional study of children from Zagreb, Croatia. Int J Pediatr Otorhinolaryngol. 63(1):41-48. https://doi.org/10.1016/S0165-5876(01)00646-2

33- Köse E, Canger, EM, Göller Bulut D (2018) Cone beam computed tomographic analysis of paranasal variations, osteomeatal complex disease, odontogenic lesion and their effect on maxillary sinus. Meandros Med Dent J. 19(4):310. https://doi.org/10.4274

34- Ali IK, Sansare K, Karjodkar FR, Vanga K, Salve P, Pawar AM (2017) Cone-beam computed tomography analysis of accessory maxillary ostium and Haller cells: Prevalence and clinical significance. Imaging Sci Dent. 47(1):33. https://doi.org/10.5624/isd.2017.47.1.33

35- Bani-Ata M, Aleshawi A, Khatatbeh A, Al-Domaidat D, Alnussair B, Al-Shawaqfeh R (2020) Accessory maxillary ostia: prevalence of an anatomical variant and association with chronic sinusitis. Int J Gen Med. 13:163. https://doi.org/10.2147/IJGM.S253569

36- Yenigun A, Fazliogullari Z, Gun C, Uysal II, Nayman A, Karabulut AK (2016) The effect of the presence of the accessory maxillary ostium on the maxillary sinus. Eur Arch Otorhinolaryngol. 273:4315-4319. https://doi.org/10.1007/s00405-016-4129-8

37- Ghosh P, Kumarasekaran P, Sriraman G (2018) Incidence of accessory ostia in patients with chronic maxillary sinusitis. Int J Otorhinolaryngol Head Neck Surg. 4(2):443-447.

38- Shpilberg KA, Daniel SC, Doshi AH, Lawson W, Som PM (2015) CT of anatomic variants of the paranasal sinuses and nasal cavity: poor correlation with radiologically significant rhinosinusitis but importance in surgical planning. AJR Am J Roentgenol. 204(6):1255-1260. https://doi.org/10.2214/AJR.14.13762

39- Laine F, Smoker W (1992) The ostiomeatal unit and endoscopic surgery: anatomy, variations, and imaging findings in inflammatory diseases. AJR Am J Roentgenol. 159(4):849-857. https://doi.org/10.2214/ajr.159.4.1529853

40- Stammberger H, Wolf G (1988) Headaches and sinus disease: the endoscopic approach. Ann Otol Rhinol Laryngol. 97(5):3-23. https://doi.org/10.1177/000348948809705501

41- Al-Qudah M, Mardini D (2015) Computed tomographic analysis of frontal recess cells in pediatric patients. Am J Rhinol Allergy. 29(6):425-429. https://doi.org/10.2500/ajra.2015.29.4243

42- Shokri A, Miresmaeili A, Farhadian N, Falah-Kooshki S, Amini P, Mollaie N (2017) Effect of changing the head position on accuracy of transverse measurements of the maxillofacial region made on cone beam computed tomography and conventional posterior-anterior cephalograms. Dentomaxillofac Radiol. 46(5):20160180. https://doi.org/10.1259/dmfr.20160180

43- Bolger WE, Parsons DS, Butzin CA (1991) Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. Laryngoscope. 101(1):56-64. https://doi.org/10.1288/00005537-199101000-00010

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Original Research

Tinnitus and Cochlear Functions in Hearing Impaired and Normal Hearing Individuals

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ABSTRACT

Objective: In order to determine the pathophysiology of tinnitus and deciding on treatment, the function of peripheral hearing organs is very important. The aim of the study is to evaluate the cochlear functions in tinnitus patients with or without hearing-loss (HL).

Methods: Participants with tinnitus were divided into two groups; 16 participants with accompanying HL were included in the first study group (SG-I), and 15 participants without HL were included in the second group (SG-II). 21 normal-hearing subjects without tinnitus included as control group (CG). Tinnitus discomfort levels was determined with Tinnitus Handicap Inventory (THI). Besides pure-tone audiometry, Otoacoustic Emissions (OAE), to evaluate cochlear functions and to decide dead regions (DR), Threshold Equalizing Noise-(TEN) was used.

Results: The threshold-shift was observed with TEN in subjects in SG-I and these levels were statistically different from SG-I and CG. There were both threshold-shift and DR in SG-I according to TEN. Transient Otoacoustic Emissions (TEOAE) did not differ between SG-I and CG. The Distortion Product Otoacoustic Emissions (DPOAE) results for SG-I showed significant decreases in emission amplitudes at 6 & 8 kHz.

Conclusion: While Tinnitus patients with HL can be evaluated with conventional tests, evaluating patients with normal hearing tinnitus with additional tests such as OAE and TEN allows us to get more precise results on the functions of peripheral hearing organs.

Keywords: Tinnitus, TEN Test, Dead Region, Hair Cells

INTRODUCTION

Tinnitus can be defined as an auditory illusion or a phantom sensation of sound in the absence of external stimulation, i.e., the perception of a sound in the absence of any objective physical sound source (ANSI, 1969). In fact, tinnitus is a symptom that may cause decreased quality of life, somatization disorders, or depression. Regardless of the source of tinnitus, it is perceived in the auditory cortex [1]. The incidence of tinnitus has been reported to be 10–15% in adult population all over the world.

Various attempts have been made to understand the mechanism of tinnitus, especially as related to cochlear function. Spontaneous OAEs have frequently been reported in studies related to tinnitus. Many studies have shown that TEOAE and DPOAE tests can be used as methods to detect early hearing loss (HL), without it being seen in an audiogram [2, 3]. Reported OAE-results related to tinnitus were contradictory. Although lower TEOAE or DPOAE amplitudes in subjects with tinnitus was reported in some studies [3, 4], some others reported increased amplitudes of TEOAEs or DPOAEs in subjects with tinnitus [5, 6]. It could be concluded that OAE finding related to tinnitus demonstrate altered OHC functions.

Another test that used to evaluate cochlear functions especially inner hair cells function in tinnitus is Threshold equalizing noise (TEN) tests [7]. Similar to OAE, there are also contradictory results for TEN tests. Although Weisz et al. (2006) reported that there were cochlear dead region (DR) in 8 tinnitus subjects out of 11 (72.7%) [8], Thabet et al. (2009) found DR in only 3 of 20 (15%) subjects [9]. Buzo & Carvallo (2014) reported significantly increased thresholds in TEN in tinnitus patients with normal hearing even if there was no DR [10].

Although it is difficult to determine the pathophysiology of tinnitus, it is important to test the peripheral hearing correctly in order to decide on the treatment approach. As a result our

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hypothesis was that the TEN and OAE test results of tinnitus patients with normal hearing would be different from the control group. Therefore, the aim of the current study was to evaluate cochlear functions in tinnitus patient with or without hearing loss (HL). In this study, while OAE was use to evaluate outer hair cell function OAE, TEN test was used to evaluate inner hair cells activity in the cochlear region.

METHODS

The study was approved by Hacettepe University Clinical Research Ethics Committee (KA-180134/ Date: 10.01.2019). Informed consents were given to the all subjects. This study is based on first author's master dissertation.

Subjects

Subjects with at least six-month of tinnitus at least one ear were included in the study. The subjects were divided into two study groups according to the presence of HL. The first study group (SG-I) included subjects with tinnitus accompanying sensorineural HL, and the second study group (SG-II) included subjects with tinnitus with normal-hearing thresholds. Normal-hearing subjects without tinnitus were included as the control group. The age range of the subjects was 18 to 45 years. Retro-cochlear pathology, neurologic problems, psychological problems, temporomandibular joint problems, pulsatile tinnitus, or conductive HL were regarded as exclusion criteria. Tinnitus Handicap of Inventory was used to decide tinnitus discomfort levels and define subjects' profiles.

Audiological Evaluation

A detailed anamnesis was obtained from all subjects. Air-conduction thresholds were measured between 125 and 12,000 Hz through TDH-39 headphones and bone-conduction thresholds between 500 and 4000Hz through B71 bone vibrator with the Grason Stadler (GSI) Audiostar. Warble tone stimulus was used for testing. ANSI (1969) standards were used to classified the degrees of HL

Evaluation of Tinnitus

The subject's history was used to determine tinnitus localization. To define frequency and pitch of tinnitus, the method proposed by Vernon was used [11]. In this method, two sounds of different frequencies are presented to the patient (f1 and f2, f1<f2) and the patient is asked which of these two sounds is closer to the tinnitus. In loudness matching, the patient is presented with the sound in the determined tinnitus frequency range and by asking the patient whether it is louder or softer, this range is narrowed and the closest loudness level is matched. Accordingly, while evaluation begins with the worse ear in cases of bilateral tinnitus; when tinnitus is perceived equally in both ears, then the left ear was the first ear to evaluate [12]. In case of unilateral tinnitus, just one ear was tested. If the subject defines tinnitus as perceived in side of head, these cases accepted as bilateral tinnitus. The Turkish version of the Tinnitus Handicap Inventory (THI) was used to determine subjects discomfort level. The THI includes 25 items with three answers. The discomfort level of tinnitus is determined according to the total score.

Main Points:

- Understanding the pathophysiology of tinnitus is complex, especially in those with normal hearing. This study contributed to the literature in this regard.
- This study showed that degenerations in the basal region of the cochlea may not be reflected on the audiogram and may lead to tinnitus.
- It is an exemplary study to show that the TEN test is fast and easy to apply and to disseminate its clinical use.

Threshold Equalizing Noise Test

For all subjects, the TEN was applied at 500, 1000, 2000, and 4000 Hz frequencies using a Grason Stadler (GSI) Audio Star Pro audiometer device and TDH39 headphones. In subjects with bilateral tinnitus, TEN were conducted in both ears. In case of unilateral tinnitus, only effected ear was tested.

TEN levels were determined based on the hearing thresholds of the subjects, as described by Brian Moore et al (2000) [7]. When hearing thresholds were better than 25dB, in order to prevent false positive responses, the TEN was set at 50dB; when hearing thresholds were between 25 and 60 dB, the TEN was 70dB, and for thresholds worse than 60 dB, the TEN was set 10 dB higher than the threshold. The TEN should adjusted maximum 90 dB, due to cochlear sensitivity [13]. Additionally, researchers proposed that TEN could performed at different severity levels [8, 9].

Otoacoustic Emission Tests

TEOAE and DPOAEs were measured for all subjects in the study using 26.41.0 version number Autodynamics EZ Screen. TEOAEs were measured in ears with tinnitus in quick screen mode using a 260 sweep at 84 dB SPL at 80 msec. TEOAEs from each stimulus were recorded at 1000 Hz, 1414 Hz, 2000 Hz, 2828 Hz, 4000 Hz and both the signal-to-noise ratios (SNR) and the amplitudes of the response were recorded. For DPOAEs, amplitudes and SNRs recorded responses generated at 1001, 2002, 3003, 4004, 6006, 7996 Hz frequencies (2f1-f2) ratio and L1/L2-65/55 dB SPL intensity levels;) with average of 500 sweeps.

Statistical Analysis

Statistical analyses were carried out using the Windows-based SPSS version 23.00 package program. The obtained results were analyzed by visual (histogram and scatter charts) and statistical (Kolmogorov Smirnov-Shapiro Wilks) methods. Descriptive analysis was conducted and median and interquartile ranges were used for non-normally distributed variables; the mean (X) and standard deviation (SD) were used for this. A median and interquartile range were used in the analysis along with Kruskal-Wallis test. A Bonferroni test was used for double post-hoc comparisons. In the comparisons between the two groups, an independent sample t test was used when the data showed normal distribution. values below 0.05 were considered significant.

RESULTS

Demographic Data

In the study groups, there were 31 subjects in total; 16 (7F, 9M) with tinnitus and HL in SG-I and 15 (6F, 9M) with only tinnitus in SG-II. In CG, there were 21 (12F, 9M) subjects with neither tinnitus nor hearing loss. The mean age for SG-I was 37.2 and in for SG-II was 28.73; the mean age for CG was 24.42. There was no age difference between the male and female (p>0.05). (see Table 1).

