ISSN 2564-7784
EISSN 2564-7040

Indexed in Web of Science

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Formerly Gaziantep Medical Journal

VOLUME 30 ISSUE 2 APRIL 2024

eurjther.com

ISSN 2564-7784
EISSN 2564-7040

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Formerly Gaziantep Medical Journal

VOLUME 30 ISSUE 2 APRIL 2024

eurjther.com

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

About the Journal

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.

The European Journal of Therapeutics will be published bimonthly, commencing in 2024 (six issues a year in February, April, June, August, October and December).

European Journal of Therapeutics aims to contribute to the international literature by publishing Original Articles, Reviews, Case Reports, Special Editorial, Short Communication, Technical Notes, Letters to the Editor, Reply by Authors, Image, Withdrawn, Erratum, Retraction Notice, Editorial (EIC use only), In memory of (Invited by EIC only) and Book Review (Invited by EIC only) in the fields of medical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.

European Journal of Therapeutics is indexed in Web of Science-Emerging Sources Citation Index, Journal Citation Reports, Master Journal List, TUBITAK ULAKBIM TR-DİZİN, ERIH PLUS, EBSCO, GALE, Scilit, Researcher.Life, NLM Library Catalog, Asian Science Citation Index (ASCI), ResearchGate, Google Scholar, ABCD Index, Crossref, The Open Ukrainian Citation Index (OUCI), idealonline, TürkMedline, Sobiad, Türkiye Atıf Dizini, Index Copernicus (ICI Journals Master List).

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), National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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.

European Journal of Therapeutics (Eur J Ther) is publication organ of the Gaziantep University School of Medicine. All expenses of the journal are covered by the Gaziantep University School of Medicine. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Gaziantep University School of Medicine, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

Editor in Chief: Prof. Ayşe Balat
Address: Gaziantep Üniversitesi Tıp Fakültesi, 27310 Şehitkamil, Gaziantep, Türkiye
Phone: +90 342 360 60 60
Fax: +90 342 360 16 17
E-mail: info@eurjther.com

Publishing Service: Pera Publishing Services
Address: Ataköy 3-4-11 Kısım Mah. Dr Remzi Kazancıgil Cd. O-114 N:12 D:7 Bakırköy İstanbul, Türkiye
E-mail: info@perayayincilik.com
Web page: perayayincilik.com

Printing–Binding
Pınarbaş Matbaacılık Ltd. Şti.
Tel: 0212 544 58 77

OPEN ACCESS

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Instructions to Authors

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 and its publication language is 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 Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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.

Manuscripts submitted to European Journal of Therapeutics will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

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.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

The similarity rate limit determined for our journal is 24%.

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors **(ICMJE - www.icmje.org).** The ICMJE recommends that authorship be based on the following 4 criteria:

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.

European Journal of Therapeutics requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests,

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

European Journal of Therapeutics requires each submission to be accompanied by a Copyright Agreement and Acknowledgement of Authorship Form (available for download at www. eurjther.com). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s). By signing this form, authors agree that the article, if accepted for publication by the European Journal of Therapeutics, will be licensed under a Creative Commons Attribution-Non Commercial 4.0 International License (CC-BY-NC).

Statements or opinions expressed in the manuscripts published in European Journal of Medical Sciences reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

Manuscript Types

Authors should determine the type of paper before submitting it and indicate the type of paper on the title page. This is because, depending on the type of paper, the rules to be followed, including formatting and word limits, change.The categorization system is at the discretion of the Editor-in-Chief. Authors may be asked to change the article type at the request of the editor at any stage of submission, including after acceptance.
The following types of papers will be considered for publication.

Original Articles: This is the most important type of article since it provides new information based on original research.
Abstracts should not exceed 500 words and should be structured with the following subheadings: Objective, Methods, Results, and Conclusion.
The main text should be structured with the following subheadings: Introduction, Material and Methods, Results, Discussion, Limitations, Conclusions, Acknowledgments, References, Main Points, and Figure Legends.
The main text should not exceed 3000 words, excluding the abstract, references, tables, and figure legends.
There should be a maximum of 50 references.
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).
Please check Table 1 for the limitations for Original Articles.

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.

Case Report: In the European Journal of Therapeutics, very interesting or rare cases can be published as Case Reports. However, due to the limited number of publications determined for this category, it is recommended that you submit such articles as Letter to the Editor. For the instructions for Letter to the Editor, please see below.

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.

Letter to the Editor: The European Journal of Therapeutics encourages authors to write letters to the editor on all topics covered by the journal. There is no abstract requirement for this type of manuscript. If authors prefer to include an abstract in the letter, they may include a short unstructured abstract of no more than 200 words.
It is recommended that a letter contains up to 10 references.
The letter recommends adding "Dear Editor" at the beginning of the main text and "Yours sincerely" at the end.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3000	500 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	200	20	5	1 or total of 5 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

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.

Authors are required to submit the following:
- Copyright Agreement and Acknowledgement of Authorship Form
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors during the initial submission)

These forms are available for download at https://eurjther.com/index.php/home/forms.

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

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

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.

Authors are responsible for the accuracy of references.

References

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

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/.....").

Use abbreviations for journal names. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed.

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

Example for Journal Article without English Titles
Aktan-İkiz A, Üçerler H, Orhan M (2007) Anatomic features of fossa navicularis at the skull base and its clinical importance [Kafa iskeletinde fossa navicularis'in anatomik özellikleri ve klinik önemi]. Sendrom 19:34–36 ([In Turkish])

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

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

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

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].

Author-Suggested Reviewers

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.

Corrections, Retractions, and Republications

European Journal of Therapeutics follows and implements the International Committee of Medical Journal Editors (ICMJE) recommendations on Corrections, Retractions, Republications and Version Control.

Corrections, Retractions, Republications and Version Control*

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

If a correction is needed, journals should follow these minimum standards:

- The journal should publish a correction notice as soon as possible detailing changes from and citing the original publication; the correction should be on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing.
- The journal also should post a new article version with details of the changes from the original version and the date(s) on which the changes were made.
- The journal should archive all prior versions of the article. This archive can be either directly accessible to readers or can be made available to the reader on request.
- Previous electronic versions should prominently note that there are more recent versions of the article.
- The citation should be to the most recent version.

Pervasive errors can result from a coding problem or a miscalculation and may result in extensive inaccuracies throughout an article. If such errors do not change the direction or significance of the results, interpretations, and conclusions of the article, a correction should be published that follows the minimum standards noted above.

Errors serious enough to invalidate a paper's results and conclusions may require retraction. However, retraction with republication (also referred to as "replacement") can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then retraction with republication of the changed paper, with an explanation, allows full correction of the scientific literature. In such cases, it is helpful to show the extent of the changes in supplementary material or in an appendix, for complete transparency.

* Corrections, Retractions, Republications and Version Control https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html Date of Access: 05.10.2023

Editor in Chief: Prof. Ayşe Balat
Address: Gaziantep Üniversitesi Tıp Fakültesi, 27310 Şehitkamil, Gaziantep, Türkiye
E-mail: info@eurjther.com

Publishing Service: Pera Publishing Services
Address: Ataköy 3-4-11 Kısım Mah. Dr Remzi Kazancıgil Cd. O-114 N:12 D:7 Bakırköy İstanbul, Türkiye
E-mail: info@perayayincilik.com
Web page: perayayincilik.com

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Contents

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Contents

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):e8-e9.
https://doi.org/10.58600/eurjther2073

Editorial

Welcome to the April 2024 Issue (Vol: 30, No: 2) and Current News of the European Journal of Therapeutics

Ayşe Balat [1, 2], Şevki Hakan Eren [3], Mehmet Sait Menzilcioğlu [4], İlhan Bahşi [5], İlkay Doğan [6], Davut Sinan Kaplan [7], Mehmet Karadağ [8], Ayşe Aysima Özçelik [9], Fatih Sarı [10], Hamit Yıldız [11], Murat Akbaba [12], İlyas Başkonuş [13]

[1] *Department of Pediatric Nephrology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[2] *Department of Pediatric Rheumatology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[3] *Department of Emergency Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[4] *Department of Radiology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[5] *Department of Anatomy, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[6] *Department of Biostatistics, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[7] *Department of Physiology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[8] *Department of Child and Adolescent Psychiatry, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[9] *Department of Pediatric Neurology, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[10] *Department of Prosthodontics, Faculty of Dentistry, Gaziantep University, Gaziantep, Türkiye*
[11] *Department of Internal Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[12] *Department of Forensic Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*
[13] *Department of General Surgery, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye*

Published Online: 2024-04-30

Corresponding Author
Ayşe Balat
Address: Department of Pediatric Nephrology and Rheumatology, Gaziantep University School of Medicine, Gaziantep, Türkiye
E-mail: aysebalat@hotmail.com

Dear Colleagues,

We have started to reap the rewards of the improvements we have realized within about a year of being appointed to the editorial team. We are happy to see that the number of articles submitted to the *Eur J Ther* is increasing day by day. Moreover, this situation allows us to be even more selective in article acceptance.

Due to many improvements and updates, we can now publish many articles in early view. Moreover, the early view articles of the *Eur J Ther* are now indexed as “Early Access” by Web of Science without being assigned to the issue [1].

On the occasion of this editorial, we would like to thank once again all the authors, reviewers, editors, and technical team who contributed to the *Eur J Ther*. We encourage you to submit your valuable work to the Eur J Ther.

We hope to continue to bring you good news on future issues.

Sincerely yours,

REFERENCES

[1] Web of Science Advanced Search. https://www.webofscience.com/wos/alldb/summary/46c0e10a-c128-4076-9dca-f739904863ee-b171868a/date-descending/1 Accessed Date: 29 February 2024

How to Cite;

Balat A, Eren ŞH, Menzilcioğlu MS, Bahşi İ, Doğan İ, Kaplan DS, Karadağ M, Özçelik AA, Sarı F, Yıldız H, Akbaba M, Başkonuş I (2024) Welcome to the April 2024 Issue (Vol: 30, No: 2) and Current News of the European Journal of Therapeutics. Eur J Ther. 30(2):e8-e9. https://doi.org/10.58600/eurjther2073

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):e10-e12.
https://doi.org/10.58600/eurjther2135

Special Editorial

March 14 Medicine Day

Alphan Cura

Retired Professor, Department of Pediatric Nephrology, Faculty of Medicine, Ege University, Bornova, Izmir, Türkiye

Received: 2024-04-08 **Accepted**: 2024-04-29 **Published Online**: 2024-04-30

Corresponding Author
Alphan Cura, MD
Address: Department of Pediatric Nephrology, Faculty of Medicine, Ege University, Bornova, Izmir, Türkiye.
E-mail: alphan.cura@gmail.com

Throughout history, people have assigned special meanings to some days of the year and commemorated that day or days every year in line with their ascribed meaning. Some of these are universal, such as the first day of the New Year or the beginning of spring. Those for commercial purposes, such as Mother's, Father's, and Valentine's Days, have also spread to large audiences. However, the most common are the special days of the faiths. There are also special days celebrated on different dates in different societies, which are similar in meaning and content, on which that group of people have achieved success, profit and superiority.

A few special days are specific to professions, such as Medicine Day. Most of them are ignored even among colleagues within that profession. Because of the strong influence of the medical profession on society, Medicine Day is celebrated in many countries on different days (July 1 in India, August 23 in Iran, December 3 in Cuba, etc.). Special days that drift on the flowing river of time have changed, except those which belong to the world of faith. For example, while Turkish society initially experienced November 10 (the passing away day of Mustafa Kemal Atatürk) as a day of great pain and mourning, it now commemorates it as a day of gratitude, respect and hope for a bright future.

Medical education in the Ottoman Empire began for the first time on March 14, 1827, during the reign of Sultan II. Mahmud. March 14 is also the name of the resistance against foreign occupation forces in 1919, during an unfortunate period when the Ottoman Empire was in its last days and the homeland was occupied. This day is considered a special day for those working in the medical field. The starting point of March 14, Medicine Day, is attributed to the Medical School student Hikmet Boran. However, just ten years ago, the number of people who knew the name of Hikmet Boran among medical students was very small. What is the history of this name? Why has the name Hikmet Boran come to the fore today? While examining the concept of March 14, perhaps we can reach the real definition of March 14 and understand whether it is a feast.

During the reign of reformist Sultan II. Mahmut (1808 – 1839), the structure of the army and the military education began to be reorganized. The opportunity to learn foreign languages arose in military schools, and while the eastern languages such as Arabic and Persian declined, French and German came to the fore. When military school students began to read magazines and publications in foreign languages, they started to develop the concept of social class,

followed by their search for national identity. The discussions on freedom, independence and democratic government that began in military schools shook the monarchy order and brought constitutional government to the country's agenda. In this context, the military Medical School, which had its share on reform movements and was called "Mektep-i Tıbbiye-i Şahane-i Hümayun" since 1839, played a leading role. In 1867, a civilian Medical School, "Mektep-i Tıbbiye-i Mülkiye", was established in a room of the military Medical School, and 1908, military and civilian Medical Schools were combined under the name "Darulfünun Faculty of Medicine".

Military Medical School students would live barracks life and receive medical education with the order and discipline of a boarding school. The students' uniforms were elegant and worthy of a Sultan. Friday was a holiday. Students would leave school wearing clothes equipped with gold cords, epaulettes, silver rapiers, patent leather boots and silver spurs. When the Sultans went to the Friday greetings, the people gathered there traditionally shouted, "Don't be arrogant, my Sultan; there is a God greater than you!" Upon exit, all university students lined up according to their faculty. Similarly, as the royal carriage was passing in front of them, they shouted, "Long live my Sultan" upon the signal given. Every new Medical School student had been informed by an older one in the upper class on the first Friday morning that the "Medical School students do not shout at the Friday greetings". This action, carried out with the discourse of a superior, is important in understanding the differences of military students. After the daily education, in the evening meetings, an expert assistant or sometimes a successful senior elder brother, called a "repetitor (re-teller)," would briefly re-explain the lessons taught that day to the cadets and clarifies unclear issues. Repetitors would also convey information about the country's situation and military, political and economic problems to military students who was lack communication opportunities those days. Students were encouraged to ask questions, propose and discuss their own solutions. With this ideological background, some Medical School students participated in the Balkan wars (October 8, 1912 - August 10, 1913) as bouncers. The İttihat ve Terakki Fırkası, which came to power under Ottoman rule, established Teşkilatı Mahsusa units, which would operate secretly under state control. Medical School students interrupted their education and volunteered in this organization, and some were dispersed to regular army units. The Medical School did not have any graduates in 1915. In 1917, only 17 students graduated from the school as Medical Captains.

It is understandable that the students of an institution whose culture is engraved with the ideals and love of homeland and nation, independence and freedom, join the lines of fire as volunteers when the homeland is in danger. These students discussed the issue of identity and chose their sides at a very young age. The ideas of autonomy, freedom and independence of military Medical School students have been transmitted, inherited and protected as a genetic code for years.

The British partially occupied Istanbul on 13 November 1918 and fully occupied on 16 March 1920. The Medical School in Haydarpaşa is a majestic building overlooking the Marmara Sea. When the occupying forces wanted to evacuate the building and use it for their purposes, they encountered unexpected resistance from the medical faculty, experts, assistants and students. The resistance bore fruit, with the intervention of the Ottoman administrators, a border separation was created in the school with a wooden curtain, and British forces settled on one side of the school. On the other side, students resisted, sometimes enduring harsh conditions, but decidedly did not leave the building.

The Medical School supported the Anatolian movement, which started in May 1919, with all its might and stood behind Mustafa Kemal Pasha. Ahmet Nuri (Bursa), a senior student (congress member), and Hikmet (Boran), a third-year student, were selected to attend the Sivas congress held in September. Ahmet Nuri (Bursa), who spoke before the vote in an environment where the idea of a mandate was dominant, changed the atmosphere of the Congress with his high oratory power and faithful nationalist words. When the session was recessed, opponents of the mandate, including Mustafa Kemal, met together, and Hikmet spoke. In line with the education he received and the awareness he gained, Hikmet uttered those words by saying, "On behalf of the Medical Schools that I represent". That young man says, "We cannot accept the mandate regime. Either Independence or Death". Hikmet, an enterprising student, became the symbol of resistance as he hung the Turkish Flag on the school's towers among all the Medical School students who resisted the British forces trying to occupy the school on March 14, 1919. After this resistance and action, the date of March 14 came to the country's agenda once again with the spirit and mentality represented by the Medical School. Medical students are the pioneers of the rebellion of the people accustomed to freedom. Therefore, we

must remember our debt of gratitude to them. We have Medical School elders who have created a Medical School tradition that integrates with March 14, who prioritize the homeland above all else, who do not evade responsibility even in the most challenging conditions, who are sent to duty for the homeland both themselves and their children just like Ahmets and Hikmets, and stand behind them like the mountains.

We wish "gratitude and respect to our teachers" in the medical oath. It is very appropriate. We, and those who will join the profession afterwards, should remember our teachers who have grown Hüseyin Hulkis, Ahmet Nuris, and Hikmet Borans, who created the concept of March 14 with all their sacrifices, even with their lives. We should remember our martyrs with God's mercy and grace.

Is March 14 a feast?

Dear colleagues, March 14 has changed depending on the year. Sometimes, it was a feast, balls were held, and sports festivals were celebrated. Sometimes, there was disappointment and pain. Halls were raided asking, "Can we celebrate March 14 under these conditions?" and sometimes, anthems were sung, and oaths of freedom and independence were sworn. However, each passing year, March 14 as a concept has risen and become a monument. March 14 is the epic of the efforts and sacrifices Medical School students gave to our country at the expense of their lives on the path to freedom and independence. It is sacred. It should be celebrated in any way, according to the conditions of the time and in line with the concept it contains.

Sincerely yours,

Professor Alphan Cura, MD
Retired Professor, Department of Pediatric Nephrology, Faculty of Medicine, Ege University, Bornova, Izmir, Türkiye

How to Cite;

Cura A (2024) March 14 Medicine Day. Eur J Ther. 30(2):e10-e12. https://doi.org/10.58600/eurjther2135

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):e13-e18.
https://doi.org/10.58600/eurjther2134

Special Editorial

Biostatistics Leader in Türkiye from the Eyes of His Students: Prof. Kadir Sümbüloğlu

Seval Kul [1], İlkay Doğan [1], Ayşe Balat [2], Bektaş Açıkgöz [3], Zeliha Nazan Alparslan [4], Alper Serçelik [5], Mustafa Berhuni [6]

[1] Department of Biostatistics, Gaziantep University School of Medicine, Gaziantep, Türkiye
[2] Department of Pediatric Nephrology and Rheumatology, Gaziantep University School of Medicine, Gaziantep, Türkiye
[3] Retired Professor, Brain and Nerve Surgery, Antalya, Türkiye
[4] Retired Professor, Department of Biostatistics, Çukurova University School of Medicine, Adana, Türkiye
[5] Department of Cardiology, SANKO University School of Medicine, Gaziantep, Türkiye
[6] Department of Ophthalmology, Erciyes University, School of Medicine, Kayseri, Türkiye

Received: 2024-04-08 **Accepted**: 2024-04-28 **Published Online**: 2024-04-30

Corresponding Author
İlkay Doğan, PhD
Address: Department of Biostatistics, Gaziantep University School of Medicine, 27310, Gaziantep, Türkiye.
E-mail: ilkay_dgn58@hotmail.com

In the scientific community, there has always been a need for leaders who will benefit and guide everyone. Thanks to these leaders, future generations will undoubtedly be able to reach their goals more easily [1].

In this special editorial, we aimed to tell about a master and leader, Dr Kadir Sümbüloğlu, who was the pioneer of biostatistics in Türkiye and who guided us, his students, opened our horizons and made important contributions to our academic life to get to this point and to express our gratitude to our teacher.

Regards,

Seval Kul, PhD
İlkay Doğan, PhD
Ayşe Balat, MD
Bektaş Açikgöz, MD
Zeliha Nazan Alparslan, PhD
Alper Serçelik, MD
Mustafa Berhuni, MD

From Prof. Seval Kul

The Leader of the Biostatistics Community in Türkiye, Prof. Kadir Sümbüloğlu (PhD)

The academic and scientific legacy of Prof. Kadir Sümbüloğlu stands as a cornerstone in Türkiye's medical education and research landscape. His influence has been felt broadly, from his students to his colleagues. Kadir Sümbüloğlu's pioneering role in the field of biostatistics paved the way for a profound transformation at Hacettepe University and medical education institutions throughout Türkiye.

Kadir Sümbüloğlu's life symbolizes the beginning of an era that revolutionized medical education and scientific research. His education in community health at the Gevher Nesibe Health Education Institute directed him towards becoming a trailblazer in the fields of medical statistics and biostatistics. His academic journey at Hacettepe University under the guidance of Nusret Fişek led to the official establishment and development of biostatistics in Türkiye.

Throughout his teaching career, Kadir Sümbüloğlu's dedication to his students and colleagues solidified his role as a pioneer in advancing science and academic development. Under his leadership, the importance of research and educational programs in biostatistics at Hacettepe University Faculty of Medicine grew significantly. His wisdom, courtesy, and exemplary character among his students made him not just a teacher but also a mentor and guide.

In this editorial, I will delve into a comprehensive analysis of Kadir Sümbüloğlu's academic achievements and personal attributes, accompanied by heartfelt expressions from his students. Many academics and researchers he has influenced will share their experiences, emphasizing the significant impact of Kadir Sümbüloğlu as a prominent figure in their careers and personal development as well as mine.

After sharing his CV, I leave you alone with these valuable writings.

Regards,

Prof. Seval KUL, PhD
Gaziantep University, Medical Faculty, Head of Department of Biostatistics, Gaziantep, Türkiye

Prof. Kadir Sümbüloğlu's Curriculum Vitae

Prof. Kadir Sümbüloğlu (Fig. 1) was born in Sivas, Zara, on June 1, 1936. He completed his primary and secondary education in Sivas. In 1968, he graduated from Gevher Nesibe Health Education Institute with a degree in Public Health. In the same year, he was appointed as an assistant in the Department of Community Medicine under Prof. Nusret Fişek's supervision at Hacettepe University Faculty of Medicine. Prof. Fişek expressed his intention to train him as a medical statistics professor.

Fig. 1. Prof. Kadir Sümbüloğlu

He obtained his PhD in Medical Statistics and Medical Documentation from Hacettepe University Faculty of Health Sciences in 1972. He was appointed as the coordinator of this program in the same year and continued his duties as a lecturer in the Department of Community Medicine. These two roles are the official starting point of Biostatistics in Türkiye. During those years, "medical statistics" was recognized as a department by the Interuniversity Board for Associate Professorship, and its name was changed to "Biostatistics" in 1975.

After becoming an Associate Professor of Biostatistics in 1977, he initiated efforts to establish Biostatistics as an interdisciplinary field in medical faculties, with Hacettepe University taking the lead. After the establishment of the Higher Education Council (Yükseköğretim Kurulu-YÖK) in 1981, he ensured the establishment of the Biostatistics Department within the Department of Medical Biology at Hacettepe University Faculty of Medicine in 1982. He was granted the title of Professor of Biostatistics in 1988. Since 1993, the Biostatistics departments have been affiliated with the Department of Basic Medical Sciences.

In 1997, Prof. Kadir Sümbüloğlu founded the Biostatistics Association with seven founding members to promote the development of biostatistics, elevate the academic careers of healthcare personnel, and protect the rights of its members. He served as the president of the association until 2014 and is currently its Honorary President. Throughout his academic career, he supervised the theses of 13 master's and 12 doctoral students and made significant contributions to the training of numerous faculty members in Biostatistics.

Prof. Kadir Sümbüloğlu has authored 26 national books and eight international book chapters in the field of biostatistics. One of his internationally authored chapters is in the book titled "Formation Patterns and Health" by the World Health Organization (WHO). He was thanked in the preface of the book for his valuable contributions as an author to WHO's book titled "Teaching Health Statistics Lesson and Seminar Outlines Second Edition". He has published 17 national and international articles in addition to providing biostatistics and research consultancy for numerous scientific studies. He has been the principal investigator in four national and two international scientific projects. He received a one-year international scholarship from WHO and a five-month international scholarship from Fulbright.

He served on the Sub-Committee for Health Information Systems of the 7th and 8th Development Plans, provided statistical consultancy in the Türkiye Clinics Medical Sciences Competitions from 1986 to 1993, and offered consultancy services in various capacities for institutions such as the Ministry of Health, State Planning Organization (Devlet Planlama Teşkilatı: DPT), State Institute of Statistics (Devlet İstatistik Enstitüsü: DİE), and WHO. He has also participated in two different book projects with WHO.

Prof. Kadir Sümbüloğlu retired in 2003 but continues to attend biostatistics conferences, where he meets with all the academicians he has contributed to and continues to share his knowledge and experiences.

From Prof. Ayşe Balat;

Dear Prof. Kadir Sümbüloğlu

It was my first year at Hacettepe University, Faculty of Medicine. While we focused on health-related courses and tried to understand people with all our strengths, we met a teacher in biostatistics explaining the importance of numbers. He said, "You will have a lot of data throughout your lives, but what is important is how you make sense of this data". He defined biostatistics and emphasized the importance of collecting data accurately and transforming it into information while providing healthcare services and/or working as a researcher. He explained many comparison methods and comments on numbers and pointed out that some things we think are important may only work if they are statistically significant.

He made a classic exam that we all fear but stated that we could use the book. We were all surprised. Later, he congratulated me as a student with 100 points on this exam. I said, "Sir, the book was already open, and I did it easily". He gave another lesson: "The important thing is not to memorize statistical methods, but to know which method to use and where."

This professor is the esteemed Prof. Kadir Sümbüloğlu, the Founding Head of the Biostatistics Department at Hacettepe University between 1982 and 1987. I always remember with respect our valuable teacher, who first taught us statistical literacy and made us like biostatistics. I am proud to be one of the thousands of students he trained.

Regards,

Prof. Ayşe Balat, MD
Gaziantep University, Medical Faculty, Department of Pediatric Nephrology & Rheumatology, Gaziantep, Türkiye

From Prof. Bektaş Açıkgöz;

Dear Prof. Kadir Sümbüloğlu

Taking into consideration the scientific discussions within the European Association of Neurological Surgeons and the European Academy of Neurosurgery, the Department of Neurosurgery at Hacettepe University offered a PhD program within the Hacettepe University Institute of Neurological Sciences to ensure that Neurosurgeons are trained as academicians in the post-residency period.

I began this program as a PhD student in February 1988, and the first course I enrolled in at the institute was the biostatistics course, where I had the opportunity to get to know Prof. Kadir Sümbüloğlu. In his classes, he taught us the methods of questioning as a scientist, searching for answers to questions, evaluating findings based on previous experiences, and drawing conclusions from these findings.