Tinnitus discomfort level on the THI showed variations from 1 to 5 for both SG-I and SG-II. There was no significant difference between the THI levels of the two groups (p: 0.14) (p> 0.05). In SG-II tinnitus frequencies showed variations, they mostly focus on high frequencies (4-12 kHz). In the SG-I group, tinnitus was generally detected at frequencies with hearing loss.

The HL configurations were sloping in 11 participants, flat in 4 participants, and 6 kHz notch in 1 participant. According to Pure Tone Averages (PTA), moderately severe HL was detected in 5 individual, moderate HL in 4 individual, and mild HL in 3 individuals. While PTAs of other individuals were within normal limits, SNHL was present at high frequencies. (See Figure 1). When the patient's anamnesis was examined, there was no chronic disease and none of the hearing losses were congenital.

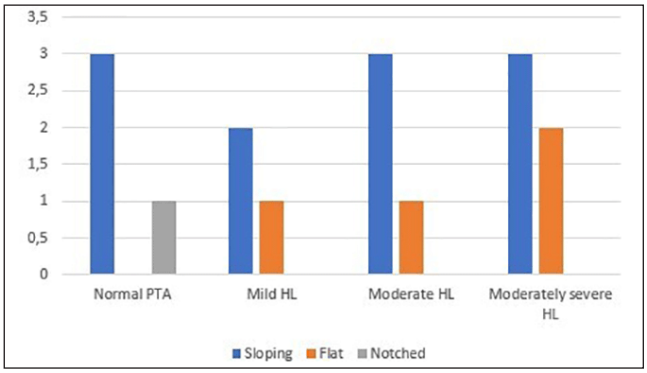

Figure 1. Hearing loss Information of Participants in SG–I PTA: Pure Tone Avarage, HL: Hearing Loss)

TEN Test Results

In the current study, the accepted criteria for a DR was that the masked threshold should be at least 10 dB worse than the unmasked threshold. Threshold changes in the presence of TEN at all frequencies were analyzed. In SG-II and CG, there were no subjects DRs. In contrast and as expected in SG-I, there were two subjects with DRs. One of the subjects (#32) was a 39-year-old with sloping bilateral SN hearing loss and tinnitus. All hearing thresholds were increased with TEN and DR was detected at 4 kHz in the right ear. The other subject (#56) was 25-year-old with bilateral flat, moderately severe SN hearing loss and tinnitus. In this subject, DRs were observed bilaterally at 0.5 kHz, 1 kHz and 4 kHz.

Unlike the control group, it was observed that the all thresholds in study group increased with TEN. The difference was significantly different between groups at all frequencies (see Table 2). Threshold increases in SG-I were significantly different from thresholds in the control group and SG-II. When SG-II was compared with CG, there were significant differences at 0.5 kHz ($p<0.05$); however, there was no significant difference at other frequencies ($p>0.05$) (see Table 2).

OAE Tests Results

For TEOAE and DPAOE tests, SNR and emission response amplitudes were evaluated. Because the subjects in the SG-I had hearing loss, either minimum OAE amplitudes were observed or no OAE was observed. Only 5 participants in this group responded in OAE tests with amplitudes ranging from -12.5 to 8.6 dB. Therefore, only SG-II and CG were compared.

There was no significant difference between SG-II and CG in relation to SNR and amplitudes at 1000Hz, 1414Hz, 2228Hz, and 4000Hz. When compared the SNRs in DPOAE test, similarly with TEOAE, there was no significant difference between SG-II and CG at 1, 1.5, 2, 3, 4, 6, and 8 kHz. However, emission response amplitudes at 6 kHz and 8 kHz were significantly decreased in SG-II (respectively p: 0.030; p: 0.015 $p<0.05$).

Table 1. Profiles of Subjects

	Number of Subjects	Mean Age	Localization of Tinnitus			Hearing Loss	
			Bilateral	Unilateral	Inside the Head	Degree	Type
Study Group I	16 (7F, 9M) (22 Ear)	37.2	4	10	2	Mild (10 of 22) (%45)	Flat (2 of 22) (%9)
						Moderate (5 of 22) (%22)	Sloping (19 of 22) (%86)
						Moderately– Severe (1 of 22) (%4.5)	Notched (1 of 22) (%4.5)
Study Group II	15 (6F, 9M) (22 Ear)	28.73	4	8	3	Normal	–
Control Group	21 (12F, 9M) (42 Ear)	24.42	–	–		Normal	–

F: Female, M: Male

Table 2. Amount of change in thresholds of groups in the presence of TEN noise.

Groups	N	Frequency (kHz)	Min. (dB)	Max (dB)	Mean (dB)	Median (dB)	IQR	P values	
								CG	**SG-II**
SG-I	22	0.5	0	14	**4.82**	4.0	4.5	0.002*	1.00
		1	4	14	**6.00**	6.0	2	0.00*	0.017*
		2	0	8	**4.00**	4.0	4	0.00*	0.001*
		4	0	20	**6.32**	5.0	4	0.00*	0.002*
								CG	**SG-I**
SG-II	22	0.5	0	8	**3.73**	4.0	4	0.022*	1.00
		1	2	6	3.91	4.0	4	0.22	0.017*
		2	−6	6	0.73	0	2	0.9	0.001*
		4	−2	8	1.82	2.0	4	0.19	0.002*
								SG-II	**SG-I**
CG	42	0.5	−10	6	**1.05**	2.0	4	0.022*	0.002*
		1	−2	6	2.81	4.0	2	0.22	0.00*
		2	−6	6	−0.24	0	4	0.9	0.00*
		4	−10	4	−0.14	0	4	0.19	0.00*

kHz: Kilohertz, IQR: Inter Quantile Range, SG-I: Study group 1, SG-II: Study group 2, CG: Control group, N: Number of tested ears, Min:Minimum, Max: Maximum *: p<0.05

DISCUSSION

It is widely accepted that severe damage to the auditory pathways can cause tinnitus-related hearing loss [14]. As it is known, the destructive effects that cause hearing loss and tinnitus first damage OHC [15]. However, evaluation with conventional audiometer does not provide the opportunity to determine whether the damage is OHC or IHC. Therefore, in this study with HL and, tinnitus patients who had normal thresholds on the audiogram were evaluated with tests evaluating OHC and IHC. functions. In this way, the widely accepted theory was tested.

TEN Test: Dead Regions and Elevated Thresholds

In the current study it was hypothesized that tinnitus patient with HL (SG-I) would have increased hearing thresholds in the TEN when compared to tinnitus patient with normal-hearing (SG-II). The TEN test results of SG-I were significantly different from SG-II and CG. The TEN showed that hearing thresholds were increased in all subjects with tinnitus in SG-I. Additionally, in SG-I, there were two subjects who had DRs. Especially in SG-I, OAE was absent or minimally observed. The sensorineural-based tinnitus model explains tinnitus as damage to hair cells, degenerated spiral ganglia, and decreased outputs on the frequency-specific nerve endings of the auditory nerve [16]. This damage to SNHL may have occurred in both OHC and IHC. For example, if the total hearing loss at a given frequency is 60 dB, 40 dB of that loss might be due to OHC damage and 20 dB to IHC damage [7]. Absence or minimal presence of OAEs in SG-I indicates a decrease or loss of function of OHC at the tested frequency, while an increase in TEN thresholds indicates loss of function of IHC. In the literature, only hearing loss due to OHC damage is stated to be no more than about 50 dB at low frequencies and 65 dB at high frequencies [15,17]. However, even though the HL levels in this group were lower than the specified levels, the increase in the thresholds in the TEN test made us think that the damage may have reached the IHC even if there was no DR.

Also, when while taking subjects' history in SG-I, they reported that their first compliant with hearing loss and then they suffer from tinnitus appeared. It is known that auditory deprivation could cause hyperactivity in nerve fibers and auditory nuclei and, as a result, the plasticity in the central auditory level increases. Input deprivation in the nervous system is the strongest factor that can activate neural plasticity [18]. In cases of auditory plasticity, changes can alter the processing of sounds and cause hyperactivity that can promote tinnitus and hyperacusis in the CNS. In particular, cochlear degeneration, which eliminates the neural output of the cochlea, can induce or intensify the phantom sound perception of tinnitus [14].

In the TEN test results of the tinnitus patients with normal hearing, significantly lower thresholds were found at all frequencies except 500 Hz compared to the tinnitus patients with HL; compared to the control group, a higher threshold was obtained at all frequencies and a significant difference was obtained only at 500 Hz. Conflicting results have been obtained

in studies in the literature [8-10, 19]. Moore et al. (2000) stated that during the TEN tests, if there is a 10 dB or more increase in hearing thresholds in the presence of noise, it is accepted that there is a "dead region" at that frequency [7]. However, if this increase in threshold is less than 10 dB, there may be a degeneration in that frequency region; even if there is no specific DR, there may be a disruption in the central pathways of hearing or auditory neuropathy [7, 20]. In the current study, even though there was no detected DR in normal- hearing subjects with tinnitus, an increase in hearing thresholds presence of TEN could be accepted as sign of degeneration in the cochlea and may also be seen as the early sign of hidden hearing loss. The elevation of thresholds in presence of TEN was explained as poor processing efficiency either caused by a reduction of neural synchrony or by synaptopathy in literature [21]. In order for IHCs to be damaged, stronger disrupting factors are needed than OHCs. It was reported that even if up to 80% of IHC is damaged, in very rare cases, audiometric thresholds may not be affected [22]. In the literature on hidden hearing loss, there are some studies that have found that a DR could be observed in normal-hearing subjects with tinnitus [8]. Obtaining different results in studies may be related to the variability of the underlying etiologies of tinnitus.

OAEs

In addition to TEN, OAE also were used to evaluate use of cochlear function, especially in OHC. OAEs in the normal-hearing subjects with tinnitus (SG-II) were slightly different from control group. TEOAE amplitudes and SNRs were similar in both groups. However, DPOAE results showed significant decreases in emission amplitudes at 6 and 8 kHz in normal-hearing subjects with tinnitus. Fabijanska et al. reported significantly reduced amplitudes in DPOAE in normal-hearing subjects with tinnitus [3]. It is known that destructive effects of noise, ototoxic effects, metabolic imbalances on the hair cells starting from the basal region of the cochlea [23]. Degeneration on the basal region result in decrement in OAE amplitudes. The decrease in input in this region may have triggered the tinnitus. However, TEN test was limited to 4000Hz and so there is no chance to test this statement. Our results could be a guide for future studies.

Tinnitus Handicap Inventory

THI was applied to all subjects with tinnitus in the study group to determine and evaluate the tinnitus discomfort level. THI evaluates the perceived effect of tinnitus on a subject's life quality. Ratnayake S et al. (2009) reported that THI was affected by hearing loss and thus, hearing-loss subjects with tinnitus had higher scores [24]. However, Newman CW et al. (1996) reported no significant difference on THI scores between normal-hearing subjects and subjects with hearing loss [25]. Similar to Newman et al.'s results, there was no significant difference in THI scores between the study groups in the current study.

Limitations

To determine audiometric thresholds, TDH-39 headphones were used and only thresholds up to 12 kHz were measured. Not including higher frequencies is the main limitations of the study.

CONCLUSION

In conclusion, when tinnitus occurs with hearing loss, both the TEN and OAE produce different results, supporting the theory of hair cell degeneration in the cochlea in both IHC and OHC. Evaluations with conventional audiometers are insufficient to evaluate tinnitus individuals with normal hearing; high frequency thresholds should be tested and TEN and similar tests should be used for IHC functions.

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Ethics Committee Approval: The study was approved by Hacettepe University Clinical Research Ethics Committee (KA-180134/ Date: 10.01.2019). Informed consents were given to the all subjects. This study is based on first author's master dissertation.