Throughout the PhD program and beyond, I personally observed the contributions of Prof. Kadir Sümbüloğlu in our participation in national and international scientific meetings, our research activities, and publications, and how his efforts enriched us and paved the way forward.

During my tenure as Dean of the Faculty of Medicine at Zonguldak Karaelmas University and later as Rector, our

faculty members expressed their desire to receive biostatistics training. We immediately contacted our mentor. They and their team came to Zonguldak and devoted days and labor to training our faculty members. With our insistence, they left Prof. Vildan Sümbüloğlu (his wife and biostatistician) at our university.

Prof. Vildan Sümbüloğlu established the biostatistics PhD program, trained many valuable faculty members, and worked tirelessly for the institutionalization of science at the university. At this stage, my wife and I consider ourselves very fortunate to have gained the friendship of Prof. Kadir and Prof. Vildan Sümbüloğlu.

We wish Prof. Kadir and Prof. Vildan Sümbüloğlu many healthy and happy years.

With our regards.

Prof. Bektaş Açıkgöz, MD
Retired Professor
Zonguldak Bülent Ecevit University, Medical Faculty, Head of Department of Neurosurgery, Zonguldak, Türkiye

From Prof. Z. Nazan Alparslan;

Dear Prof. Kadir Sümbüloğlu,

I would like to begin by reiterating the words I expressed when I received my retirement plaque from our professional association (2022):

"My greatest gratitude in my professional life belongs to Kadir Sümbüloğlu, my mentor, who took my hand 40 years ago and never let go through my challenges."

When I moved to Adana due to marriage (winter of 1980), I was offered the opportunity to teach "medical statistics (as it was called at that time)" at the Faculty of Medicine of Çukurova University. Since my undergraduate and graduate education were suitable, I accepted the offer and started working in the summer of 1980.

The discipline of biostatistics was still very new in our country, and training personnel was necessary. In 1982, news of Hacettepe University's doctoral program in my field reached my faculty.

It was at this stage Prof Kadir Sümbüloğlu entered my life, and at each stage of my professional life, I discovered different characteristics of my mentor. When I went to Ankara for the exam, the way I learned about the exam results gave me the first clue about my mentor. Over time, I named this characteristic: "dedication to the field he founded." My mentor was relentless; he informed me of the exam results of a candidate in Adana through an "intercity" phone call. Thus, a new path opened up for me.

Prof. Kadir Sümbüloğlu was attentive, compassionate, helpful, and understanding. I completed my doctorate by travelling back and forth to Ankara.

After my doctorate, there are, of course, stages, and there are staff matters. This time, I saw other characteristics of my mentor: extremely protective and supportive of me, self-sacrificing, but demanding (sometimes uncompromisingly) towards my institution when necessary. During these years, my mentor, who came to Adana to support the courses I opened for faculty members and the student juries I organized, also participated in rector's programs.

In addition to all these supportive characteristics, and in my opinion, the most important feature, is that Prof. Kadir Sümbüloğlu is 'reliable'. I always trusted my mentor. Prof. Kadir Sümbüloğlu's energy and positive attitudes have always been a source of motivation for me as well. There were certainly times and situations when he was pessimistic, but he never reflected it; he always showed his positive, cheerful, fatherly side.

To my dear mentor, whom I always felt the spiritual support of even during my spouse's illness and passing: I wish you many healthy, peaceful years with your loved ones and those who love you.

Prof. Z. Nazan Alparslan, PhD
Retired Professor, Department of Biostatistics, Çukurova University, Faculty of Medicine, Adana, Türkiye

From Assoc. Prof. Alper Serçelik;

A Legend; Prof. Kadir Sümbüloğlu

In the late 1980s, we were studying at the medical faculty of Hacettepe University. For each topic we were about to start, we would search for references. We did the same research when we were about to start to study biostatistics. No matter whom we

asked about biostatistics references, the answer always led to one address: Prof. Kadir Sümbüloğlu. That was the first time I heard his name. He had many books on biostatistics. I also learned that he was the founding chairman of the Biostatistics department at Hacettepe University. Then, he began teaching our classes.

His self-confidence while teaching was remarkable. His sense of humor allowed us to follow his lectures without getting bored. His lectures were followed with great interest by the students. I have seen many professors at Hacettepe University who added value to their departments with their presence. Prof. Kadir Sümbüloğlu was one of them. We learned a lot from him medically and for personal development. He was one of the legends of Hacettepe University.

Decades later, I learned that he was the husband of Prof. Vildan Sümbüloğlu, the head of the Biostatistics department at our university. Seeing my legendary mentor 35 years later at Sanko University Hospital, where I worked, touched, and excited me. Despite his advanced age, his mental functions were superb. When the time came, he continued with his subtle touches of humor. He had some heart-related problems, and I feel lucky to have had the opportunity to help my mentor with this.
My mentor, you are one of the people who add color to this world. May God bless you with health and a long life. I will always remember you with gratitude.

Assoc. Prof. Alper SERÇELİK, MD
Department of Cardiology, SANKO University, Faculty of Medicine, Gaziantep, Türkiye

From MD Surg. Mustafa Berhuni;
To my mentor, and mentor of mentors; Prof. Kadir Sümbüloğlu,

During the years when I led a very simple life in the Ceylanpınar district of Şanlıurfa and harbored great dreams, I had only one goal: to get admitted to Hacettepe University Faculty of Medicine. And I achieved this goal in the year 2000. I was literally flying with joy. I got into the best medical faculty. Until the age of eighteen, I had never ventured beyond Şanlıurfa. I was going to live in Ankara, a big and capital city. I was filled with excitement. Upon my first arrival in Ankara, what caught my attention were the crowds and the traffic of the city, which made me nervous. The first year of my university life, joining preparatory class, was a chance for me to acclimate to the city. After the preparatory class, I started the first grade in 2001. But among them was one professor who, from the very first sight, I declared as my idol: Prof. Kadir Sümbüloğlu. His stance, mastery of the subjects and fatherly attitude caught my attention. Some of our friends did not take the biostatistics course seriously. Actually, these friends did not aware of that; being a physician was not just about diagnosis and treatment of patients, it was also about being a good researcher and scientist. We later understood how important biostatistics was in scientific and academic research. Indeed, when it came to biostatistics in Türkiye, perhaps even globally, Prof. Kadir Sümbüloğlu was one of the few names that came to mind. Prof. Kadir Sümbüloğlu was the mentor of mentors and had trained many professors. After biostatistics courses, I would approach him and ask questions related to the lessons. He was extremely gentle, calm, and sweet-tongued. He would listen to our questions with great seriousness and answer them in the best way possible. I must also mention this, Prof. Kadir Sümbüloğlu was also very charismatic. When he entered the classroom, everyone would fall silent, and no one would make a noise. I never witnessed him warning the class to be quiet. All the students showed him a serious respect. Prof. Kadir Sümbüloğlu had become an idol in my mind during my teenage years. Years flew by. I graduated from medical school in 2007 and started my residency in Ophthalmology at Kayseri Erciyes University Faculty of Medicine. I completed my residency in 2013. One day, while working in the ophthalmology clinic at Gaziantep Dr. Ersin Arslan Training and Research Hospital, I suddenly saw Prof. Kadir Sümbüloğlu and his esteemed wife Prof. Vildan Sümbüloğlu in front of me. The memories of my youth at the faculty flashed before my eyes, and I became very excited. Prof. Vildan Sümbüloğlu asked me to examine my mentor Prof. Kadir Sümbüloğlu. At that moment, I kissed the hands of both, and said, "I am your student, you have a special place in my heart," and we chatted for a while. They both had come to SANKO University. I was fortunate enough to examine my idol, Prof. Kadir Sümbüloğlu. After that, we met occasionally, and I provided follow-up and treatment for my mentor. Prof. Vildan Sümbüloğlu provided me with great support in my scientific research. Both of them have hearts as pure as diamonds. I wish them both a healthy, happy, and peaceful life.

With endless respect...

MD Surg. Mustafa BERHUNİ
Ophthalmologist

Gaziantep Provincial Health Directorate Dr. Ersin Arslan Education Research Hospital, Department of Ophthalmology, Gaziantep, Türkiye

REFERENCES

[1]. Habal MB (2023) On Leaders and Leadership That Will Shape Our Future Direction in the Presence of the Winds of Change and the Waves of Progress. J Craniofac Surg 34:2243-2244. https://doi.org/10.1097/SCS.0000000000009785

How to Cite;

Kul S, Doğan İ, Balat A, Açıkgöz B, Alparslan ZN, Serçelik A, Berhuni M. (2024) Biostatistics Leader in Türkiye from the Eyes of His Students: Prof. Kadir Sümbüloğlu. Eur J Ther. 30(2):e13-e18. https://doi.org/10.58600/eurjther2134

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):e19-e22.
https://doi.org/10.58600/eurjther2099

Special Editorial

Panagiotis Lefakis (?-1940). The Blind Majestic Obstetrician Who Had Been Loved by the Ottomans

Gregory Tsoucalas [1], Theodoros Kyrkoudis [1,2], Evangelia Mourellou [1], Ioannis Tentes [3], Aliki Fiska [2]

[1] History of Medicine and Medical Deontology Department, School of Medicine, University of Crete, Greece
[2] History of Medicine, Anatomy Department, School of Medicine, Democritus University of Thrace, Greece
[3] Biochemistry Laboratory, School of Medicine, Democritus University of Thrace, Greece

Received: 2024-03-19 **Accepted**: 2024-04-11 **Published Online**: 2024-04-14

Corresponding Author
Gregory Tsoucalas
Address: History of Medicine and Medical Deontology, School of Medicine, University of Crete, Greece.
E-mail: gregorytsoukalas@uoc.gr

Abstract

Sometimes, during an era of clashes, appears a man to promote humanism. Such a man was Panagiotis Lefakis who dedicated his life to treat the helpless inhabitants of Dedeagats (later Alexandroupolis) regardless of nationality and religion. With studies in Constantinople and Paris he practiced general medicine and obstetrics in Thrace. Lefakis, completely lost his eyesight by cause of retinal detachment but continued his work. With the help of his daughter Elli, he was the most preferable physician among the Muslims, as his blindness was an advantage due to cultural reasons. Muslim families felt secure as a blind man could not offend a Muslim female patient or a pregnant woman. His skills and temper helped him to achieve greatness and although he had been accused by his countrymen, the Ottoman authorities recognized his contribution.

Keywords: Alexandroupolis, Dedeagats, Thrace, Elli Manatou.

INTRODUCTION

Gynecological examination in Ottoman Empire was a practice established since the era of the medical evolution during the Golden Age of Caliphs [Figure 1A]. In some cases, female physicians were completely devoted into examining female patients due to cultural issues of the Empire [Figure 1B]. However, female physicians were performing operations in female bodies, while evidence of some female medical practice in the Ottoman Empire do exist, originally named as “tabibe” (meaning female physician) [1]. Furthermore, there was a long tradition of females practicing midwifery during the Ottoman reign and midwives appear in legal texts, palace archives and court records. Midwives were present on harem and attending procedures as witnesses to birth and related matters [2-3]. Three classes of midwifes were being referred, i) those of the palace (saray-i hümayun ebesi), ii) those of the noble (kibar ebesi), and iii) those of the common people (ahad-i nas ebesi). There is a general perception that females had preferred to be treated at their residence by female physicians, midwives or healers. This predilection was only made for the protection of the female according to Muslim culture and did not signify any concept of underrating them. In need, male physicians, even non-Muslims, were allowed to treat female patients for a life to be saved. Progressively “ethno-gynecology” in Ottoman Empire moved towards a western type reforms. The Imperial Medical School of Istanbul reports male physicians, some non-Muslim, treating Muslim female patients at the school clinic [3].

Among those non-Muslim men who treated females in Ottoman Empire, was the Greek physician Panagiotis Lefakis, an obstetrician who practiced obstetrics and gynecology in Dedeagats (today Alexandroupolis, modern Greek territory).

Early years and life

Panagiotis Lefakis (?-1940) [Figure 2], son of Aristides Lefakis, who was a captain from the island of Andros, was a student of the High School in Chalkida city, where he was a classmate with prolific novelist Alexandros Papadiamantis (1851-1911). He continued his studies to become a physician initially in Constantinople and later in Paris, during the Russian-Turkish war in 1878. His first child, named Aristides after his grandfather, was born in Paris and studied mineralogy, Unfortunately, he had lost his life in the Black Sea when the ship he was traveling with, sank under unknown conditions. His second child, Katina, was born in 1883 in Alexandroupolis, which shows that the family had already settled in the city, where her daughters Elli and Cleio were also been born [4]. Dedeagats was built in poor land full of marshes and villagers suffered by continuous infections [5]. Lefakis and his family were among the first parishioners from Greece, having a Hellenic citizenship to settle in Dedeagats [Figure 3 A-D] [4]. Lefakis is mentioned in the Trade Guides of the era, appearing in "L' Indicateur Ottoman du Commerce" of the year 1881 in Dedeagats, meaning he had already established his private cabinet [6].

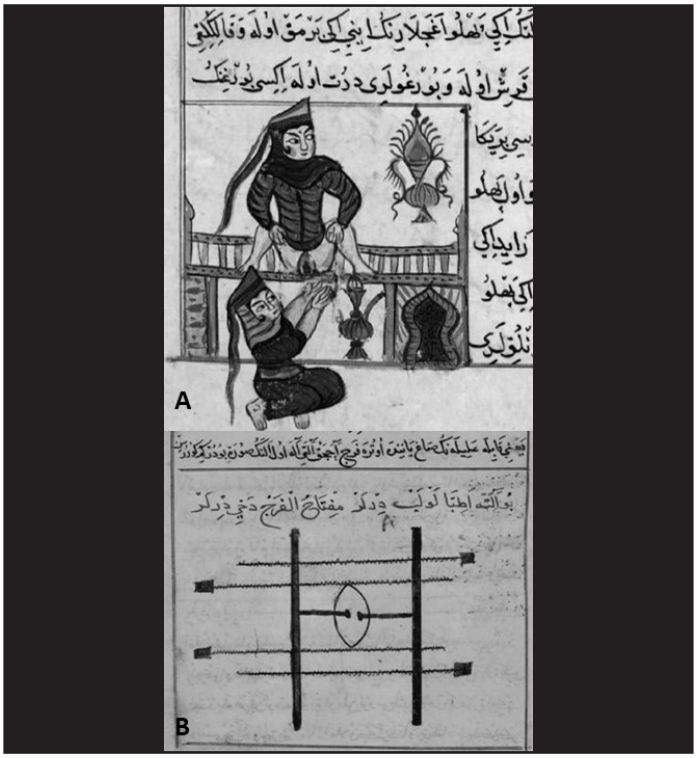


Figure 1. A. Depiction of a speculum, Bibliothèque Nationale de France, Turc 693 f. 113r & **B.** Female gynecologist removes with the help of a speculum a fetus that died during labor. Bibliothèque Nationale de France, Turc 693 f. 118v. Imperial Surgery, Şerafeddin Sabuncuoğlu (1385-1468), 1465.

Figure 2. Panagiotis Lefakis, portrait, Archive of his great-grandson, Professor of Medicine Ioannis Tentes.

Figure 3. A. Municipality Garden street in Dedeagatch, **B.** The Lighthouse street, **C.** Inauguration of the Ottoman Imperial Bank in 1909 & **D.** The Hotels street. Photo-archive of George Alepakos.

In addition to being an excellent physician, he was also a great humanist. He lived in times of clashes, revolts and war but his home rendered to a treatment place for the afflicted regardless of nationality and religion [Figure 4 A-B]. In 1906, following the proposal of the Greek Consul Ion Dragoumis (1878-1920), he was decorated for his practice with the Silver Cross medal. On May 31, 1910 in the French newspaper "Le Temps", in a text originated from the "Societe de medecine de Paris", Lefakis' scientific opinion was recorded. Lefakis sent for publication three cases of complete heterotaxy (Situs Inversus Totalis), describing the complete inversion of the viscera of the chest and abdomen. He noted that in malarial countries the hypertrophy of

the spleen may help physicians to diagnose the inversion of the visceral organs. Lefakis was one of the beloved physicians of the Greek Orthodox Metropolitan Bishop of Smyrna, and later a Saint, Chrysostom (1867-1922) [7]. On February 17, 1911, he wrote a letter to Prime Minister Eleftherios Venizelos (1864-1936), to express his complaints about the behavior of the Vice-consul Apostolos Tserepis (who later attempted to assassinate Venizelos in Paris) and physician Georgios Papadopoulos, as they had denounced him to the Grand Vizier as a figure conspirator against the Empire [8]. The Ottomans rightfully neglected the accusations and Lefakis stayed and practiced obstetrics and general medicine in Dedeagats, where he died in July 17th of 1940 at an age of over 90 years [7].

Figure 4. A. The first house of the Greek physician Panagiotis Lefakis in Alexandroupolis, Photo-archive of Eleftherios Sindarakis & **B.** The two floor second house of Panagiotis Lefakis, later on Town Hall for the Bulgarians and then for the Greeks of the city of Alexandroupolis, Photo-archive of Athanasios Kritou.

Lefakis, completely lost his eyesight due to retinal detachment sometime in the year 1870, while he was still living in Paris during the siege of the city by the Prussians. However, it is of interest that his daughter Cleio also lost her eyesight by retinal detachment signifying a potential genetic trait. Nevertheless, despite his blindness, Lefakis, wrote a number of books, medical and other. His most famous treatise was "The Fight against Alcoholism" (Greek: Ο Ανταλκοολικός Αγών) in 1931. Lefakis, was also a benefactor, donating his home to the Municipality of Alexandroupolis for the 4th Primary School to be built and named after him. Ha had also donated a piece of land where Alexandroupolis' City Hall and offices of the Medical Association of Evros are housed today [4].

The snake folklore tale

Lefakis' charismatic nature as a physician may be demonstrated by the following oral testimony of his great-grandson Ioannis Tentes, Professor of the School of Medicine of the Democritus University of Thrace in Greece. A mentally disturbed Greek peasant boy was brought by his parents to Lefakis. The boy was under the strong belief that he had swallowed a snake. For hours Lefakis had tried hard to convince him that such a thing could not have been happened. The only remaining solution to the problem was to improvise of a placebo trick. To that end, Lefakis gave the boy a number of pills made of flour powder, sugar and other non-curative ingredients to be taken daily for two weeks as the only possible effective treatment. In the meantime, Lefakis ordered his assistant to find him a snake. When the young boy returned upon completion of the regimen, Lefakis gave him an emetic containing grated chalk to drink. Naturally, the peasant boy suddenly started to vomit. While the boy was in a state of mess and vomiting hard in a basin, Lefakis craftily threw the snake in, as a standing proof that he was finally relieved of the physical cause of his torment. The boy left Lefakis' house absolutely convinced that he was cured [7].

The obstetrician

Lefakis had practiced obstetrics in the city of Alexandroupolis, gaining high reputation for his skills. His fame resulted into requests for neighboring areas. Occasionally, he had to traveled to Soufli, Makri, Maronia, Ainos, and Samothrace and other neighboring places in order to help the locals. Lefakis' blindness, a huge and immense misfortune for others, did not prevent him from practicing medicine. He was driven and guided from house to house to examine patients by his friend and assistant Nikolaos Kavourtzikis from Antheia and later on by his daughter and secretary Elli Manatou (Elli was married then to a lawyer named Konstantinos Manatos). Soon, Elli, started helping her father as a practical midwife. Surprisingly, his incapacity became a benefit among the Ottomans and especially among

the Turkish population. Turkish families felt protection and a kind of security and had all been choosing him to examine their wives and help them upon delivery, exactly because his contact offered the best possible discretion for he, a non Moslem practitioner, could not offend them. This fact alone, that he could not see them, provided an ethical advantage according to their cultural beliefs. Elli, for several years, was always invariably been stood in by his side, and her presence was an additional advantage for Lefakis, as her gender made her too, a favorite for the Turks [9-10].

Epilogue

Panagiotis Lefakis was a skillful obstetrician and humanist. He was blind but with a great desire to exercise his art. He had lived in times and lands of great turbulence. However, he had tried to keep the balance between Greece and the Ottoman Empire and always had a good medical practice for all, for both Christians and Muslims.

REFERENCES

[1] Kadioğlu NS, Ögenler O, Uzel İ (2011) Şerefeddin Sabuncuoğlu's drawings of gyneco-obstetric instruments. Turkish Journal of Medical Sciences 41(1):1-5. https://doi.org/10.3906/sag-0911-442

[2] Kassell L, Hopwood N, Flemming R (2018) Reproduction. Antiquity to the Present Day. Cambridge University Press, Cambridge.

[3] Sari N. Women Dealing with Health during the Ottoman Reign (1996) The New History of Medicine Studies 2-3:11-64.

[4] Kritou Ath (1995) Alexandroupolis one hundrend year of history 1878-1978. Alexandroupolis.

[5] Kyrkoudis Th, Tsoucalas G, Fiska A. Alexandroupolis (Dedeagatch): A city born of infections and the first documented death of the Italian civilian Giuseppe Bigheti (2020) Le Infezioni in Medicina 2:273-277.

[6] L'Indicateur Ottoman. Annuaire almanach du commerce de l'industrie, de l'administration et de la magistrature (1881). Constantinople.

[7] Kyrkoudis Th (2023) Medicine in Thrace from the 18th century until the Second World War. An approach through data of visual culture. Thesis. School of Medicine, Democritus University of Thrace.

[8] Lefakis P (1911) Epistle to Eleftherios Venizelos. Eleftherios Venizelos archive.

[9] Papathanasi Mousiopoulou K (1976) Hellenic Consulates in Thrace. Athens.

[10] Alepakos P (2010) Dedeagats in late Ottoman period. Citizen of Thrace, number 245.

How to Cite;

Tsoucalas G, Kyrkoudis T, Mourellou E, Tentes I, Fiska A. (2024) Panagiotis Lefakis (?-1940). The Blind Majestic Obstetrician Who Had Been Loved by the Ottomans. Eur J Ther. 30(2):e19-e22. https://doi.org/10.58600/eurjther2099

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):e23-e25.
https://doi.org/10.58600/eurjther1995

Special Editorial

AI in Medical Education Curriculum: The Future of Healthcare Learning

Waqar M. Naqvi [1,2], Habiba Sundus [3], Gaurav V. Mishra [4], Ramprasad Muthukrishnan [5], Praveen Kumar Kandakurti [5]

[1] Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, UAE.
[2] Faculty of Interdisciplinary Sciences, Datta Meghe Institute of Higher Education and Research, Wardha, India.
[3] National Institute of Unani Medicine, Ghaziabad, India.
[4] Department of Radiodiagnosis, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, India.
[5] Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, UAE.

Received: 2024-01-04 **Accepted**: 2024-01-22 **Published Online**: 2024-01-29

Corresponding Author
Waqar M. Naqvi, PhD,
Address: Department of Physiotherapy, College of Health Sciences, Gulf Medical University, Ajman, UAE.
E-mail: dr.waqar@gmu.ac.ae

To address the evolving, quantitative nature of healthcare in the twenty-first century, it is imperative to integrate artificial intelligence (AI) with healthcare education. To bridge this educational gap, it is imperative to impart practical skills for the utilisation and interpretation of AI in healthcare settings, integrate technology into clinical operations, develop AI technologies, and enhance human competencies [1].

The swift rise of AI in contemporary society can be ascribed to the progress of intricate algorithms, cost-effective graphic processors, and huge annotated databases. AI has been a crucial component of healthcare education in recent years and has been implemented by numerous medical institutions globally. AI is widely prevalent in medical education in Western countries, in contrast to developing countries. The disparity could be mitigated through more infrastructural assistance from medical institutions in underdeveloped nations. It is crucial to raise awareness among medical educators and students regarding AI tools to facilitate the development and integration of AI-based technologies in medical education [2]. AI can impact the student learning process through three methods: direct instruction (transferring knowledge to the student in a teacher-like role), instructional support (assisting students as they learn), and learner empowerment (facilitating collaboration among multiple students to solve complex problems based on teacher feedback). Incorporating artificial intelligence (AI) tools into education can augment students' knowledge, foster skill acquisition, and deepen comprehension of intricate medical topics [2,3].

Virtual reality (VR) can enhance the immersion of learning sessions with virtual patients. Virtual Reality (VR) is a software-driven technology that generates a virtual environment with three-dimensional characteristics. Virtual Reality (VR) uses a head-mounted display or glasses to build a computer-simulated environment that provides a convincing and lifelike experience for the user. Conversely, augmented reality (AR) enhances the real-world environment by superimposing virtual elements onto a user's perspective of the actual world through a smartphone or similar device. By integrating these technologies, learners are

able to investigate and actively participate in intricate clinical situations, resulting in a more pleasurable and efficient learning experience [4,5].

AI-powered games utilise data mining methodologies to examine the data gathered during gameplay and enhance the player's knowledge and abilities. In addition, they provide a personalised and engaging encounter that adapts the speed and level of challenge according to the player's achievements. Incorporating game components such as points, badges, and leaderboards enhances the enjoyment and engagement of the learning process. The implementation of gamification in the learning process boosts student engagement, fosters collaborative efforts, and optimises learning results. Additionally, they offer chances for clinical decision-making without any potential risks and provide instant feedback to the students, thereby becoming an essential component of undergraduate medical education [6].

By incorporating artificial intelligence (AI) techniques into learning management systems (LMS), learners are equipped with the necessary resources to achieve mastery at their own individualised pace. These computer algorithms assess the learner's level of understanding and deliver personalised educational material to help them achieve mastery of the content. The AI-powered platforms guide learners by effectively organising and arranging learning experiences, and then implementing targeted remedial actions. These customised and adaptable teaching techniques enhance the effectiveness and efficiency of learning.

Virtual patients are computer-based simulations that replicate real-life clinical events and are used for training and education in health professions. Virtual patients are built to simulate authentic symptoms, react to students' treatments, and create dynamic therapeutic encounters. The student assumes the position of a healthcare provider and engages in activities such as gathering information, proposing potential diagnoses, implementing medical treatment, and monitoring the patient's progress. These simulations can accurately reproduce a range of medical settings and expose trainees to the problems they might encounter in real-world situations. Medical students can enhance their communication and clinical reasoning skills by engaging with virtual patients in a simulated environment that closely resembles real-life situations [6,7].

Furthermore, AI-driven solutions can be advantageous for educational purposes in diagnostic fields such as radiology, pathology, and microbiology. Content-based image retrieval (CBIR) is a highly promising method utilised in the field of radiology for educational and research purposes. CBIR facilitates the search for photos that have similar content with a reference image, utilising information extracted from the images [8]. Moreover, artificial intelligence (AI) integrated with machine learning techniques is currently being employed to accurately diagnose microbial illnesses. This application of AI has significant potential in training and educating specialists in the field of microbiology. Conversely, the current progress in AI-driven deep learning technologies that specifically target cellular imaging has the potential to revolutionise education in diagnostic pathology [9].