REFERENCES

1. Shailer MJ, Tyler RS, Coles RRA (1981) Critical masking bands for sensorineural tinnitus. Scand. Audiol. 10(3):157-162. https://doi.org/10.3109/01050398109076176

2. Eggermont JJ (2012) The neuroscience of tinnitus, First. ed. Oxford University Press, UK. https://doi.org/10.1093/acprof:oso/9780199605606.001.0001

3. Fabijańska A, Smurzyński J, Hatzopoulos S, Kochanek K, Bartnik G, Raj-Koziak D, Skarżyński H (2012) The relationship between distortion product otoacoustic emissions and extended high-frequency audiometry in tinnitus patients. Part 1: normally hearing patients with unilateral tinnitus. Med Sci Monitor. 18(12):CR765. https://doi.org/10.12659/msm.883606

4. Kowalska S, Sułkowski W (2001) Tinnitus in noise-induced hearing impairment. Med. Pr. 52(5):305-313. PMID: 11828843

5. Ami M, Abdullah A, Awang MA, Liyab B, Saim L (2008) Relation of distortion product otoacoustic emission with tinnitus. The Laryngoscope, 118(4):712-717. https://doi.org/10.1097/MLG.0b013e318161e521

6. Ishak W. S, Zhao F, Rajenderkumar D, Arif M (2013) Measurement of subtle auditory deficit in tinnitus patients with normal audiometric thresholds using evoked otoacoustic emissions and threshold equalizing noise tests.

Int. Tinnitus J. 18(1):35-44. https://doi.org/10.5935/0946-5448.20130006

7. Moore BCJ, Huss M, Vickers DA, Glasberg, BR, Alcántara JI (2000) A test for the diagnosis of dead regions in the cochlea. Br J Audiol 34(4):205-224. https://doi.org/10.3109/03005364000000131

8. Weisz N, Hartmann T, Dohrmann K, Schlee W, Norena, A (2006) High-frequency tinnitus without hearing loss does not mean absence of deafferentation. Hearing Res. 2 222(1-2):108-114. https://doi.org/10.1016/j.heares.2006.09.003

9. Thabet EM (2009) Evaluation of tinnitus patients with normal hearing sensitivity using TEOAEs and TEN test. Auris Nasus Larynx. https://doi.org/10.1016/j.anl.2009.01.002

10. Buzo BC, Carvallo RMM (2014) Psychoacoustic analyses of cochlear mechanisms in tinnitus patients with normal auditory thresholds. Int. J. Audiol. 53(1):40-47. https://doi.org/10.3109/14992027.2013.840931

11. Vernon JA, Meikle MB (2003) Tinnitus: clinical measurement. Otolaryng Clin N Am. 36(2):293-305. https://doi.org/10.1016/S0030-6665(02)00162-7

12. Henry JA (2016) "Measurement" of tinnitus. Otol. Neurotol. 37(8):276-285. https://doi.org/10.1097/MAO.0000000000001070

13. Moore BC, Glasberg BR, Stone MA (2004) New version of the TEN test with calibrations in dB HL. Ear and Hear. 25(5):478-487. https://doi.org/10.1097/01.aud.0000145992.31135.89

14. Møller AR, Langguth B, DeRidder D, Kleinjung, T (Eds.) (2010) Textbook of tinnitus. Springer Science & Business Media. https://doi.org/10.1007/978-1-60761-145-5

15. Yates GK (1995) Cochlear structure and function. Hearing, 2:41-74. https://doi.org/10.1016/B978-012505626-7/50004-2

16. Eggermont, JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci. 27(11):676-682. https://doi.org/10.1016/j.tins.2004.08.010

17. Marmel F, Cortese D, Kluk K (2020) The ongoing search for cochlear synaptopathy in humans: Masked thresholds for brief tones in Threshold Equalizing Noise. Hearing Res. 392:107960. https://doi.org/10.1016/j.heares.2020.107960

18. Møller AR (2008) Neural plasticity: for good and bad. Theor. Phys. 173:48-65. https://doi.org/10.1143/PTPS.173.48

19. Kara E, Aydın K, Akbulut AA, Karakol SN, Durmaz S, Yener HM, Kara, H (2020) Assessment of hidden hearing loss in normal hearing individuals with and without tinnitus. J. Int. Adv. Otol., 16(1):87. https://doi.org/10.5152/iao.2020.7062

20. Starr A, Michalewski HJ, Zeng FG, Fujikawa-Brooks S, Linthicum F, Kim CS, Keats B (2003) Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene (Tyr145→Ser). Brain, 126(7):1604-1619. https://doi.org/10.1093/brain/awg156

21. Furman AC, Kujawa SG, Liberman MC (2013) Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. J. Neurophysiol. 110(3):577-586. pp. 577-586 https://doi.org/10.1152/jn.00164.2013

22. Lobarinas E, Salvi R, Ding D (2013) Insensitivity of the audiogram to carboplatin induced inner hair cell loss in chinchillas. Hearing Res. 302:113-120. https://doi.org/10.1016/j.heares.2013.03.012

23. Ruggero MA, Rich NC, Recio A, Narayan SS, Robles L (1997) Basilar-membrane responses to tones at the base of the chinchilla cochlea J. Acoust. Soc. Am. 101(4):2151-2163. https://doi.org/10.1121/1.418265

24. Ratnayake SAB, Jayarajan V, Bartlett J (2009) Could an underlying hearing loss be a significant factor in the handicap caused by tinnitus?" Noise and Health 11(44):156. https://doi.org/10.4103/1463-1741.53362

25. Newman CW, Jacobson GP, Spitzer JB (1996) Development of the tinnitus handicap inventory. Arch. otorhinolaryngol.-head neck surg. 122(2):143-148. https://doi.org/10.1001/archotol.1996.01890140029007

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Original Research

Comparison of Resilience and Depression in Children and Adolescents with Epilepsy and Healthy Controls

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ABSTRACT

Objective: The purpose of this study was to compare the depression and resilience scores of children and adolescents with epilepsy and healthy controls. Furthermore, its purpose was to investigate whether resilience mediates the relationship between epilepsy and depression.

Methods: 100 children and adolescents (46 patients and 54 healthy controls) were included in the study. Questionnaire on sociodemographic data was administered to the all participants at the time of application to our center and all participants were asked to complete the Anxiety and Depression Scale in Children-Revised (RCADS-CV) and Child and Adolescent Psychological Resilience Scale (CYRM-12).

Results: 46 epilepsy patients had higher RCADS-CV depression scores (P=0.008) and lower psychological resilience scores (P= 0.001) compared to the control group. Although there was a negative correlation between psychological resilience scores and RCADS-CV depression scores in epilepsy patients and the control group, this correlation was not statistically significant.

Conclusion: We found that children and adolescents with epilepsy had lower psychological resilience and higher depression symptoms compared to healthy controls.

Keywords: Epilepsy, depression, resilience, child and adolescent

INTRODUCTION

Epilepsy is a neurological disease that occurs with excessive electrical discharges of brain cells and is characterized by recurrent seizures due to disturbances in the electrical functions of the brain. Seizures can cause serious suicide risk, premature death, social exclusion and depression in patients and affect their quality of life. Epilepsy is the most common neurological disorder in children and its prevalence in childhood is estimated to be 0.05-1% [1]. The fact that it is the most common among chronic neurological diseases makes the studies on this subject more important. Studies focusing on the prevalence of psychopathology in pediatric epilepsy have also documented that children with epilepsy have an estimated overall risk of childhood psychopathology of 16-77% [2, 3].

Children with epilepsy often have negative mood disorders such as depression. Depression in children manifests as mood swings, impulsivity, poor self-esteem, self-harm, suicide, and abdominal pain, which can have undesirable consequences for both the patient and the family [4]. There were many studies about childhood and adolescents epilepsy that report neuropsychiatric disorders in 35–50% of these patients [5]. Patients with epilepsy exhibit a 4-5 higher rate of depression compared with healthy population. In studies on epilepsy was found that the age of the patient, the age of onset of the seizure, the seizure type, the seizure frequency, the life span with the disease, the education level, the use of antiepileptic drugs and the socioeconomic status of the patient were associated with depression [6].

Psychological resilience, on the other hand, comes from the concept of "resilience", which derives from the Latin verb "salire" that meaning to jump again. It has been translated into Turkish with terms such as resilience, psychological resilience and flexibility [7]. The concept of psychological resilience, which is the ability of individuals to recover themselves or to overcome what they have experienced despite many challenges and difficulties they encounter in life, has been the subject of many studies in the literature [8]. Studies on the psychological resilience of depressed children and adolescents; shows that psychological resilience may play a role in the etiology of depression [9, 10].

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Many previous studies have shown that self-esteem is an important predictor of resilience [11-13]. In patients with epilepsy, the age of diagnosis of epilepsy is low, the duration of living with epilepsy is increased, uncontrolled seizures, the uncertainty of when the seizures will occur, loss of consciousness and body control during the seizure, difference in recovery time after the seizure, fear of being labeled, non-compliance with drug therapy negatively affects its life quality [14, 15]. Situations such as epilepsy patients experiencing unpredictable and suddenly developing seizures, losing control during seizures, growing socially isolated, families having a protective approach, and deterioration in social relations may cause individuals to lose their self-esteem [16].

Many studies have shown that epilepsy reduces resilience and causes depression but these studies have been conducted in adults with epilepsy or in families of children with epilepsy, the relationship between resilience and depression in children with epilepsy is among the barren areas. Therefore, in this study, we aimed to compare the depression and resilience scores of children and adolescents with epilepsy and healthy controls, and to investigate whether resilience mediates the relationship between epilepsy and depression.

METHODS

Study Population

This Study was planned as a single-center, prospective cohort study. Patients aged 8-17 years who applied to the Pediatric Neurology Clinic of Gaziantep University Medical Faculty Hospital and who had been diagnosed with epilepsy for at least 1 year, and healthy children aged 8-17 who applied to the Gaziantep University Medical Faculty Hospital Pediatric Clinic who were not diagnosed with any disease were included in the study. Patients with missing or incomplete data, patients with seizures below 6 months, patients younger than 8 years old, patients older than 17 years of age, and cases with psychiatric disorders such as autism or mental retardation were not included in the study. Dieter Schmidt's 2007 study showed that the response to antiepileptic drugs in the first 6 months is an excellent indicator of the response at 12 months in patients with epilepsy [17]. Therefore, patients with a seizure-free at least 6 months were preferred in order to exclude acute psychological symptoms of seizures and seizure side effects in patients with epilepsy in addition to reach more objective results by preventing antiepileptic drug changes during this period. Ethical consent was obtained for the study (Gaziantep University Faculty of Medicine Ethics Committee; decision dated 24.02.2021 and numbered 2021/34). Informed consent was obtained from all individuals included in the study. Questionnaires applied during the application to our center are Sociodemographic Data Form, Anxiety and Depression Scale in Children-Revised (RCADS-CV), Child and Adolescent Psychological Resilience Scale (CYRM-12).

Main Points:

- Many studies have shown that epilepsy reduces resilience and causes depression, but these studies have been conducted in adults with epilepsy or in families of children with epilepsy, the relationship between resilience and depression in children with epilepsy is among the barren areas.
- In this study, it was found that 46 patients with epilepsy who were followed up in the Pediatric Neurology Clinic of Gaziantep University Medical Faculty Hospital had higher RCADS-CV depression scores and lower psychological resilience scores compared to the control group.
- Parenting styles in Turkish society and the overprotective attitudes of families with children with epilepsy may also have contributed to low resilience scores and high depression scores.

Scales

Sociodemographic Data Form: In this form, there are questions about the sociodemographic characteristics of the child, such as gender, date of birth, class, number of siblings, and whether he applied to the psychiatry clinic. The form also includes information about the age and professional status of the parent. In addition, epilepsy-specific information such as drugs used by children and adolescents with epilepsy, time of diagnosis of epilepsy, seizure type, time of last seizure, and EEG results were collected. This form was completed by the clinician.

Anxiety and Depression Scale in Children-Revised (RCADS-CV): The RCADS-CV was developed by Chorpita et al. for children 3-12 grades. It consists of a total of 47 items and measures separation anxiety, social phobia, obsessive compulsive disorder, panic disorder, generalized anxiety disorder and major depressive disorder [18]. The validity and reliability of the Turkish version was made by Vahdet Söylemez, Ayse Kılınçaslan, Abdurrahman Cahid Örengül, Chad Ebesutani, İlyas Kaya, Veysi Ceri, Serhat Nasıroğlu, Mekiya Filiz & Bruce Chorpita [19]. Each item is scored between never (0), sometimes (1), often (2), and always (3) in the four-Likert scale. A high score indicates a high level of anxiety or depression symptoms.