Ultimately, incorporating AI training into the medical education curriculum is a transformative step that will shape the future of healthcare practitioners. This sequence provides enhanced diagnostic precision, personalised learning prospects, and heightened ethical awareness. These potential benefits surpass the obstacles, initiating a new era in medical education where human beings and technology collaborate to deliver optimal patient care. The purposeful and calculated integration of AI into medical education will have a pivotal impact on shaping the future of healthcare as we navigate this unexplored territory.

Keywords: Medical education, Artificial intelligence, Curriculum development, Healthcare technology, Adaptive learning

REFERENCES

[1] Pucchio A, Eisenhauer EA, Moraes FY (2021) Medical students need artificial intelligence and machine learning training. Nat Biotechnol 39:388-389. https://doi.org/10.1038/s41587-021-00846-2

[2] Basu K, Sinha R, Ong A, Basu T (2020) Artificial Intelligence: How is It Changing Medical Sciences and Its Future? Indian J Dermatol 65:365-370. https://doi.org/10.4103/ijd.IJD_421_20

[3] Kumar Y, Koul A, Singla R, Ijaz MF (2023) Artificial intelligence in disease diagnosis: a systematic literature review, synthesizing framework and future research agenda. J Ambient Intell Humaniz Comput 14:8459-8486.

https://doi.org/10.1007/s12652-021-03612-z

[4] Almusaed A, Almssad A, Yitmen I, Homod RZ (2023) Enhancing Student Engagement: Harnessing "AIED"'s Power in Hybrid Education—A Review Analysis. Education Sciences 13. https://doi.org/10.3390/educsci13070632

[5] Mir MM, Mir GM, Raina NT, Mir SM, Mir SM, Miskeen E, Alharthi MH, Alamri MMS (2023) Application of Artificial Intelligence in Medical Education: Current Scenario and Future Perspectives. J Adv Med Educ Prof 11:133-140. https://doi.org/10.30476/JAMP.2023.98655.1803

[6] Akgun S, Greenhow C (2022) Artificial intelligence in education: Addressing ethical challenges in K-12 settings. AI Ethics 2:431-440. https://doi.org/10.1007/s43681-021-00096-7

[7] Bajwa J, Munir U, Nori A, Williams B (2021) Artificial intelligence in healthcare: transforming the practice of medicine. Future Healthc J 8:e188-e194. https://doi.org/10.7861/fhj.2021-0095

[8] Farhud DD, Zokaei S (2021) Ethical Issues of Artificial Intelligence in Medicine and Healthcare. Iran J Public Health 50:i-v. https://doi.org/10.18502/ijph.v50i11.7600

[9] Ahuja AS (2019) The impact of artificial intelligence in medicine on the future role of the physician. PeerJ 7:e7702. https://doi.org/10.7717/peerj.7702

How to Cite;

Naqvi WM, Sundus H, Mishra GV, Muthukrishnan R, Kandakurti PK. (2024) AI in Medical Education Curriculum: The Future of Healthcare Learning. Eur J Ther. 30(2):e23-e25. https://doi.org/10.58600/eurjther1995

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):102-116.
https://doi.org/10.58600/eurjther1999

Original Research

A Science Mapping Analysis of Brazilian Literature on Oral and Maxillofacial Surgery

Ricardo Grillo [1,2*], Mariana Aparecida Brozoski [1], Agnelo Lucamba [3], Yuri Slusarenko da Silva [4], Alexandre Meireles Borba [5]

[1] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of São Paulo, São Paulo, Brazil
[2] Department of Oral and Maxillofacial Surgery, Postgraduation Program, Faculdade Patos de Minas, Brasília, Brazil
[3] Department of Oral and Maxillofacial Surgery, Hospital Josina Machel, Luanda, Angola
[4] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Guanambi, Guanambi, Brazil
[5] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Cuiabá, Cuiabá, Brazil

Received: 2024-01-07 **Accepted:** 2024-02-07 **Published Online:** 2024-02-09

Corresponding Author
Ricardo Grillo, DDS, MSc
Address: Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of São Paulo, São Paulo
E-mail (s): grillo@usp.br; doutorgrillo@uol.com.br

ABSTRACT

Objectives: Bibliometrics serves as a valuable tool for assessing scholarly articles. The objective of this study is to conduct a bibliometric analysis of Brazilian literature on oral and maxillofacial surgery across various years.

Methods: Following the principles outlined in the Leiden Manifesto, a bibliographic search was conducted on the Web of Science using oral and maxillofacial terms. Parameters such as number of citations, citations per year, authors, and publication year were examined. Visual representations of authorship and keywords were generated using VOSviewer. These steps were essential for compiling a comprehensive list and comparing it to all published articles on the topic. Statistical tests were carried out, with significance determined at a 95% confidence interval.

Results: A ranking comprising 71 articles across seven different subject areas was compiled, with variables discussed individually. The USA leads in terms of publication volume, followed by Brazil. Noteworthy authors and institutions were identified through citation analysis. The visualization of data was assessed, and findings regarding subscription versus open access articles were discussed. The importance of selecting appropriate keywords was also highlighted.

Conclusions: This study presents a thorough bibliometric analysis of Brazilian literature on oral and maxillofacial surgery. The presence of Brazil among the top ten most prolific countries in oral and maxillofacial surgery underscores its significant contribution to the global discourse and advancements within the field. It serves as a valuable reference and source of inspiration for oral and maxillofacial surgeons, academics, and researchers.

Keywords: Bibliometrics; Citation Analysis; Scientometrics; Top-cited articles; Orthognathic Surgery; Maxillofacial Injuries; Surgery, Oral; Pathology, Oral; Ameloblastoma; Cleft Lip

INTRODUCTION

Knowledge has intrigued mankind for thousands of years. In the beginning, science involved speculation and dogmatism, but the procedures have been changed over the years. Galileu Galilei developed the scientific method, and for this reason is considered the father of the modern science [1]. From Galileu onwards,

science made great strides. Remarkable advances were seen more and more. But one question remains. Can we measure science? A useful tool is scientometrics, the metric values of scientific papers. Bibliometrics is only one method used in scientometrics [2]. It uses statistical methods to measure books, articles and other scholarly works. A common instrument of bibliometrics is citation analysis, a traditional method for assessing scientific impact [3,4]. From simple events to rocket science, any scientific matter could be evaluated. Each with its own peculiarities. Oral and maxillofacial surgery (OMFS) is part of this great diversity.

OMFS in Brazil has witnessed a remarkable evolution, shaped by historical context and contemporary advancements. Originating in the early 20th century to address facial trauma, the field has undergone significant refinement, bolstered by dedicated training programs and technological breakthroughs. Brazil now stands as a global highlight in OMFS research and innovation, with a focus on Virtual Surgical Planning protocols, interdisciplinary collaboration, and public health initiatives [5]. Academic institutions offer robust training programs, ensuring a steady supply of skilled professionals, while outreach efforts target prevalent oral health issues. As OMFS in Brazil continues to evolve, fueled by a commitment to excellence and patient care, its practitioners are poised to make enduring contributions to the field and improve outcomes for patients nationwide.

Main Points:

- The article highlights the importance of scientometrics and specifically bibliometrics in measuring the impact and productivity of scientific research. The use of citation analysis as a method for assessing scientific impact is emphasized, particularly in the field of oral and maxillofacial surgery.
- The study explores the geographic distribution of research output in oral and maxillofacial surgery. The article provides insights into the collaboration trends, research productivity, and global ranking of Brazil in various subtopics within the field.
- The University of São Paulo emerges as a leading institution in terms of research output in oral and maxillofacial surgery. Prolific authors such as Prof. Ricardo Santiago Gomez and Prof. Belmiro Cavalcanti do Egito Vasconcelos are highlighted, along with their respective h-index and citation counts, showcasing their significant contributions to the field.
- The article discusses the trends in the number of publications over the years for different topics within oral and maxillofacial surgery. Additionally, it notes the dominance of English as the primary language for publications, highlighting the need for international collaboration and suggesting the potential benefits of national or international cooperation programs for research universities.

Geographic bibliometrics plays a crucial role in understanding the distribution of research output across different regions, fostering collaboration, and identifying geographic trends, thereby contributing significantly to the advancement of scientific knowledge and global research networks [6]. Hence, the objective of this study was to conduct a bibliometric assessment of Brazilian literature on OMFS. A comprehensive compilation of the top 10 most referenced articles within each OMFS-related topic has been established. This research serves as a valuable resource for those engaged in the field, offering updated scientific insights and supporting ongoing scholarly endeavors.

MATERIALS AND METHODS

This work follows the principles of the Leiden Manifesto [7]. The selection criteria for articles in this literature search aimed to ensure the retrieval of relevant and high-quality literature within the field of OMFS. Articles with at least one Brazilian author were included to focus on international contributions, while only those indexed on Web of Science (WS) were considered to maintain consistency and reliability. Additionally, articles unrelated to OMFS were excluded to uphold the relevance of the retrieved literature. The choice of bibliometric indicators, including sorting by main topic, year of publication, and journal impact factor (IF), facilitated the organization and analysis of the data, enabling easy comparison across different subjects, tracking temporal trends, and assessing the quality and influence of the journals in which the articles were published. These criteria and indicators were selected to enhance the validity and comprehensiveness of the literature search, ultimately contributing to a better understanding of advancements within the field.

The data collected underwent manual input into Mendeley software (Elsevier, London, UK) to compile bibliometric indicators. Following refinement, all documents and results were gathered. Microsoft Excel was utilized for the collection

and analysis of values retrieved from Web of Science (WS). A global comparison with Brazil was conducted across all topics, considering variables such as institutional affiliation, publication language, Hirsch index (h-index), citations, and authorship. Inclusion and exclusion criteria for articles were determined through consensus between two authors (RG and AMB). Adjustments to the general search were made to ensure a maximum of 10,000 articles in each search, involving the removal of conference articles, specific search terms, or year of publication restrictions, as WS does not allow citation reports with more than 10,000 results. Impact Factor (IF) and Scimago Journal Ranking (SJR) journals were obtained from the same source to mitigate bias. A compilation of the 10 most cited articles on each topic was generated, including reference, year of publication, number of citations by WS, and citation density (number of citations per year). Articles from specialties unrelated to OMFS were excluded from this top 10 list.

Graphs and tables were crafted using Microsoft Excel and Microsoft PowerPoint (Microsoft Corporation, Redmond, USA) to facilitate bibliometric visualization. VOSviewer free software (Leiden University, The Netherlands) was employed to create graphical representations of critical elements, offering a visual form of bibliometric analysis. Statistical analyses were conducted, considering significance at a 95% confidence interval. As a bibliometric analysis, this study is exempt from institutional review board approval, as the data were sourced from publicly available electronic platforms and did not involve specific patient information.

RESULTS

A total of 39,979 articles were retrieved, of which 3,225 were published by at least one Brazilian author (n=8.06%). The USA leads in the seven subjects assessed (n=9,410; 23.53%). Brazil is among the top ten most productive countries on all subjects assessed (Fig. 1) and ranks second in third molar (n=260), oral pathology (n=872) and maxillofacial trauma (n=776). In addition, a fourth place in cleft lip (n=656) and two fifth places in orthognathic surgery (n=479) and temporomandibular (TMJ) surgery (n=124). The subject with the fewer published articles worldwide, odontogenic infections (n=1,426), Brazil ranks seventh (n=58).

The vast majority were published in English language (n=3,159; 97.95%). Articles were also published in Portuguese (n=57; 1.77%), Spanish (n=8; 0.25%) and only one in German (n=0.03%). There has been a clear upward trend in the number of publications for all seven topics over the years (Fig. 2). A more robust trend is found in orthognathic surgery ($R^2 = 0.8887$), oral pathology ($R^2 = 0.8597$), cleft lip ($R^2 = 0.8554$), maxillofacial trauma ($R^2 = 0.7887$) and third molar ($R^2 = 0.7884$). A moderate upward trend in TMJ surgery ($R^2 = 0.5253$) and a weak upward trend in odontogenic infections ($R^2 = 0.3691$).

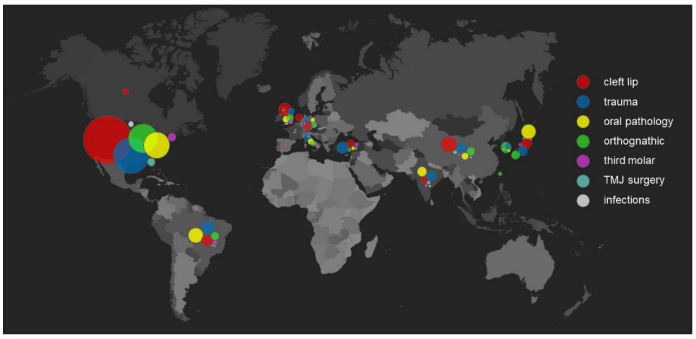


Figure 1. World map of oral and maxillofacial publications. The size of the circles is related to the number of publications.