Child and Youth Resilience Scale (CYRM-12): The original 28-item form of the scale consists of three subscales and eight sub-dimensions [20]. The short form study was done by Liebenberg, Ungar, and LeBlanc (2013), and a 12-item structure was obtained as a result of two different studies [21]. The Turkish validity and reliability study of the scale was performed by Arslan et al. [22]. This form was completed by children and adolescents. The measurement tool, which has a five-point Likert structure, is rated between "Describes me completely (5)" and "Does not describe me at all (1)". A high score indicates a high level of resilience.

Statistical Analysis

The sociodemographic and medical data of the participants were made using descriptive statistical methods. The normal distribution of numerical variables was tested with the Shapiro Wilk test. The Mann Whitney U test was used to compare the skewed variables between the two groups, and the Kruskal Wallis test was used for multiple comparisons. The relationships

between the skewed numerical variables were tested using the Spearman rank correlation coefficient, and the relationships between the categorical variables were tested using the Chi-square test. SPSS for Windows version 22.0 was used for statistical analysis. P value <0.05 was considered statistically significant.

RESULTS

The mean age of the children was 12.64 ± 2.74 (8-18 years), the mean age of onset of disease was 10.52 ± 2.26 (7 -14), and the mean disease duration was 36.63 ± 17.19 (12 -102 months). Data from a total of 100 children and adolescents, 31 males (31%) and 69 females (69%), were analyzed. Of the patients 32 (69.6%) had generalized epilepsy and 27 (58.7%) had seizure remission in the past year. Most of the participants' parents were not college graduates. Table 1 shows the comparison of the sociodemographic characteristics of the children and adolescents participating in the study. There was no significant difference in terms of age, gender, class, number of siblings, father's education, income status and having a room of their own. However a significant difference was found in terms of maternal education level (p=0.039). The mother's education level was higher in the control group.

The comparison of depression and resilience scores of children with epilepsy and control groups is shown in Table 2. According to the data obtained, the RCADS-CV Depression Score of children with epilepsy was 11.17 ± 14.03; the children in the control group were found to be 5.7 ± 5.75 (p=0.008). In the comparison made in terms of psychological resilience scores, it was found that the children with epilepsy were 44.57 ± 7.57 and the control group was 53.07 ± 9.03 (p=0.001). When these results were evaluated, it was found that children with epilepsy were more depressed and had lower psychological resilience. Although there was a negative relationship between psychological resilience scores and RCADS-CV depression scores in epilepsy patients (P=0.285) and control group (P=0.233), this relationship was not statistically significant (Table 3).

In the study, the age of onset of the disease, the duration of the disease, the number of siblings, the number of antiepileptic drugs [23], the type of seizure, gender, number of seizure-free years, and consanguinity between parents were found to be unrelated to RCADS-CV depression and psychological resilience scores. (Table 4,5) In the Kruskal Wallis test performed, no statistically significant correlation was found between the type of antiepileptic drug used in adolescents with epilepsy, seizure time, EEG (electroencephalography) findings and RCADS-CV depression and psychological resilience scores (p>0.05).

Table 1. Comparison of sociodemographic characteristics of children and adolescents with epilepsy with healthy controls

Variables		Control (n=54)	Patient (n=46)	
Continuous Variables		**Median (Min-Maks)**	**Median (Min-Maks)**	**P[a]**
Age		12 (8 – 18)	12.5 (8 – 18)	0.136
Grade		6.5 (1 – 11)	7 (3 – 12)	0.073
Number of siblings		3 (1 – 7)	3 (0 – 5)	0.462
Categorical Variables		**N (%)**	**N (%)**	**P[b]**
Gender	Female	41 (75.9)	28 (60.9)	0.105
	Male	13 (24.1)	18 (39.1)	
Father's education	Only literate	1 (1.9)	2 (4.3)	0.443
	Primary school	14 (25.9)	17 (37.0)	
	Secondary school	8 (14.8)	7 (15.2)	
	High school	15 (27.8)	13 (28.3)	
	University degree	16 (29.6)	7 (15.2)	
Mother's education	Only literate	0 (0)	4 (8.7)	**0.039**
	Primary school	20 (37.0)	25 (54.3)	
	Secondary school	7 (13.0)	5 (10.9)	
	High school	14 (25.9)	6 (13.0)	
	University degree	13 (24.1)	6 (13.0)	
İncome rate	Less than the minimum wage	9 (16.7)	8 (17.4)	0.694
	The minimum wage	24 (44.4)	23 (50.0)	
	The minimum wage x2	9 (16.7)	9 (19.6)	
	The minimum wage x3	12 (22.7)	6 (13.0)	
Child's own room	Yes	25 (46.3)	19 (41.3)	0.616
	No	29 (53.7)	27 (58.7)	

P[a]: Mann Whitney U test was used to evaluate the level of significance. P[b]: Chi-square test was used to evaluate the level of significance.

Table 2. Comparison of resilience and RCADS-CV depression scores of adolescents with epilepsy and control group

	Patient (n=46)	Control (n=54)	P
RCADS-CV Depression Score	11.17 ± 14.03	5.7 ± 5.75	0.008*
CYRM-12 Resilience Score	44.57 ± 7.57	53.07 ± 9.03	0.001*

*Significant at the 0.05 level, Mann Whitney U test was used to evaluate the level of significance. RCADS-CV: Anxiety and Depression Scale in Children, CYRM-12: Child and Adolescent Psychological Resilience Scale

Table 3. Correlation between RCADS-CV depression scores and resilience scores in adolescents with epilepsy

Group			CYRM-12 Resilience Score
Control	RCADS-CV Depression Score	R	-0.165
		P	0.233
Patient	RCADS-CV Depression Score	r	-0.161
		P	0.285

*Significant at the 0.05 level; r: Spearman rank correlation coefficients RCADS-CV: Anxiety and Depression Scale in Children, CYRM-12: Child and Adolescent Psychological Resilience Scale

Table 4. Correlation between RCADS-CV depression and CYRM-12 resilience scores in adolescents with epilepsy, number of antiepileptic drugs, number of siblings, duration of disease, age of onset of disease

Group			Number of AEDs	Number of siblings	Duration of disease	Age of onset of disease
Patient	RCADS-CV Depression Score	r	-0.008	0.196	-0.150	0.112
		P	0.958	0.192	0.321	0.460
	CYRM-12 Resilience Score	r	-0.036	0.025	-0.055	-0.036
		P	0.810	0.869	0.717	0.814

*Significant at the 0.05 level; r: Spearman rank correlation coefficients RCADS-CV: Anxiety and Depression Scale in Children, CYRM-12: Child and Adolescent Psychological Resilience Scale, AED: Antiepileptic drug

Table 5. Comparison of the RCADS-CV depression and CYRM-12 resilience scores of the patient group according to the number of seizure-free years, seizure type, gender, and consanguinity between parents

Variables		RCADS-CV Depression Score	CYRM-12 Resilience Score
Number of seizure-free years	1 year	9.44 ± 12.35	43.67 ± 7.29
	6 months	13.63 ± 16.15	45.84 ± 7.98
	P	0.292	0.288
Seizure type	Focal	7.57 ± 7.035	45.29 ± 5.823
	Generalize	12.75 ± 16.016	44.25 ± 8.289
	P	0.235	0.756
Gender	Female	11.93 ±13.741	45.82 ± 6.401
	Male	10 ± 14.789	42.61 ± 8.952
	P	0.348	0.241
Consanguinity between parents	Yes	11.38 ± 13.362	44.29 ± 8.804
	No	11 ± 14.838	44.80 ± 6.545
	P	0.465	0.982

*Significant at the 0.05 level, Mann Whitney U test was used to evaluate the level of significance, RCADS-CV: Anxiety and Depression Scale in Children, CYRM-12: Child and Adolescent Psychological Resilience Scale,

DISCUSSION

In the current study, which aimed to compare the depression and resilience scores of children and adolescents with epilepsy and healthy controls and to investigate whether resilience mediates the relationship between epilepsy and depression; it was determined that 46 patients with epilepsy who were followed up in the Pediatric Neurology Clinic of Gaziantep University Medical Faculty Hospital had higher RCADS-CV depression scores and lower psychological resilience scores compared to the control group. (Table 2) Although there was a negative relationship between psychological resilience scores and RCADS-CV depression scores in epilepsy patients (P=0.285) and control group (P=0.233), this relationship was not statistically significant (Table 3).

While the first reaction of parents who have children with epilepsy is to deny it, over time, families experience the stages of shock, devastation, disappointment, mourning and depression. Families may develop an overprotective attitude towards the child at the end of this fear/anxiety process [24]. This attitude of the families causes the child to become suppressed and overly dependent [25]. Epilepsies seen in childhood cause parents to develop a more conservative approach and accordingly individuals become dependent on others [26]. Families in Turkey often dictate and expect normative behavior and this attitude leads to repression of negative emotions by punishing them frequently [27]. Trying to manage something by suppressing is not among the most effective coping methods [27]. Since parenting that teaches children to deal with their emotions constructively is not common in Turkey, feelings of fear or helplessness are tried to be suppressed by the child [28]. This either leads to increased mood problems or manifests as psychosomatic problems [29].

Resilience and parenting style have been found to be inextricably linked. Studies have found that parenting styles have a positive or negative effect on their children's resilience [30].

According to the study of Wu et al. higher resilience is associated with a better positive coping style [31]. Individuals with low psychological resilience may not be able to develop adequate coping mechanisms when exposed to diseases, so these individuals may be more likely to experience depression. Therefore, parenting styles in Turkish society and the overprotective attitudes of families with children with epilepsy may also have contributed to low resilience scores and high depression scores [32].

In a study by Tedrus et al. in 2020, seizure control, normal EEG background activity and antiepileptic drug monotherapy were associated with greater resilience. Higher resilience has been associated with improved cognitive performance and less depressive symptom formation [33]. In our study, although there was a negative relationship between psychological resilience scores and RCADS-CV depression scores in patients with epilepsy, this relationship was not significant at the $p<0.05$ level. (Table 3) This may be due to the low sample size.

In a study conducted by Oguz A. et al. at Dokuz Eylül University in 2002 was determined that epilepsy-related factors such as duration of epilepsy, seizure frequency, and polytherapy increased anxiety and depression, while seizure onset age, seizure type, and electroencephalographic findings were not associated with anxiety and depression [34]. In our study, as in Dokuz Eylul, seizure onset age, seizure type, and EEG findings were not correlated with RCADS-CV depression scores, but unlike the study, RCADS-CV depression scores were also found to be unrelated with gender, number of siblings, frequency of seizures, seizure type, seizure time, AED type and polytherapy (Table 4,5). Ekinci et al. also suggested that AED use or AED type are not consistent predictors of depression [35].

According to a study conducted in China, the psychological resilience of the first child was found to be significantly lower than that of the only child [36]. Although there was no relationship between the number of siblings and psychological resilience in our study, more detailed results can be obtained by adding the parameters of one child and first child (Table 4).

In the study by Tedrus et al. greater reslience was observed in patients with epilepsy who had controlled seizures, normal EEG background activity, and took a single AED. There were no significant differences between resilience of groups in gender, seizure type, lateralized epileptic activity on EEG, epilepsy with lateralization of TLE-HS (Temporal lobe epilepsy and hippocampal sclerosis) [33]. In our study, however, no correlation was found between the number of seizure-free years, EEG findings, gender, seizure type, age at onset of epilepsy disease, number of antiepileptic drugs, and psychological resilience scores. This difference between studies can be explained that by the larger sample size in the study conducted in Brazil. At the same time, many studies have shown that having recurrent seizures affects the resilience and depression scores of people with epilepsy, especially when compared with those in seizure remission [37-40]. In our study, however since patients who had seizure in 6 months or less than 6 months were excluded, no significant results could be obtained.

During the reliability and validity testing phase, participants in the pilot study were limited to one hospital and the sample size was small. Therefore, it is necessary to further expand the sample size and improve the representativeness of the sample in the next study to validate the results of the study.

One of the strengths of this study was young people's involvement in interviews rather than their parents, thus providing a unique view on family processes. Furthermore many studies have shown that epilepsy reduces resilience and causes depression, but these studies have been conducted in adults with epilepsy or in families of children with epilepsy, the relationship between resilience and depression in children with epilepsy is among the barren areas. Current findings provided a overview of the relationship between resilience and depression in children.

Since resilience scores may vary according to parenting attitudes, it may be more useful to include them in the study. Although there was no relationship between the number of siblings and psychological resilience in our study, more detailed results can be obtained by adding the parameters of only child and first child.

Since puberty may also affect depression and resilience scores, two samples can be formed before and after puberty to exclude the effects of puberty.

In order to distinguish whether epilepsy directly affects psychological resilience negatively and causes a tendency to depression, a study can be conducted to evaluate the psychological resilience of adolescents with epilepsy by forming two groups as those with and without depressive complaints.

Educating families about mood disorders may provide earlier diagnosis of depression and easier access to psychiatric treatment in children with epilepsy. At the same time, providing families with information on how to communicate with their children with epilepsy and how to manage the crisis can increase positive coping mechanisms and psychological resilience and decrease the frequency of depression.

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Ethics Committee Approval: The study was approved by Gaziantep University Clinical Research Ethics Committee (Approval Number: 2021/34, Date: 24-02-2021). Informed consents were given to the all subjects. This study is based on first author's master dissertation.

REFERENCES

1. Aaberg KM, Gunnes N, Bakken IJ, Lund Søraas C, Berntsen A, Magnus P, Lossius MI, Stoltenberg C, Chin R, Surén P (2017) Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. Pediatrics 139. https://doi.org/10.1542/peds.2016-3908

2. Dharmadhikari AS, Sinha VK (2017) Psychiatric Comorbidity in Children with Epilepsy: A Cross-sectional 5 Years Rural Prevalence Study. J Neurosci Rural Pract 8:179-184. https://doi.org/10.4103/jnrp.jnrp_487_16

3. Chiang KL, Cheng CY (2014) Prevalence and neuropsychiatric comorbidities of pediatric epilepsy in Taiwan: a national population-based study. Epilepsy Res 108:1451-1460. https://doi.org/10.1016/j.eplepsyres.2014.07.004

4. Schraegle WA, Titus JB (2017) The relationship of seizure focus with depression, anxiety, and health-related quality of life in children and adolescents with epilepsy. Epilepsy Behav 68:115-122. https://doi.org/10.1016/j.yebeh.2016.12.009

5. Almane DN, Jones JE, McMillan T, Stafstrom CE, Hsu DA, Seidenberg M, Hermann BP, Oyegbile TO (2019) The Timing, Nature, and Range of Neurobehavioral Comorbidities in Juvenile Myoclonic Epilepsy. Pediatr Neurol 101:47-52. https://doi.org/10.1016/j.pediatrneurol.2019.03.011

6. Yang C, Hao Z, Mao Y, Xu Q, Zhao L, Zhang LL (2020) Depression in children with epilepsy from western China: A cross-sectional survey. Medicine (Baltimore) 99:e20647. https://doi.org/10.1097/md.0000000000020647

7. Turner K, La Briola F, Vignoli A, Zambrelli E, Chiesa V, Fongoni L, Baldi O, Canevini MP (2023) Living with Epilepsy in Adolescence in Italy: Psychological and Behavioral Impact. Healthcare 11:687

8. Błaszczyk B, Czuczwar SJ (2016) Epilepsy coexisting with depression. Pharmacol Rep 68:1084-1092. https://doi.org/10.1016/j.pharep.2016.06.011

9. GİZİR C, AYDIN G (2006) Psikolojik sağlamlık ve ergen gelişim ölçeği'nin uyarlanması: geçerlik ve güvenirlik çalışmaları. Turkish Psychological Counseling and Guidance Journal 3:87-99

10. Çetin F, Yeloğlu HO, Basım HN (2015) Psikolojik dayanıklılığın açıklanmasında beş faktör kişilik özelliklerinin rolü: Bir kanonik ilişki analizi. Türk Psikoloji Dergisi 30:81-92

11. Wu YL, Zhao X, Ding XX, Yang HY, Qian ZZ, Feng F, Lu SS, Hu CY, Gong FF, Sun YH (2017) A prospective study of psychological resilience and depression among left-behind children in China. J Health Psychol 22:627-636. https://doi.org/10.1177/1359105315610811

12. Zheng K, Chu J, Zhang X, Ding Z, Song Q, Liu Z, Peng W, Cao W, Zou T, Yi J (2022) Psychological resilience and daily stress mediate the effect of childhood trauma on depression. Child Abuse & Neglect 125:105485. https://doi.org/https://doi.org/10.1016/j.chiabu.2022.105485

13. Chung JOK, Li WHC, Cheung AT, Ho LLK, Xia W, Chan GCF, Lopez V (2021) Relationships among resilience, depressive symptoms, self-esteem, and quality of life in children with cancer. Psychooncology 30:194-201. https://doi.org/10.1002/pon.5548

14. Khampirat B (2020) The relationship between paternal education, self-esteem, resilience, future orientation, and career aspirations. PLoS One 15:e0243283. https://doi.org/10.1371/journal.pone.0243283

15. Wang Y, Zheng Z, Duan X, Li M, Li Y (2022) The Relationship between Mindfulness and Social Adaptation among Migrant Children in China: The Sequential Mediating Effect

of Self-Esteem and Resilience. Int J Environ Res Public Health 19. https://doi.org/10.3390/ijerph192316241

16. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, Di Lazzaro V (2021) Epilepsy and quality of life: what does really matter? Neurological Sciences 42:3757-3765. https://doi.org/10.1007/s10072-020-04990-6

17. Baranowski CJ (2018) The quality of life of older adults with epilepsy: A systematic review. Seizure 60:190-197. https://doi.org/https://doi.org/10.1016/j.seizure.2018.06.002

18. Yeni K, Tulek Z, Simsek OF, Bebek N (2018) Relationships between knowledge, attitudes, stigma, anxiety and depression, and quality of life in epilepsy: A structural equation modeling. Epilepsy & Behavior 85:212-217. https://doi.org/https://doi.org/10.1016/j.yebeh.2018.06.019

19. Schmidt D (2007) How reliable is early treatment response in predicting long-term seizure outcome? Epilepsy & Behavior 10:588-594. https://doi.org/https://doi.org/10.1016/j.yebeh.2007.02.011

20. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE (2000) Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. Behaviour research and therapy 38:835-855

21. Gormez V, Kılınçaslan A, Orengul AC, Ebesutani C, Kaya I, Ceri V, Nasıroglu S, Filiz M, Chorpita B (2017) Psychometric properties of the Turkish version of the Revised Child Anxiety and Depression Scale–Child Version in a clinical sample. Psychiatry and Clinical Psychopharmacology 27:84-92

22. Liebenberg L, Ungar M, Vijver FVd (2012) Validation of the child and youth resilience measure-28 (CYRM-28) among Canadian youth. Research on social work practice 22:219-226

23. Liebenberg L, Ungar M, LeBlanc JC (2013) The CYRM-12: a brief measure of resilience. Canadian Journal of Public Health 104:e131-e135

24. Arslan G (2015) Çocuk ve Genç Psikolojik Sağlamlık Ölçeği'nin (ÇGPSÖ) psikometrik özellikleri: Geçerlilik ve güvenirlik çalışması. Ege Eğitim Dergisi 16:1-12

25. [25] Helmstaedter C, Elger C (2009) Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease? Brain 132:2822-2830

26. Qiu Y, Xu L, Pan Y, He C, Huang Y, Xu H, Lu Z, Dong C (2021) Family Resilience, Parenting Styles and Psychosocial Adjustment of Children With Chronic Illness: A Cross-Sectional Study. Front Psychiatry 12:646421. https://doi.org/10.3389/fpsyt.2021.646421

27. Fong CY, Chang WM, Kong AN, Rithauddin AM, Khoo TB, Ong LC (2018) Quality of life in Malaysian children with epilepsy. Epilepsy Behav 80:15-20. https://doi.org/10.1016/j.yebeh.2017.12.032

28. Rani A, Thomas PT (2019) Stress and perceived stigma among parents of children with epilepsy. Neurol Sci 40:1363-1370. https://doi.org/10.1007/s10072-019-03822-6

29. Uslucan HH (2009) [Domestic violence, parenting styles and well-being of German and Turkish juveniles]. Prax Kinderpsychol Kinderpsychiatr 58:278-296. https://doi.org/10.13109/prkk.2009.58.4.278

30. Özyürek A, Aydin A, Şirin Ş, Turan R, İrken F (2020) OKUL ÖNCESİ ÇOCUĞA SAHİP TÜRKİYE'DE ve YURTDIŞINDA YAŞAYAN TÜRK EBEVEYNLERİN ÇOCUK YETİŞTİRME TUTUMLARININ KARŞILAŞTIRILMASI (LIVING THE COMPARISON OF TURKISH ATTITUDE OF PARENTS OF PRESCHOOL CHILDREN HAVING CHILDREN GROWING IN TURKEY and ABROAD). TURAN : Stratejik Arastirmalar Merkezi 12:215-222. https://doi.org/https://doi.org/10.15189/1308-8041

31. Selçuk, B. (2015). Bilge Selçuk ile söyleşi: Türkiye'de Ebeveynlik, Cogito, 81, 108-116.

32. Ding X, Zheng L, Liu Y, Zhang W, Wang N, Duan H, Wu J (2023) Parenting styles and psychological resilience: The mediating role of error monitoring. Biol Psychol 180:108587. https://doi.org/10.1016/j.biopsycho.2023.108587

33. Wu Y, Yu W, Wu X, Wan H, Wang Y, Lu G (2020) Psychological resilience and positive coping styles among Chinese undergraduate students: a cross-sectional study. BMC Psychology 8:79. https://doi.org/10.1186/s40359-020-00444-y

34. Kurtses Gürsoy B, Köseoğlu Toksoy C (2023) Psychological Resilience and Stress Coping Styles in Migraine Patients. Neuropsychiatr Dis Treat 19:63-72. https://doi.org/10.2147/ndt.S398838

35. Tedrus G, Limongi JMJ, Zuntini JVR (2020) Resilience, quality of life, and clinical aspects of patients with epilepsy. Epilepsy Behav 103:106398. https://doi.org/10.1016/j.yebeh.2019.06.041

36. Al Kiyumi H, Al-Huseini S, Mirza H, Al Balushi N, Al-Risi K, Al Toubi A, Al Hosni A, Al-Mashaikhi T, Al Balushi R, Al-Adawi S (2021) Depressive Symptoms and Its Correlate Among Children with Epilepsy at Single-center Study in Oman. Oman Med J 36:e329. https://doi.org/10.5001/omj.2021.112

37. Ünalp A, Kutlu A, Karaoğlu P, Yılmaz Ü, Çakaloz B (2022) Evaluation of Quality of Life and Psychiatric Aspects of Children with Epilepsy and Their Families Using Self-assessment Questionnaires. Turk Arch Pediatr 57:282-289. https://doi.org/10.5152/TurkArchPediatr.2022.21173

38. Morgan T, Yang S, Liu B, Cao Y (2020) A comparison of psychological resilience and related factors in Chinese firstborn and only children. Asian Journal of Psychiatry 53:102360. https://doi.org/https://doi.org/10.1016/j.ajp.2020.102360

39. De Silva S, Isuru A, Rodrigo A, Kuruppuarachchi L (2021) Prevalence and correlates of depression in patients with epilepsy in Sri Lanka. Ceylon Med J 66:138-143. https://doi.org/10.4038/cmj.v66i3.9492

40. Baniya GC, Verma K (2022) Prevalence of depression, risk factors, and quality of life in patients with epilepsy in a remote area of western Rajasthan. Epilepsy Behav 127:108488. https://doi.org/10.1016/j.yebeh.2021.108488

41. Gao Y, Tang X, Wen Y, Qian D, Pan X, Zhang L (2022) Effects of the hospital-community-family ternary linkage continuous nursing model on compliance, cognitive function, resilience, and quality of life for children with epilepsy: a retrospective study. Transl Pediatr 11:239-248. https://doi.org/10.21037/tp-22-21

42. [42] Taylor J, Jacoby A, Baker GA, Marson AG, Ring A, Whitehead M (2011) Factors predictive of resilience and vulnerability in new-onset epilepsy. Epilepsia 52:610-618. https://doi.org/10.1111/j.1528-1167.2010.02775.x

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Case Report

Scary Acute Left Main Coronary Artery Thrombus as an Initial Presentation of a Hereditary Thrombophilia: When to Go Out of Routine?