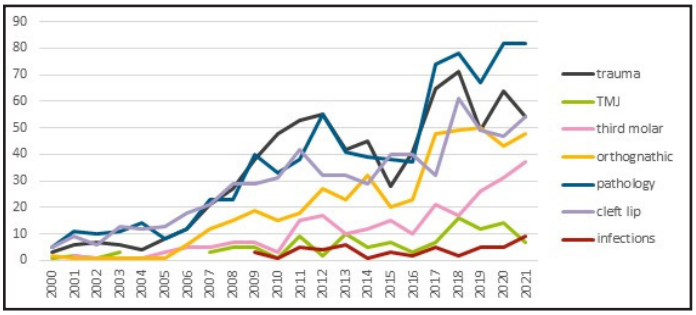


Figure 2. Number of Brazilian publications on this topic over the years

The University of São Paulo leads as institutional affiliation (n=987; 30.60%), followed by the University of Campinas (n=448; 13.89%) and the State University of São Paulo (n=338; 10.48%). Table 1 summarizes the first ten examples of each. Of particular note are Prof. Ricardo Santiago Gomez (n=423, H-index=39, citation count=11,215) from the Federal University of Minas Gerais and Prof. Belmiro Cavalcanti do Egito Vasconcelos (n=147, H-index=21, citation count=1,456), from the Federal University of Pernambuco. They are the most prolific authors related to oral pathology (Prof. Gomez) and maxillofacial surgery (Prof. Belmiro). Prof. Gomez is one of the more prolific not only from Brazil but from all over the world. Figure 3 shows a graphical representation of the authorship with VOSviewer.

The most cited article is "*Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes*" [8] by Kondo et al (582). The article with the highest citation density article is "*Essentials of oral cancer*" [9] by Rivera (46.71). A list of the 10 more cited publications on each topic was compiled, reaching 71 articles (Table 2) [10-78].

The Journal of Craniofacial Surgery was the journal with the most publications (n=273). The mean h-index of the journals with the ten greatest number of publications on each topic can be regarded as very high (h-index=90.39). A table listing the more common journals in each topic was created (Table 3).

Four themes were associated with a higher number of median citations in subscription access articles (third molar, orthognathic surgery, oral pathology, and maxillofacial trauma). While for three topics (TMJ surgery, cleft lip, and odontogenic infections) the number of average citations were higher in open access. A t-test was performed to assess the correlation between the type of article access and the number of citations. Neither subscription article nor open access articles are associated with a higher number of citations for OMFS ($t = -0.157106$; $p = 0.88031$).

After removing generic words "humans", "male", and "female", the most frequent keywords in the articles were "adults", "middle aged", "aged", "adolescent" and "mouth neoplasms". Figure 4 shows a graphical representation of the MeSH keywords using a network visualization (VOSviewer, Leiden University, Netherlands). VOSviewer is a tool helpful to construct and visualize bibliometric networks. The sizes of the circles are related to the numbers of citations using the determined keywords.

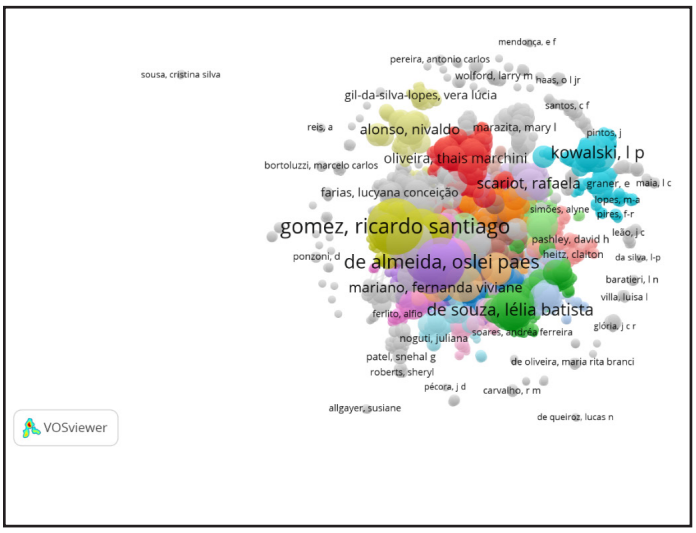


Figure 3. Graphic analysis of authorship

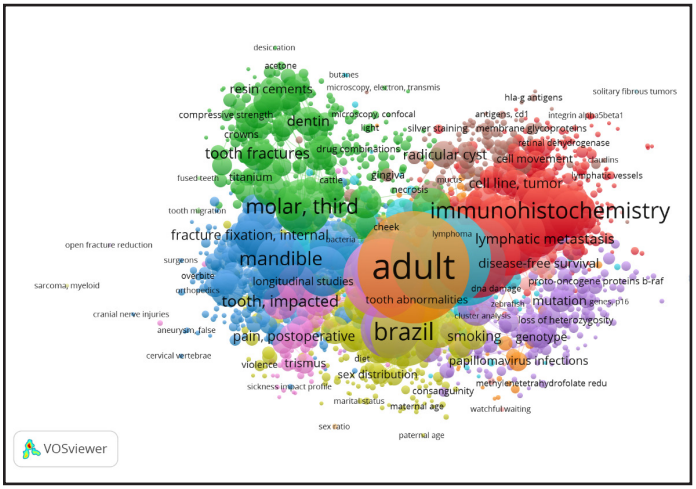


Figure 4. Graphic analysis of MeSH keywords

Table 1. Strategies used in bibliographic search.

1. ("third molar" AND surgery)
2. (Orthognathic surgery)
3. (Odontogenic Cysts OR Odontogenic Tumors OR Ameloblastoma OR Mouth Neoplasms)
4. (Temporomandibular Arthrocentesis OR Temporomandibular Arthroplasty OR Temporomandibular Joint Prosthesis OR Temporomandibular Ankylosis)
5. (Mandibular Fractures OR Maxillary Fractures OR Zygomatic Fractures)
6. ("Cleft lip")
7. (Odontogenic infections)

Table 2. The ten most cited articles by Brazilian authors on each topic

Third molar surgery					
rank	**reference**	**year**	**title**	**citations**	**CD**
1	Laureano Filho et al	2005	The influence of cryotherapy on reduction of swelling, pain and trismus after third-molar extraction - A preliminary study [10]	67	3.94
2	de Santana-Santos et al	2013	Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables [11]	65	7.22
3	Gomes et al	2008	Sensitivity and specificity of pantomography to predict inferior alveolar nerve damage during extraction of impacted lower third molars [12]	63	4.50
4	Alcantara et al	2014	Pre-emptive effect of dexamethasone and methylprednisolone on pain, swelling, and trismus after third molar surgery: a split-mouth randomized triple-blind clinical trial [13]	57	7.12
5	Falci et al	2012	Association between the presence of a partially erupted mandibular third molar and the existence of canes in the distal of the second molars [14]	56	5.60
6	Cerqueira et al	2004	Comparative study of the effect of a tube drain in impacted lower third molar surgery [15]	53	2.94
7	Colombini et al	2006	Articaine and mepivacaine efficacy in postoperative analgesia for lower third molar removal: a double-blind, randomized, crossover study [16]	52	3.25
8	Santos et al	2007	Epinephrine concentration (1 : 100,000 or 1 : 200,000) does not affect the clinical efficacy of 4% Articaine for lower third molar removal: A double-blind, randomized, crossover study [17]	47	3.13
9	Rosa et al	2002	Influence of flap design on periodontal healing of second molars after extraction of impacted mandibular third molars [18]	47	2.35
10	Célio-Mariano et al	2012	Comparative Radiographic Evaluation of Alveolar Bone Healing Associated With Autologous Platelet-Rich Plasma After Impacted Mandibular Third Molar Surgery [19]	42	4.20
Orthognathic surgery					
1	de Oliveira et al	2009	Observer reliability of three-dimensional cephalometric landmark identification on cone-beam computerized tomography [20]	132	10.15
2	Aragon et al	2016	Validity and reliability of intraoral scanners compared to conventional gypsum models measurements: a systematic review [21]	83	13.83
3	Mattos et al	2011	Effects of orthognathic surgery on oropharyngeal airway: a meta-analysis [22]	66	6.00
4	Gonçalves et al	2008	Postsurgical stability of counterclockwise maxillomandibular advancement surgery: Affect of articular disc repositioning [23]	60	4.28
5	Esperão et al	2010	Oral health-related quality of life in orthognathic surgery patients [24]	54	4.50
6	Weissheimer et al	2015	Fast three-dimensional superimposition of cone beam computed tomography for orthopaedics and orthognathic surgery evaluation [25]	51	7.28
7	Nicodemo et al	2008	Effect of orthognathic surgery for class III correction on quality of life as measured by SF-36 [26]	50	3.57
8	Magalhães et al	2010	The influence of malocclusion on masticatory performance A systematic review [27]	48	4.00
9	Brasileiro et al	2009	An in Vitro Evaluation of Rigid internal Fixation Techniques for Sagittal Split Ramus Osteotomies: Advancement Surgery [28]	48	3.69
10	Haas et al	2015	Computer-aided planning in orthognathic surgery-systematic review [29]	46	6.57
10	Trindade et al	2003	Effects of orthognathic surgery on speech and breathing of subjects with cleft lip and palate: Acoustic and aerodynamic assessment [30]	46	2.42

Oral Pathology					
1	Rivera	2015	Essentials of oral cancer [9]	327	46.71
2	Guha et al	2007	Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: Results of two multicentric case-control studies [31]	225	15.00
3	Barreto et al	2000	PTCH gene mutations in odontogenic keratocysts [32]	148	6.72
4	Fregnani et al	2003	Lipomas of the oral cavity: clinical findings, histological classification and proliferative activity of 46 cases [33]	147	7.73
5	Pires et al	2007	Intra-oral minor salivary gland tumors: A clinicopathological study of 546 cases [34]	144	9.60
6	Schlecht et al	1999	Interaction between tobacco and alcohol consumption and the risk of cancers of the upper aero-digestive tract in Brazil [35]	112	4.86
7	Lopes et al	1999	A clinicopathologic study of 196 intraoral minor salivary gland tumours [36]	97	4.21
8	Crivelini et al	2003	Cytokeratins in epithelia of odontogenic neoplasms [37]	95	5.00
9	Velly et al	1998	Relationship between dental factors and risk of upper aerodigestive tract cancer [38]	95	3.95
10	Ledesma-Montes et al	2008	International collaborative study on ghost cell odontogenic tumours: calcifying cystic odontogenic tumour, dentinogenic ghost cell tumour and ghost cell odontogenic carcinoma [39]	92	6.57
TMJ Surgery					
1	Lobo Leandro et al	2013	A ten-year experience and follow-up of three hundred patients fitted with the Biomet/Lorenz Microfixation TMJ replacement system [40]	73	8.11
2	Manganello-Souza, Mariani	2003	Temporomandibuar joint ankylosis: Report of 14 cases [41]	72	3.78
3	Ribeiro-Dasilva et al	2009	Estrogen receptor-alpha polymosphisms and predisposition to TMJ disorder [42]	70	5.38
4	Cevidanes et al	2014	3D osteoarthritic changes in TMJ condylar morphology correlates with specific systemic and local biomarkers of disease [43]	52	6.50
5	Vasconcelos et al	2009	Surgical treatment of temporomandibular joint ankylosis: Follow-up of 15 cases and literature review [44]	43	3.30
6	Dela Coleta et al	2009	Maxillo-mandibular counter-clockwise rotation and mandibular advancement with TMJ Concepts ® total joint prostheses Part I – Skeletal and dental stability [45]	41	3.15
7	Wolford, Gonçalves	2015	Condylar resorption of the temporomandibular joint: How do we treat it? [46]	38	5.42
8	Firmino et al	2017	Oral health literacy and associated oral conditions. A systematic review [47]	36	7.20
9	Pinto et al	2009	Maxillo-mandibular counter-clockwise rotation and mandibular advancement with TMJ Concepts ® total joint prostheses Part III – Pain and dysfunction outcomes [48]	33	2.53
10	Pereira et al	1995	Surgical treatment of the fractured and dislocated condylar process of the mandible [49]	32	1.18
Maxillofacial trauma					
1	Brasileiro, Passeri	2006	Epidemiological analysis of maxillofacial fractures in Brazil: A 5-year retrospective study [50]	199	12.43
2	Kramer et al	2003	Traumatic dental injuries in Brazilian preschool children [51]	120	6.31
3	Gabrielli et al	2003	Fixation of mandibular fractures with 2.0-mm miniplates: Review of 191 cases [52]	106	5.57
4	Rocha, Cardoso	2001	Traumatized permanent teeth in Brazilian children assisted at the Federal University of Santa Catarina, Brazil [53]	103	4.90