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ABSTRACT

Patients with either hereditary or acquired thrombophilia can present with arterial and venous thrombotic complications. However, it is unclear to whom the thrombophilia panel should be assessed, particularly in patients presenting with a common cardiovascular risk factor and acute coronary thrombus. Herein, we presented the management of an active smoker female patient who presented to our emergency room with inferior acute ST-segment elevation myocardial infarction, and hereditary thrombophilia has been diagnosed due to the presence of substantial left main coronary artery thrombus.

Keywords: acute coronary syndrome, coronary thrombus, thrombophilia

INTRODUCTION

Acute left main coronary artery (LMCA) occlusion is a life-threatening condition that can cause ventricular arrhythmias, cardiogenic shock, and sudden cardiac death. The LMCA as an infarct-related artery in acute ST-segment elevation myocardial infarction (STEMI) is rare [1]. Acute myocardial infarction may occur in patients with no traditional risk factors and who also have normal coronary arteries. No consensus exists in clinical practice as to which patients with acute coronary syndromes and coronary artery disease should be tested for thrombophilia. Mutations related to the coagulation pathway can be investigated in patients who are unexpectedly having coronary artery disease. Herein, we presented the management of an active smoker female patient who presented to our emergency room with acute inferior STEMI, and hereditary thrombophilia has been diagnosed due to the presence of a substantial LMCA thrombus.

CASE

A 64-year-old female patient with a diagnosis of anxiety disorder applied to the emergency room with the first episode of resting angina pectoris lasting more than 30 minutes. Her past medical history was unremarkable except for a two package year of smoking. She had not been taking any medication, including oral contraceptives. Family history was also unremarkable for premature coronary artery disease. Physical examination on admission revealed no abnormal findings with stable vital signs. Initial laboratory test results were within normal reference limits, including cardiac biomarkers. The chest X-ray was also normal. 12-lead electrocardiography on admission indicated infero-postero-lateral STEMI (ST-segment elevation at II, III, aVF, V_{4-6}, V_{7-9} leads) (Figure 1). Bedside emergent echocardiography revealed a motion abnormality at the posterior and inferior walls. Emergency room medications included unfractionated heparin, ticagrelor, aspirin, and statin administration. She has been immediately transferred to the catheter angiography room. Coronary angiography showed a non-dominant right coronary artery (RCA) and a huge thrombus at the left main coronary artery, which has moved along the left circumflex coronary artery during contrast injection (Figure 2, Video 1). However, none of the coronary segments revealed a complete occlusion. There were also atherosclerotic lesions at the osteal and mid segments of the left anterior descending (LAD) artery. The thrombus aspiration catheter was non-available in our catheter laboratory at the time of coronary angiography. Following intracoronary bolus tirofiban administration, no change in thrombus size was observed. Continuous infusion of unfractionated heparin and tirofiban was given for 24 hours. Lipoprotein (a) level was 49.5 mg/dl (normal reference range: 5.6-33.8 mg/dl), low-density lipoprotein (LDL)-cholesterol level was 133.4 mg/dl, high-density lipoprotein (HDL)-cholesterol level was 56.7 mg/dl, triglycerides

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level was 99 mg/dl. After intensive antiplatelet and anticoagulant therapy, a control coronary angiography revealed no thrombus in any coronary segment except the LAD artery distal segment (Video 2). A 3.0x20 mm drug-eluting stent (DES) and a 4.5x12 mm bare-metal stent (BMS) were implanted in the LAD artery mid and osteal 70% lesions. Percutaneous coronary angioplasty was also performed with a 2.0x12 mm balloon in the distal LAD artery segment, which resulted in a TIMI 1 flow. Her detailed physical examination and systemic symptom assessment were negative for any rheumatologic disease.

Rheumatologic markers, including ANA, ENA, RF, C3, C4, lupus anticoagulant, protein C activity, anti-dsDNA, anticardiolipin antibody IgG & IgM were negative. Only the beta-2 glycoprotein IgM level was 46.8 RU/ml, above the reference limit (normal reference level of <20 RU/ml). Fibrinogen level was 444.93 mg/dl (normal reference range: 180-350 mg/dl), and homocysteine level was 15.4 µmol/L (normal reference level of <15 µmol/L). Genetic thrombophilia panel including factor V Leiden, prothrombin, MTHFR (677), MTHFR (1298), PAI mutation analysis showed the MTHFR (677) and MTHFR (1298) heterozygote mutations and PAI 4G/4G homozygote mutation. Antiplatelet therapy on discharge was ordered as acetylsalicylic acid 1x100 mg, ticagrelor 2x90 mg, and warfarin 5 mg for 6 months. Maintenance antiplatelet therapy was planned as ticagrelor 2x90 mg and warfarin 5 mg after 6 months.

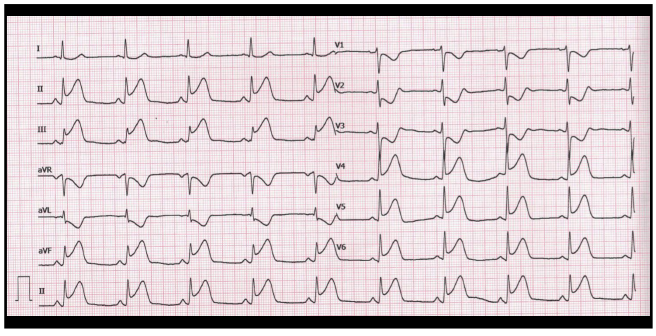


Figure 1. 12-lead electrocardiography of the patient on admission to the emergency room was consistent with an inferior ST-segment elevation myocardial infarction.

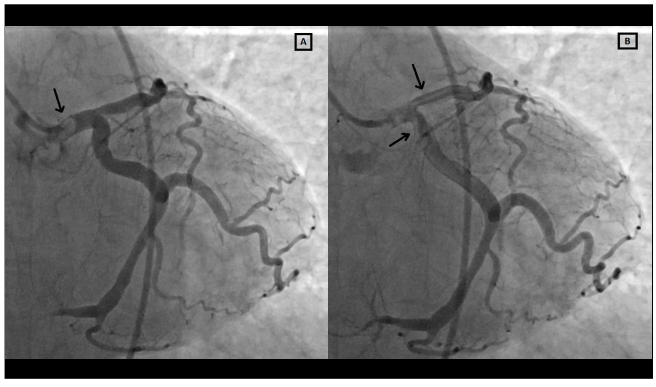
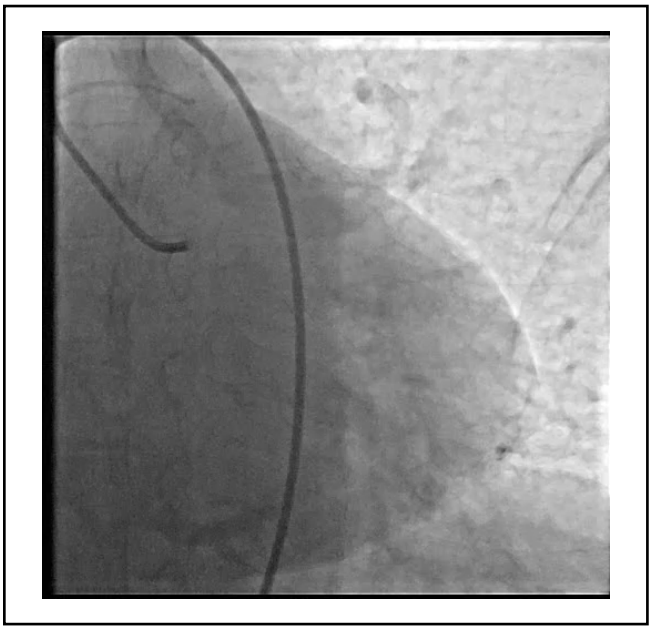
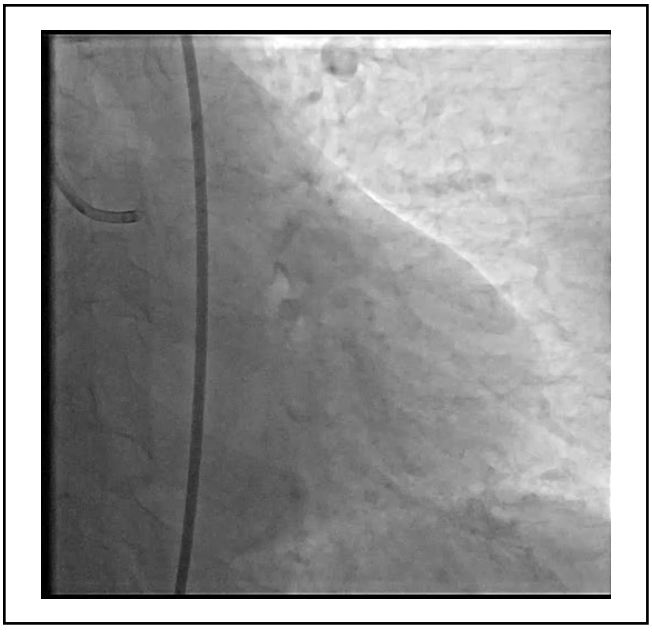


Figure 2A-B. Initial coronary angiography revealed a massive thrombus at the left main coronary artery moving along the left circumflex coronary artery.

Video 1. Initial coronary angiography showed a massive thrombus at the left main coronary artery moving along the left circumflex coronary artery.



Video 2. Control coronary angiography revealed no thrombus at the left main coronary artery.



DISCUSSION

Atherosclerotic plaque rupture is the main pathophysiological mechanism of acute myocardial infarction. Hypertension, diabetes, hyperlipidemia, and smoking are major modifiable risk factors, but rarely the underlying cause may be thrombophilia. Inherited hyper coagulopathies usually lead to the formation of venous thrombi; however, they uncommonly lead to arterial thrombosis such as in coronary arteries [2].

Acute LMCA thrombus is a very dangerous condition due to large myocardial tissue under threat and that requires immediate management and therapy. Emergency primary percutaneous coronary intervention, surgery, or thrombolysis are therapeutic options. Besides maximal antiplatelet and anticoagulant therapy, Gp IIb/IIIa inhibitors or thrombolytic agents can also be used. If the preference will be primary percutaneous coronary intervention, an adequate thrombus removal before stenting is an important factor that predicts procedural success, infarct size, long term clinical outcomes [3]. But the procedure may be complicated by distal embolization of thrombus with infarct extension [4]. In addition, thrombus aspiration can be an option especially if coronary diagnostic angiography reveals a massive thrombus like the patient described herein. However, ischemic cerebral events may occur due to embolization during the aspiration of such a thrombus in the LMCA body. In our case, after an intracoronary tirofiban bolus dose administration during the procedure, infusion of unfractionated heparin and tirofiban was continued for 24 hours. We did not administrate intracoronary thrombolytic because of normal distal coronary flow. Thrombus aspiration may be a treatment option in these patients. But the thrombus aspiration catheter was non-available in our catheter laboratory during the procedure. Furthermore, thrombus aspiration in our case might have an increased risk for cerebral or systemic thrombus embolization because of the osteal location of the thrombus.

In addition to conventional risk factors, patients with acquired or genetic thrombophilia can also present with acute coronary syndrome. It is little known in which patients mutations related to the coagulation pathway should be investigated, particularly in patients presenting with common cardiovascular risk factors and acute coronary thrombus. These mutations should be kept in mind in patients, especially without traditional risk factors or family history that predict premature coronary artery disease. When the diagnosis of thrombophilia is confirmed, adding anticoagulant agents to antiplatelet therapy may be beneficial in preventing recurrent events at long-term follow-up.

CONCLUSION

Besides well-known common cardiovascular risk factors like hypertension, diabetes, and smoking for coronary artery disease and acute coronary syndromes, acquired or genetic thrombophilia should be kept in mind and investigated, particularly in extreme cases like the presented case. The detection of abnormality in the coagulation pathway or process in such cases may change the management of patients in whom the administration of appropriate therapies can prevent further thrombotic events.

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REFERENCES

1. Lee MS, Bokhoor P, Park SJ, Kim YH, Stone GW, Sheiban I, et al (2010) Unprotected left main coronary disease and ST-segment elevation myocardial infarction: a contemporary review and argument for percutaneous coronary intervention. JACC Cardiovasc Interv. 3(8):791-5. https://doi.org/10.1016/j.jcin.2010.06.005
2. Sayin MR, Akpinar I, Karabag T, Aydin M, Dogan SM, Cil C (2012) Left main coronary artery thrombus resulting from combined protein C and S deficiency. Intern Med. 51(21):3041-4. https://doi.org/10.2169/internalmedicine.51.8341
3. Chantadansuwan T, Kehasukcharoen W, Hengrussamee K (2012) Cases report: Experience with rheolytic thrombectomy device (Angiojet) in acute ST elevation myocardial infarction with large amount of coronary thrombus. J Med Assoc Thai. 95 Suppl 8:S83-8.
4. Belli G, Pezzano A, De Biase AM, Bonacina E, Silva P, Salvadè P, et al (2000) Adjunctive thrombus aspiration and mechanical protection from distal embolization in primary percutaneous intervention for acute myocardial infarction. Catheter Cardiovasc Interv. 50(3):362-70. https://doi.org/10.1002/1522-726x(200007)50

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Short Communication

Don't Get Caught in the Wrong Journal Trap: Insights for Young Researchers

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ABSTRACT

This paper focuses on the importance of publishing research in indexed journals and the challenges encountered because of predatory publishers. This emphasizes the significance of qualitative health research and the use of evidence-based research approaches. The process of selecting indexed journals for publication is discussed, highlighting the benefits of credibility and recognition. The prevalence and detrimental consequences of predatory journals have been addressed, emphasizing the need for awareness and caution. The situation of scientific publication around the world is examined, noting the high presence of predatory journals and their impact on researchers' reputation and academic progress. Recommendations are provided to identify and avoid predatory journals as well as the need for increased education and accountability in the research community.

Keywords: Publication, Research, indexed journals, predatory journals, guidelines

INTRODUCTION

Journals are the primary means by which scholars communicate with other research groups within specialized disciplines and the general public [1]. Publications serve as the foundation for evidence-based practice, which aims to provide the most efficient patient care possible while also improving professional knowledge [2]. The concept of qualitative health research is a distinct process that has its origins in qualitative research, emphasizing different techniques and standards. Qualitative health studies aim to define, investigate, and clarify the spectrum of health illnesses and topics unique to healthcare or policy contexts. Specific research methods, such as qualitative analysis, conceptual analysis based on ethnography, and case studies, are employed in empirical health research [3]. The Evidence-Based Research approach is used to establish or plan comprehensive studies, validate research proposals, and serve as a foundation for treatment to enhance clinical outcomes and control costs, and to keep up with emerging technology and information advances. Various projects have been launched to promote and encourage Evidence-Based Research strategies, with many publications now requiring a detailed explanation when discussing the significance of a new study [4]. The EQUATOR Network provides invaluable guidelines for researchers to enhance the quality and transparency of their studies. These guidelines are specifically developed to improve the reporting of different types of research designs, including randomized controlled trials (CONSORT), systematic reviews and meta-analyses (PRISMA), observational studies (STROBE), and qualitative research (COREQ). Researchers who follow these guidelines contribute to a stronger and more reliable body of scientific knowledge.

Ladder to Publication

The manuscript must provide a concise and comprehensive account of the research. Well-reported studies are more valuable because thorough documentation helps editors, the peer-review process, and the audience appreciate the researcher's methods [5]. Citing related scientific papers is the basic tenet of published author research. Fully fledged research must document the techniques used to collect data and include the framework, motive, and justification for data generation and understanding [6]. Data citations are a systematic means of grounding scientific observations in a manuscript on the facts that support research [7]. Peer reviews conducted by experts in the field help improve articles and guide researchers. This serves as a method to screen for scientific evidence [8]. Peer review is an agreement between an author and editor on how a piece of research can be included in the literature [7]. Articles are frequently rejected for a number of reasons. One typical reason is poor research quality, which occurs when a study lacks thorough methodology, unreliable data, or inadequate analysis. Another reason for rejection is improper language usage, which includes

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grammar and writing style. Plagiarism is a serious offense that can result in rapid rejection, whether deliberate or inadvertent. Failure to follow the target journal's particular guidelines, such as formatting requirements or word restrictions, can result in article rejection. To maximize their prospects for successful publication, researchers must address these concerns thoroughly.

Choosing a Proper Indexed Journal for Publication

Choosing an indexed journal to publish a manuscript can be a difficult and perplexing process [1]. Journals indexed in PubMed, Scopus, and Web of Science maintain moral and respectable industry standards, employ peer review and publishing methods, and provide reliable research publications through both paper-version subscription journals and online publications. Thorough peer review procedures from scholars in the community are a staple of trustworthy publishers [9]. Publishing indexed journals lends credibility to research papers. Top medical journals seek articles with a direct impact on healthcare practice, as they can be widely cited, thus increasing the journal's impact and reach. While scientific accuracy is essential, clear and precise writing can also affect acceptance [10]. Publishing in indexed journals has several advantages for researchers, including gaining recognition from renowned scholars, preserving research work in a secure online library, elevating an institution's research standing, and facilitating career growth through research and travel grants.

Predators to Researchers

Scientific publications are still in the developmental phase. Therefore, it is crucial to protect them from predatory journals and publications. Extreme caution should be exercised when choosing journals [11]. Jeffrey Beall, a Scholarly Communications Librarian at the University of Colorado-Denver, is recognized for popularizing the term "predatory open access publishing." With a focus on scholarly open-access publishing, Beall dedicated his efforts to studying and identifying journals and publishers that exhibited potential predatory practices. From 2012 to 2017, he maintained a widely recognized and influential blog called Scholarly Open Access. Through this platform, Beall provided valuable insights, analyses, and critiques of questionable publishing practices. Predatory publishers are fraudulent and deceptive and target researchers, especially those new to academic research. Their primary goal is profit, tricking authors to pay for publication without providing genuine peer review or editorial services and prioritizing benefits over reliable research. Assessing the credibility of unfamiliar journals can be challenging for authors because common citation directories often do not list poor-quality journals, making it difficult for other researchers to find their work [12]. Publishing in fraudulent journals puts valuable studies at the risk of being discarded. Predatory journals pose a global challenge by accepting submissions and publishing without conducting necessary content reviews such as plagiarism checks or ethical assessments. They often publish low-quality papers and have inadequate peer-review processes [13]. Naive and inexperienced researchers are often trapped by the promise of a baffling 'impact factor' and swift approval, disregarding the detrimental consequences of publishing in fraudulent publications [14]. Predatory publications differ ethically, from market-driven approaches to publication costs and time, distorting their identity and services, lacking academic publication community guidelines and best practices, and discrediting authors' scientific work. Regulations and best practices are lacking in predatory publications, including revisions and corrections, procedures for addressing research fraud suspicions, scanning for plagiarism, updating research ethics, removing ghost and guest authors, and declaring financing and conflicts of interest [15]. Promoting genuine scientific research activities is essential for scholars, universities, editors, and publishers. Research studies have had a significant impact on faculty recruitment, progress, and incremental advancement in universities [16]. Publishing research papers leads to beneficial scientific collaborative relationships and recognition for researchers in the health care sector. However, many healthcare sector researchers, students, and professionals are unaware of the legitimate publishing forums. Publishing in fraudulent journals renders their studies useless, and their outcomes are lost to the scientific community [11]. This not only demotivates young researchers, but also denies them proper credit. Fraudulent publications often disappear, resulting in the loss of genuine and valuable papers and unethical misuse of the review process [17].

Situation across the world

The healthcare sector's publications in the world have steadily increased in predatory journals over the last decade. Deceptive metrics such as Scientific Journal Impact Factor, Global Impact Factor, and Universal Impact Factor have influenced esteemed scholars. Healthcare sector researchers should avoid publishing in journals sponsored by these metrics. Researchers are not exempt from the temptation to publish in fraudulent journals. Researchers should exercise self-control and refrain from publishing valuable studies after receiving appealing spam emails from publishing companies. The consequences of publishing in predatory journals include tarnished academic reputation, potential demotion of academic faculty, and the risk of institutions with researchers publishing in predatory journals being blacklisted [18]. Predatory journals publish many articles, contributing to the publication of misleading research results. They often conduct lower-quality randomized clinical trials with faster peer review processes [19]. Authors can employ various techniques to protect their valuable research from being published in predatory journals, such as looking for grammatical mistakes and spelling errors in official emails, ensuring clarity about the peer-review process on journal websites, and clearly stating publication fees. Researchers should check whether the journal is indexed in the sources they utilize, such as MEDLINE for biomedical journals. Email timestamps and phone numbers should align with the country of origin. Publishers' identities can be verified using checklists such as The Directory of Open Access Journals (DOAJ), The Committee on Publication Ethics (COPE), SCImago Journal Rank, National Library of Medicine (NLM) Catalog, and Stop Predatory Journals [12]. The tradition of predatory publications must be addressed, and institutions of higher learning should raise awareness of this issue. It should be included in both undergraduate and graduate courses to increase student awareness. Those intentionally submitting their work to such publications would have consequences [20]. Raising awareness among young and inexperienced researchers about

the potential implications of predatory publishing is crucial [17]. When conducting research and seeking publication, it is crucial for researchers to rely on recognized databases from research institutes and universities such as PubMed, Scopus, and Web of Science. These databases serve as reliable sources of scholarly information and play a vital role in validating the credibility of journals. Researchers should cross-check whether the journal they are considering for publication is included in these databases. Unfortunately, some predatory journals falsely claim to be indexed in these databases on their websites, deceiving unsuspecting researchers. Therefore, it is essential to exercise caution and verify the authenticity of such claims independently.

CONCLUSION

In conclusion, publishing research in indexed journals plays a crucial role in disseminating knowledge and in advancing scientific discourse. The selection of proper journals is essential to ensure the credibility and impact of research findings. However, the presence of predatory journals poses a significant challenge, particularly for young researchers. It is imperative that researchers, universities, editors, and publishers take proactive measures to promote genuine scientific research and protect researchers from predatory practices.