5	Oliveira et al	2007	Traumatic dental injuries and associated factors among Brazilian preschool children [54]	96	6.40
6	Chrcanovic et al	2012	1,454 mandibular fractures: A 3-year study in a hospital in Belo Horizonte, Brazil [55]	88	8.80
7	Cunha et al	2001	Oral trauma in Brazilian patients aged 0-3 years [56]	82	3.90
8	Passeri et al	1993	Complications of nonrigid fixation of mandibular angle fractures [57]	75	2.58
9	Passeri et al	1993	Relationship of substance-abuse to complications with mandibular fractures [58]	69	2.37
10	Cardoso, Rocha	2002	Traumatized primary teeth in children assisted at the Federal University of Santa Catarina, Brazil [59]	64	3.20
Cleft lip					
1	Kondo et al	2002	Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes [8]	582	29.10
2	Zucchero et al	2004	Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft or palate [60]	433	24.05
3	Beaty et al	2010	A genome-wide association study of cleft lip with and without cleft palate identifies risk variants near MAFB and ABCA4 [61]	408	34.00
4	Suzuki et al	2000	Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia [62]	244	11.09
5	Jezewski et al	2003	Complete sequencing shows a role for MSX1 in non-syndromic cleft lip and palate [63]	208	10.94
6	Mastroiacovo et al	2011	Prevalence at birth of cleft lip with or without cleft palate: Data from the international perinatal database of typical oral clefts (IPDTOC) [64]	196	17.81
7	Vieira et al	2005	Medical sequencing of candidate genes for nonsyndromic cleft lip and palate [65]	182	10.70
8	Rooryck et al	2011	Mutations in lectin complement pathway genes COLEC11 and MASP1 cause 3MC syndrome [66]	158	14.36
9	Jenkins et al	2007	RAB23 mutations in carpenter syndrome imply an unexpected role for hedgehog signaling in cranial-suture development and obesity [67]	152	10.13
10	Lines et al	2012	Haploinsufficiency of a spliceosomal GTPase encoded by EFTUD2 causes mandibulofacial dysostosis with microcephaly [68]	126	12.60
Odontogenic infections					
1	Siqueira, Rocas	2013	Microbiology and treatment of acute apical abscesses [69]	101	11.22
2	Sancho et al	1999	Descending necrotizing mediastinitis: a retrospective surgical experience [70]	61	2.65
3	Sato et al	2009	Eight-year retrospective study of odontogenic origin infections in a postgraduation program on oral and maxillofacial surgery [71]	32	2.46
4	Brito et al	2017	Deep neck abscesses: study of 101 cases [72]	30	6.00
5	Fernandes et al	2015	Association between immunologic parameters, glycemic control, and postextraction complications in patients with type 2 diabetes [73]	20	2.85
6	Moraes et al	2015	Distribution of genes related to antimicrobial resistance in different oral environments: a systematic review [74]	17	2.42
7	Martins et al	2017	The use of antibiotics in odontogenic infections: what is the best choice? A systematic review [75]	15	2.14
8	Antunes et al	2011	Brain abscess of odontogenic origin [76]	13	1.18
9	de Medeiros et al	2012	Orbital abscess during endodontic treatment: A case report [77]	10	1.00
10	Antunes et al	2013	Extensive cervical necrotizing fasciitis of odontogenic origin [78]	8	0.88

Table 3. Most frequently cited journals and their h-index

Journals	h-index	Number of publications						
		trauma	third molar	orthognathic	oral pathology	TMJ	cleft lip	odontogenic infections
American J Orthodontics Dental Orthopedics	**129**			39			18	
Angle Orthodontist	**91**			10			11	
British JOMS	**78**					4		
Brazilian J ORL	**36**				19		12	3
Brazilian Oral Research	**50**	19			34	3	12	
Cleft	**83**						146	
Clinical Oral Investigation	**88**		13				9	
Cranio	**47**					10		
Dental Traumatology	**86**	57						
International JOMS	**105**	35	36	66		13		
J Applied Oral Sciences	**49**	11		14			25	
J Dental Research	**192**				22		9	2
J Craniofacial Surgery	**76**	76	16	54	38	10	72	7
J Cranio Maxillofacial Surgery	**82**	24	8	26		7		
JOMS	**126**	44	34	53	21	11		3
J Oral Pathology Medicine	**88**				69			
J Maxillofacial Oral Surgery	**24**		6					
Medicina Oral Patologia Oral Cirugia Bucal	**61**		23		45	4		
OMFS	**34**	11	11	17		3		
Oral Diseases	**91**				37		9	2
Oral Oncology	**121**				36			
Quintessence International	**74**	13	5					
Triple Oral	**126**		10	11	74	5		

Legend: J – Journal; JOMS – Journal of Oral and Maxillofacial Surgery; ORL – Otorhinolaringology; OMFS – Oral and Maxillofacial Surgery; Triple Oral – Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology

DISCUSSION

The objective of this paper was to conduct a bibliometric examination of Brazilian literature in oral and maxillofacial surgery, encompassing the compilation of the ten most frequently cited articles across seven distinct topics. It is important to note that bibliometrics does not aim for surgical precision [7]. Statistical tests were conducted to enhance the comprehensibility of the information. Bibliometrics enables researchers and readers to track the development of research within a specific field over time, providing insights into both its progression and potential limitations [79].

Similar to many other fields, the United States takes the lead in the quantity of publications, with Brazil following closely behind. Two authors are considered to be the most prolific worldwide, Prof. Ricardo Santiago Gomez and Prof. Belmiro Cavalcanti do Egito Vasconcelos. Both are considered as a good h-index (n≥20) [80]. The h-index of the publications was considered good, reaching almost outstanding (n=39.21). The significance of this index varies across different scientific disciplines. In the field of OMFS, this compilation can be regarded as having a high impact, indicative of the increasing number of high-quality studies in this

area. This trend can be observed through comparisons of total citation counts, h-index values, and citation density over time. The recognition of highly prolific authors emphasizes the crucial role of individual contributions in influencing the research landscape.

Cleft lip and oral pathology are the subjects with a larger number of citations and higher citation density. On the other hand, odontogenic infections is a topic that deserves more attention, with more publications and articles in top-level journals. More than 95% of the articles were published in English language, according to other publications [81,82]. A national exchange or even an international cooperation program could benefit universities to reach a higher level of research. A significant number of articles were published in high or medium ranked journals, with a mean h-index of 90.39. Open access articles were cited as subscription articles, but without statistical significance ($p = 0.88031$).

The analysis of trends and patterns observed in the data reveals several noteworthy insights into the landscape of OMFS research. The upward trend in the number of publications across all topics underscores the growing interest and activity within the field, reflecting advancements in technology, increasing collaboration, and expanding knowledge domains. Particularly notable is the robust trend observed in orthognathic surgery, oral pathology, cleft lip, maxillofacial trauma, and third molar topics, indicating areas of significant research focus and potential avenues for further exploration. These trends suggest a dynamic and vibrant research environment within OMFS, with implications for future research priorities, interdisciplinary collaboration, and the dissemination of knowledge to advance clinical practice and improve patient outcomes.

While the USA maintains its leading position in terms of the sheer number of publications, Brazil emerges as a significant contributor, ranking among the top ten most productive countries across all subjects assessed. This highlights Brazil's growing influence and participation in shaping the global discourse within the field. Moreover, the upward trend in the number of publications observed in Brazil mirrors broader global trends, indicating a shared emphasis on advancing research and innovation in OMFS. While aligning with global trends in many respects, Brazil's emphasis on certain topics and its contributions to the overall research landscape reflect its distinct priorities and strengths. In comparison, Africa and the Middle East exhibit lower levels of research output [6,83]. This underscores Brazil's position as a leading contributor to OMFS research, with its efforts playing a crucial role in advancing the field on a global scale. Furthermore, Brazil's increasing prominence in OMFS research underscores the importance of international collaboration, as partnerships with researchers and institutions from around the world can further enrich the field's knowledge base and foster interdisciplinary innovation.

Appropriate title and keywords are critical to enable search retrieval, rendering a more precise, sensitive and efficient bibliographic search [84,85]. An effective article widespread can be achieved by selecting adequate keywords [86,87]. VOSviewer is a useful, free and easy-to-use tool for selecting these keywords and other actions [88,89].

This study's limitations encompass the exclusive reliance on data from WS, which may introduce bias by potentially excluding relevant publications indexed in other databases like PubMed and Google Scholar (GS). PubMed, despite being a widely used database in the medical field, does not employ citation analysis, while GS does, albeit necessitating other software for comprehensive analysis. The lack of data from these additional databases could result in an incomplete representation of the global landscape of OMFS research, potentially overlooking significant contributions or trends. Moreover, the scarcity of geographic bibliometric analyses in the field underscores the need for more comprehensive data collection methods to provide a more holistic understanding of regional variations and contributions to OMFS research.

Future research endeavors could focus on integrating data from multiple databases to provide a more comprehensive overview of OMFS research trends and patterns globally. Additionally, exploring collaborative networks and international partnerships within OMFS research could offer valuable insights into emerging trends and areas of mutual interest, guiding future research priorities and fostering interdisciplinary collaboration to advance the field. This bibliometric analysis serves as a foundation for identifying gaps and trends in OMFS research, providing a roadmap for future investigations aimed at addressing these knowledge deficiencies and driving innovation in the field.

CONCLUSIONS

This study presented a compilation of the most referenced articles across seven distinct topics. The bibliometric data validate that

Brazilian literature on OMFS ranks among the most prolific and frequently cited globally. The prominence of Brazil among the top ten most productive countries across all subjects highlights the nation's growing contribution to the global body of literature in OMFS. This work provides a valuable reference and stimulus for the growing body of quality publications for oral and maxillofacial surgeons, academics and researchers. Choosing an appropriate title and keywords, in addition to publishing in English language, are helpful strategies for disseminating the article.

Informed Consent: Not applicable.

Conflict of interest: The authors declare no conflicts of interest to disclose.

Funding: No source of funding.

Ethical Approval: Not applicable since this was a bibliometric study.

Author Contributions: Conception: G, R; B, MA - Design: G, R; S YS - Supervision: B; AM - Materials: G,R; B, MA; L,A - Data Collection and/or Processing: G,R; B, MA; L,A - Analysis and/or Interpretation: G,R; B, MA; L,A - Literature: S, YS; B, AM - Review: All authors - Writing: All authors - Critical Review: All authors

REFERENCES

[1] Laitman JT (2015) Through the eyes of Galileo's heirs: deciphering the laws of nature through the language of mathematics. Anat Rec (Hoboken) 298:3–4. https://doi.org/10.1002/ar.23098

[2] Martínez MA, Herrera M, López-Gijón J, Herrera-Viedma E (2014) H-Classics: Characterizing the concept of citation classics through H-index. Scientometr 98:1971–83. https://doi.org/10.1007/s11192-013-1155-9

[3] Bulut E, Dokur M, Basar E (2020) The Top 100 Cited Articles on Ocular Trauma: A Bibliometric Analysis. Eur J Ther 26:322–31. https://doi.org/10.5152/EurJTher.2020.19115

[4] Balel Y (2023) Global Mapping Analysis of Maxillofacial Trauma Literature From 1980-2022. Eur J Ther 29:445–57. https://doi.org/10.58600/eurjther1632

[5] Melhem-Elias F, Reis BAQ, Afonso FAC, Barretto MDA, Deboni MCZ (2022) An innovative universal protocol for orthognathic surgery three-dimensional virtual simulation. Int J Oral Maxillofac Surg 22:358–7. https://doi.org/10.1016/j.ijom.2022.09.001

[6] Grillo R, Al-Moraissi E, Balel Y, Eshghpour M, Samieirad S, Teixeira RG (2022) Oral and maxillofacial literature from Middle East: a bibliometric analysis and list of top-100 most cited articles. J Stomatol Oral Maxillofac Surg S2468-7855:00282–8. https://doi.org/10.1016/j.jormas.2022.09.014

[7] Hicks D, Wouters P, Waltman L, De Rijcke S, Rafols I (2015) Bibliometrics: The Leiden Manifesto for research metrics. Nature 520:429–31. https://doi.org/10.1038/520429a

[8] Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, et al (2002) Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nat Genet 32:285–9. https://doi.org/10.1038/ng985

[9] Rivera C (2015) Essentials of oral cancer. Int J Clin Exp Path 8:11884–94.

[10] Laureano Filho JR, De Oliveira e Silva ED, Camargo IB, Gouveia FMV (2005) The influence of cryotherapy on reduction of swelling, pain and trismus after third-molar extraction: a preliminary study. J Am Dent Assoc 136:774–8. https://doi.org/10.14219/jada.archive.2005.0261

[11] de Santana-Santos T, de Souza-Santos JAS, Martins-Filho PRS, da Silva LCF, de Oliveira e Silva ED, Gomes ACA (2013) Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. Med Oral Patol Oral Cir Bucal 18:e65–70. https://doi.org/10.4317/medoral.18039

[12] Gomes ACA, do Egito Vasconcelos BC, de Oliveira Silva ED, de França Caldas A, Neto ICP (2008) Sensitivity and specificity of pantomography to predict inferior alveolar nerve damage during extraction of impacted lower third molars. J Oral Maxillofac Surg 66:256–9. https://doi.org/10.1016/j.joms.2007.08.020

[13] Alcântara CEP, Falci SGM, Oliveira-Ferreira F, Santos CRR, Pinheiro MLP (2014) Pre-emptive effect of dexamethasone and methylprednisolone on pain, swelling, and trismus after third molar surgery: a split-mouth randomized triple-blind

clinical trial. Int J Oral Maxillofac Surg 43:93–8. https://doi.org/10.1016/j.ijom.2013.05.016

[14] Falci SGM, De Castro CR, Santos RC, De Souza Lima LD, Ramos-Jorge ML, Botelho AM, et al (2012) Association between the presence of a partially erupted mandibular third molar and the existence of caries in the distal of the second molars. Int J Oral Maxillofac Surg 41:1270–4. https://doi.org/10.1016/j.ijom.2012.03.003

[15] Ferreira Cerqueira PR, Vasconcelos BCE, Bessa-Nogueira RV (2004) Comparative study of the effect of a tube drain in impacted lower third molar surgery. J Oral Maxillofac Surg 62:57–61. https://doi.org/10.1016/s0278-2391(03)00675-x

[16] Colombini BL, Modena KCS, Calvo AM, Sakai VT, Giglio FPM, Dionísio TJ, et al (2006) Articaine and mepivacaine efficacy in postoperative analgesia for lower third molar removal: a double-blind, randomized, crossover study. Oral Surg Oral Med Oral Path Oral Radiol Endod 102:169–74. https://doi.org/10.1016/j.tripleo.2005.09.003