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Purva Gulrandhe: Data curation, Methodology, Manuscript Writing, and Editing

REFERENCES

1- Balch CM, McMasters KM, Klimberg VS, Pawlik TM, Posner MC, Roh M, Tanabe KK, Whippen D, Ikoma N (2018) Steps to Getting Your Manuscript Published in a High-Quality Medical Journal. Ann Surg Oncol. 25(4):850-855. https://doi.org/10.1245/s10434-017-6320-6

2- Bianchini C, Cosentino C, Paci M, Baccini M (2020) Open Access Phys Ther J. Do Predatory Journals Publish Lower-Quality Randomized Controlled Trials? Arch Phys Med Rehabil. 101(6):969-977. https://doi.org/10.1016/j.apmr.2019.12.012

3- Cousijn H, Kenall A, Ganley E, Harrison M, Kernohan D, Lemberger T, Murphy F, Polischuk P, Taylor S, Martone M, Clark T (2018) A data citation roadmap for scientific publishers. Sci Data. 5. https://doi.org/10.1038/sdata.2018.259

4- Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, Lancaster GA (2016) CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ. 355. https://doi.org/10.1136/bmj.i5239

5- Elmore SA, Weston EH (2020) Predatory Journals: What They Are and How to Avoid Them. Toxicol Pathol. 48(4):607-610. https://doi.org/10.1177/0192623320920209

6- Ferris LE, Winker MA (2017) Ethical issues in publishing in predatory journals. Biochem Med (Zagreb). 27(2):279-284. https://doi.org/10.11613/BM.2017.030

7- Grudniewicz A, Moher D, Cobey KD, Bryson GL, Cukier S, Allen K, Ardern C, Balcom L, Barros T, Berger M, Ciro JB, Cugusi L, Donaldson MR, Egger M, Graham ID, Hodgkinson M, Khan KM, Mabizela M, Manca A, Lalu MM (2019) Predatory journals: No definition, no defence. Nature. 576(7786):Article 7786. https://doi.org/10.1038/d41586-019-03759-y

8- Kreiman J (2016) On Peer Review. J Speech Lang Hear Res. 59(3):480-483. https://doi.org/10.1044/2016_JSLHR-S-16-0043

9- Lemberger T (2018) Data citation: What, when, why? Mol Syst Biol. 14(12). https://doi.org/10.15252/msb.20188783

10- Luciani M, Jack SM, Campbell K, Orr E, Durepos P, Li L, Strachan P, Di Mauro S (2019) An Introduction to Qualitative Health Research. Prof Inferm. 72(1):60-68. PMID: 31162045

11- Masten Y, Ashcraft A (2017) Due diligence in the open-access explosion era: Choosing a reputable journal for publication. FEMS Microbiol Lett. 364(21). https://doi.org/10.1093/femsle/fnx206

12- Naqvi WM, Goyal CV, Sahu A (2020) The Art and the Science of Manuscript Publication: Tips and Tricks for Health Science Students and Professionals. Indian J Forensic Med Toxicol. 14(4):4331-4339. https://doi.org/10.37506/ijfmt.v14i4.12320

13- Nicholas D (2019) How to choose a journal and write a cover letter. Saudi J Anaesth. 13(Suppl 1):S35-S41. https://doi.org/10.4103/sja.SJA_691_18

14- Patwardhan B (2017) Indian Science and Predatory Journals. J Ayurveda Integr Med. 8(1):1-2. https://doi.org/10.1016/j.jaim.2017.02.004

15- Robinson KA, Brunnhuber K, Ciliska D, Juhl CB, Christensen R, Lund H (2021) Evidence-Based Research Series-Paper 1: What Evidence-Based Research is and why is it important? J Clin Epidemiol. 129:151-157. https://doi.org/10.1016/j.jclinepi.2020.07.020

16- Samuel AJ (2021) An Indian physiotherapist's suggestions to keep out of fake journals. Physiother J Indian Assoc Physiother. 12(1):43-45. https://doi.org/10.4103/PJIAP.PJIAP_32_17

17- Samuel AJ (2018) The need for Indian physiotherapy research publications: Understanding journalology and predatory journals. AMHS. 6(1):189-191. https://doi.org/10.4103/amhs.amhs_110_17

18- Samuel AJ, Aranha VP (2018) Valuable Research in Fake Journals and Self-boasting with Fake Metrics. J Pediatr Neurosci. 13(4):517-518. https://doi.org/10.4103/JPN.JPN_66_18

19- Sharma H, Verma S (2018) Predatory journals: The rise of worthless biomedical science. J Postgrad Med. 64(4):226-231. https://doi.org/10.4103/jpgm.JPGM_347_18

20- Zakout YM-A (2020) Predatory Publishers/Journals in Medical Sciences: How to Avoid, Stop, and What to Do after Being Scammed by Them? J Gastrointest Cancer. 51(3):782-787. https://doi.org/10.1007/s12029-020-00418-8

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Letter to Editor

An Unusual Association of Coronary Cameral Fistula and Mid-Cavitary Hypertrophic Cardiomyopathy

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ABSTRACT

The presence of both myocardial hypertrophy and coronary-to-cameral fistula has been reported previously. However, the exact mechanisms are not clear. Herein, we reported a patient with mid-cavitary hypertrophic cardiomyopathy and concomitant connections between coronary arteries and left ventricular cavity.

Keywords: Hypertrophic cardiomyopathy, Coronary fistulae

To the Editor,

A 67-year-old woman with a history of hypertension and hyperlipidemia was admitted to the emergency room with anginal chest pain lasting more than 30 minutes. The physical examination was normal, and the electrocardiogram showed sinus rhythm (72 bpm) and changes compatible with left ventricular (LV) hypertrophy (Figure 1A). Transthoracic echocardiography demonstrated normal systolic functions of the LV with mid-cavitary hypertrophy (max. LV wall thickness of 16 mm) consistent with hypertrophic cardiomyopathy (HCM), with no LV outflow tract gradient and no systolic anterior motion of the mitral valve leaflet. Imaging with color flow doppler demonstrated blood flow from the epicardial surface into the LV cavity through the apical segments of the myocardium during diastole (Figure 1B, Video 1). The two-dimensional (2D) speckle-tracking echocardiography showed a relatively reduced longitudinal systolic function at the LV apex (-14.2%) (Figure 1C). Cardiac biomarker levels were within normal reference limits. During coronary angiography, there was no obstructive atherosclerotic lesion in the epicardial coronary arteries, and several connections were present in between the epicardial coronary arteries and left ventricular chamber (Figures 1D and 1E, Video 2). Beta-blocker therapy was started as anti-ischemic therapy, and the patient was discharged uneventfully. HCM Risk-SCD revealed a low sudden cardiac death risk. The patient was asymptomatic at the 6-month follow-up visit. The association of HCM with coronary cameral fistula was only reported in 39 patients untill now. This rare finding implies that genetic changes in HCM may interfere with the abnormal embryological dedifferentiation of those microvessels draining into the LV [1-3]. This letter to the editor also highlights a rare association between mid-cavitary HCM with coronary cameral fistula.

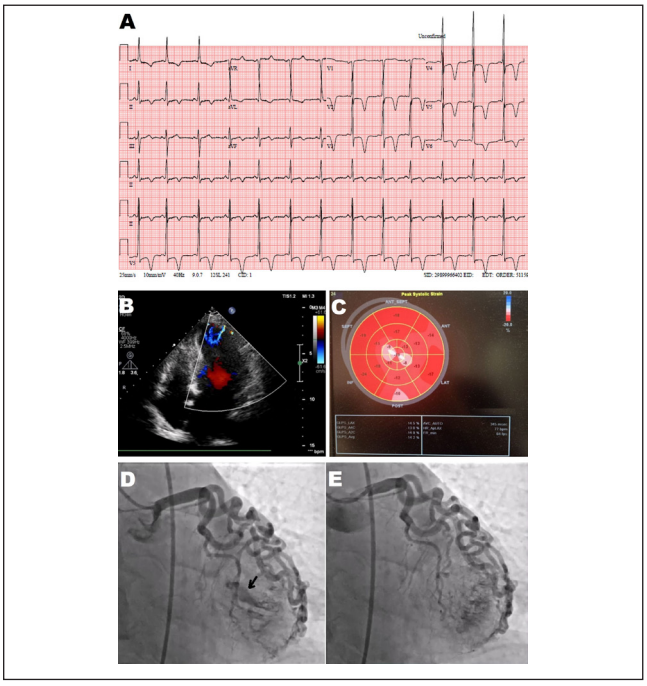

Figure 1. Electrocardiography showing sinus rhythm with voltage criteria and T wave inversion at V2-6, DI-aVL, DII-III-aVF compatible with left ventricular hypertrophy (A). Transthoracic echocardiography demonstrating trans-myocardial color flow from the epicardial surface to the endocardial border of apical LV segments (B) and 2D-speckle tracking echocardiography showed a reduced global longitudinal strain at the LV apex (C). Coronary angiography revealed no atherosclerotic lesion and multiple direct communications between the LV cavity and the epicardial coronary arteries (E).

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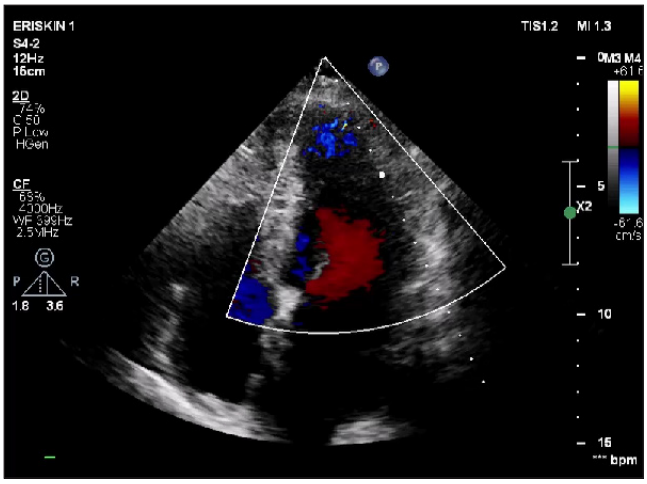
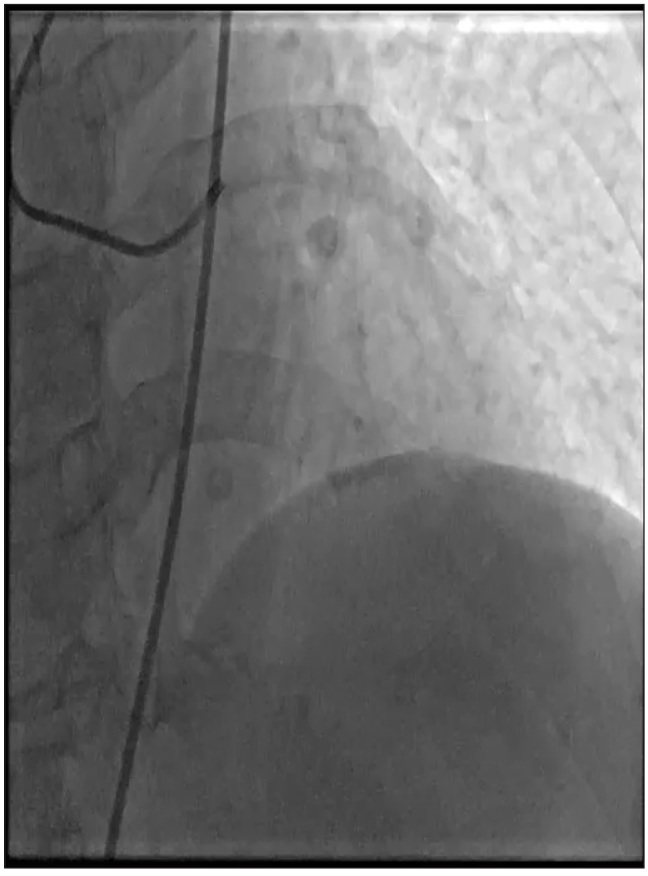


Supplementary Video 1. Echocardiography showing mid-cavitary hypertrophy and color flow Doppler demonstrating blood flow from the subepicardial to the subendocardial area of the apical segments of the myocardium.



Supplementary Video 2. Coronary angiography showing several connections in between the epicardial coronary arteries and left ventricular chamber.

REFERENCES

1. Liu Y, Wang Z, Zeng H, Yang S, Li X (2022) Congenital coronary artery-left ventricular multiple micro-fistulas and hypertrophic cardiomyopathy: a case report and literature review. BMC Cardiovasc Disord. 22(1):483. https://doi.org/10.1186/s12872-022-02926-w

2. Wattal S, Kareem H, Devasia T, Paramasivam G (2018) Coronary artery fistula and mid-cavitary obstructive hypertrophic cardiomyopathy: a rare association. BMJ Case Rep. 2018:bcr2017223174. https://doi.org/10.1136/bcr-2017-223174

3. Padfield GJ (2009) A case of coronary cameral fistula. Eur J Echocardiogr. 10(5):718-20. https://doi.org/10.1093/ejechocard/jep049