[17] Santos CF, Modena KCS, Giglio FPM, Sakai VT, Calvo AM, Colombini BL, et al (2007) Epinephrine concentration (1:100,000 or 1:200,000) does not affect the clinical efficacy of 4% articaine for lower third molar removal: a double-blind, randomized, crossover study. J Oral Maxillofac Surg 65:2445–52. https://doi.org/10.1016/j.joms.2007.04.020

[18] Rosa AL, Carneiro MG, Lavrador MA, Novaes AB (2002) Influence of flap design on periodontal healing of second molars after extraction of impacted mandibular third molars. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93:404–7. https://doi.org/10.1067/moe.2002.122823

[19] Célio-Mariano R, De Melo WM, Carneiro-Avelino C (2012) Comparative radiographic evaluation of alveolar bone healing associated with autologous platelet-rich plasma after impacted mandibular third molar surgery. J Oral Maxillofac Surg 70:19–24. https://doi.org/10.1016/j.joms.2011.03.028

[20] de Oliveira AEF, Cevidanes LHS, Phillips C, Motta A, Burke B, Tyndall D (2009) Observer reliability of three-dimensional cephalometric landmark identification on cone-beam computerized tomography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 107:256–65. https://doi.org/10.1016/j.tripleo.2008.05.039

[21] Aragón MLC, Pontes LF, Bichara LM, Flores-Mir C, Normando D (2016) Validity and reliability of intraoral scanners compared to conventional gypsum models measurements: a systematic review. Eur J Orthod 38:429–34. https://doi.org/10.1093/ejo/cjw033

[22] Mattos CT, Vilani GNL, Sant'Anna EF, Ruellas ACO, Maia LC (2011) Effects of orthognathic surgery on oropharyngeal airway: a meta-analysis. Int J Oral Maxillofac Surg 40:1347–56. https://doi.org/10.1016/j.ijom.2011.06.020

[23] Gonçalves JR, Cassano DS, Wolford LM, Santos-Pinto A, Márquez IM (2008) Postsurgical stability of counterclockwise maxillomandibular advancement surgery: affect of articular disc repositioning. J Oral Maxillofac Surg 66:724–38. https://doi.org/10.1016/j.joms.2007.11.007

[24] Garcia Esperão PT, De Oliveira BH, De Oliveira Almeida MA, Kiyak HA, Mendes Miguele JA (2010) Oral health-related quality of life in orthognathic surgery patients. Am J Orthod Dentofac Orthoped 137:790–5. https://doi.org/10.1016/j.ajodo.2008.08.031

[25] Weissheimer A, Menezes LM, Koerich L, Pham J, Cevidanes LHS (2015) Fast three-dimensional superimposition of cone beam computed tomography for orthopaedics and orthognathic surgery evaluation. Int J Oral Maxillofac Surg 44:1188–96. https://doi.org/10.1016/j.ijom.2015.04.001

[26] Nicodemo D, Pereira MD, Ferreira LM (2008) Effect of orthognathic surgery for class III correction on quality of life as measured by SF-36. Int J Oral Maxillofac Surg 37:131–4. https://doi.org/10.1016/j.ijom.2007.07.024

[27] Magalhães IB, Pereira LJ, Marques LS, Gameiro GH (2010) The influence of malocclusion on masticatory performance. A systematic review. Angle Orthod 80:981–7. https://doi.org/10.2319/011910-33.1

[28] Brasileiro BF, Grempel RG, Ambrosano GMB, Passeri LA (2009) An in vitro evaluation of rigid internal fixation techniques for sagittal split ramus osteotomies: advancement surgery. J Oral Maxillofac Surg 67:809–17. https://doi.org/10.1016/j.joms.2008.11.009

[29] Haas OL, Becker OE, De Oliveira RB (2014) Computer-aided planning in orthognathic surgery-systematic review. Int J Oral Maxillofac Surg 44(3):329–42. https://doi.org/10.1016/j.ijom.2014.10.025

[30] Trindade IEK, Yamashita RP, Suguimoto RM, Mazzottini

R, Trindade AS (2003) Effects of orthognathic surgery on speech and breathing of subjects with cleft lip and palate: acoustic and aerodynamic assessment. Cleft Palate-Craniofac J 40:54–64. https://doi.org/10.1597/1545-1569_2003_040_0054_eoosos_2.0.co_2

[31] Guha N, Boffetta P, Wünsch Filho V, Eluf Neto J, Shangina O, Zaridze D, et al (2007) Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: Results of two multicentric case-control studies. Am J Epid 166:1159–73. https://doi.org/10.1093/aje/kwm193

[32] Barreto DC, Gomez RS, Bale AE, Boson WL, De Marco L (2000) PTCH gene mutations in odontogenic keratocysts. J Dent Res 79(6):1418–22. https://doi.org/10.1177/00220345000790061101

[33] Fregnani ER, Pires FR, Falzoni R, Lopes MA, Vargas PA (2003) Lipomas of the oral cavity: Clinical findings, histological classification and proliferative activity of 46 cases. Int J Oral Maxillofac Surg 32:49–53. https://doi.org/10.1054/ijom.2002.0317

[34] Pires FR, Pringle GA, de Almeida OP, Chen SY (2007) Intra-oral minor salivary gland tumors: A clinicopathological study of 546 cases. Oral Oncol 43:463–70. https://doi.org/10.1016/j.oraloncology.2006.04.008

[35] Schlecht N, Franco E, Pintos J, Negassa A, Kowalski L, Oliveira B, et al (1999) Interaction between tobacco and alcohol consumption and the risk of cancers of the upper aero-digestive tract in Brazil. Am J Epid 150:1129–37. https://doi.org/10.1093/oxfordjournals.aje.a009938

[36] Lopes M, Kowalski L, Santos G, de Almeida O (1999) A clinicopathologic study of 196 intraoral minor salivary gland tumours. J Oral Pathol Med 28:264–7. https://doi.org/10.1111/j.1600-0714.1999.tb02036.x

[37] Crivelini MM, De Araújo VC, De Sousa SOM, De Araújo NS (2003) Cytokeratins in epithelia of odontogenic neoplasms. Oral Dis 9:1–6. https://doi.org/10.1034/j.1601-0825.2003.00861.x

[38] Velly AM, Franco EL, Schlecht N, Pintos J, Kowalski LP, Oliveira B V., et al (1998) Relationship between dental factors and risk of upper aerodigestive tract cancer. Oral Oncol 34:284–91.

[39] Ledesma-Montes C, Gorlin RJ, Shear M, Prætorius F, Mosqueda-Taylor A, Altini M, et al (2008) International collaborative study on ghost cell odontogenic tumours: Calcifying cystic odontogenic tumour, dentinogenic ghost cell tumour and ghost cell odontogenic carcinoma. J Oral Pathol Med 37(5):302–8. https://doi.org/10.1111/j.1600-0714.2007.00623.x

[40] Leandro LFL, Ono HY, De Souza Loureiro CC, Marinho K, Garcia Guevara HÁ (2013) A ten-year experience and follow-up of three hundred patients fitted with the Biomet/Lorenz Microfixation TMJ replacement system. Int J Oral Maxillofac Surg 42:1007–13. https://doi.org/10.1016/j.ijom.2013.04.018

[41] Manganello-Souza LC, Mariani PB (2003) Temporomandibudar joint ankylosis: Report of 14 cases. Int J Oral Maxillofac Surg 32:24–9. https://doi.org/10.1054/ijom.2002.0308

[42] Ribeiro-Dasilva MC, Peres Line SR, Leme Godoy dos Santos MC, Arthuri MT, Hou W, Fillingim RB, et al (2009) Estrogen Receptor-α Polymorphisms and Predisposition to TMJ Disorder. J Pain 10:527–33. https://doi.org/10.1016/j.jpain.2008.11.012

[43] Cevidanes LHS, Walker D, Schilling J, Sugai J, Giannobile W, Paniagua B, et al (2014) 3D osteoarthritic changes in TMJ condylar morphology correlates with specific systemic and local biomarkers of disease. Osteoarthritis Cartilage 22:1657–67. https://doi.org/10.1016/j.joca.2014.06.014

[44] Vasconcelos BCE, Porto G, Bessa-Nogueira R, do Nascimento M (2009) Surgical treatment of temporomandibular joint ankylosis: Follow-up of 15 cases and literature review. Med Oral Patol Oral Cir Bucal 14:e34–8.

[45] Dela Coleta KE, Wolford LM, Gonçalves JR, dos Santos Pinto A, Pinto LP, Cassano DS (2009) Maxillo-mandibular counter-clockwise rotation and mandibular advancement with TMJ Concepts® total joint prostheses. Part I - Skeletal and dental stability. Int J Oral Maxillofac Surg 38:126–38. https://doi.org/10.1016/j.ijom.2008.11.024

[46] Wolford LM, Gonçalves JR (2015) Condylar Resorption of the Temporomandibular Joint. How Do We Treat It? Oral Maxillofac Surg Clin North Am 27:47–67. https://doi.org/10.1016/j.coms.2014.09.005

[47] Firmino RT, Ferreira FM, Paiva SM, Granville-Garcia

AF, Fraiz FC, Martins CC (2017) Oral health literacy and associated oral conditions: A systematic review. J Am Dent Assoc 148:604–13. https://doi.org/10.1016/j.adaj.2017.04.012

[48] Pinto LP, Wolford LM, Buschang PH, Bernardi FH, Gonçalves JR, Cassano DS (2009) Maxillo-mandibular counter-clockwise rotation and mandibular advancement with TMJ Concepts® total joint prostheses. Part III - Pain and dysfunction outcomes. Int J Oral Maxillofac Surg 38:326–31. https://doi.org/10.1016/j.ijom.2008.11.016

[49] Pereira MD, Marques A, Ishizuka M, Keira SM, Brenda E, Wolosker AB (1995) Surgical treatment of the fractured and dislocated condylar process of the mandible. J Craniomaxillofac Surg 23:369–76. https://doi.org/10.1016/s1010-5182(05)80132-5

[50] Brasileiro BF, Passeri LA (2006) Epidemiological analysis of maxillofacial fractures in Brazil: A 5-year prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 102:28–34. https://doi.org/10.1016/j.tripleo.2005.07.023

[51] Kramer PF, Zembruski C, Ferreira SH, Feldens CA (2003) Traumatic dental injuries in Brazilian preschool children. Dent Traumatol 19:299–303. https://doi.org/10.1046/j.1600-9657.2003.00203.x

[52] Cabrini Gabrielli MA, Real Gabrielli MF, Marcantonio E, Hochuli-Vieira E (2003) Fixation of mandibular fractures with 2.0-mm miniplates: Review of 191 cases. J Oral Maxillofac Surg 61:430–6. https://doi.org/10.1053/joms.2003.50083

[53] Rocha M, Cardoso M (2001) Traumatized permanent teeth in Brazilian children assisted at the Federal University of Santa Catarina, Brazil. Dent Traumatol 17:245–9. https://doi.org/10.1034/j.1600-9657.2001.170601.x

[54] Oliveira LB, Marcenes W, Ardenghi TM, Sheiham A, Bönecker M (2007) Traumatic dental injuries and associated factors among Brazilian preschool children. Dent Traumatol 23:76–81. https://doi.org/10.1111/j.1600-9657.2005.00413.x

[55] Chrcanovic BR, Abreu MHNG, Freire-Maia B, Souza LN (2012) 1,454 mandibular fractures: A 3-year study in a hospital in Belo Horizonte, Brazil. J Craniomaxillofac Surg 40:116–23. https://doi.org/10.1016/j.jcms.2011.03.012

[56] Cunha R, Pugliesi D, Vieira A (2001) Oral trauma in Brazilian patients aged 0-3 years. Dent Traumatol 17:210–2. https://doi.org/10.1034/j.1600-9657.2001.170504.x

[57] Passeri LA, Ellis E, Sinn DP (1993) Complications of nonrigid fixation of mandibular angle fractures. J Oral Maxillofac Surg 51:382–4. https://doi.org/10.1016/s0278-2391(10)80350-7

[58] Passeri LA, Ellis E, Sinn DP (1993) Relationship of substance abuse to complications with mandibular fractures. J Oral Maxillofac Surg 51:22–5. https://doi.org/10.1016/s0278-2391(10)80383-0

[59] Cardoso M, Rocha MJC (2002) Traumatized primary teeth in children assisted at the Federal University of Santa Catarina, Brazil. Dent Traumatol 18:129–33. https://doi.org/10.1034/j.1600-9657.2002.00030.x

[60] Zucchero TM, Cooper ME, Maher BS, Daack-Hirsch S, Nepomuceno B, Ribeiro L, et al (2004) Interferon Regulatory Factor 6 (IRF6) Gene Variants and the Risk of Isolated Cleft Lip or Palate. N Engl J Med 351:769–80. https://doi.org/10.1056/NEJMoa032909

[61] Beaty TH, Murray JC, Marazita ML, Munger RG, Ruczinski I, Hetmanski JB, et al (2010) A genome-wide association study of cleft lip with and without cleft palate identifies risk variants near MAFB and ABCA4. Nat Genet 42:525–9. https://doi.org/10.1038/ng.580

[62] Suzuki K, Hu D, Bustos T, Zlotogora J, Richieri-Costa A, Helms JA, et al (2000) Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia. Nat Genet 25:427–30. https://doi.org/10.1038/78119

[63] Jezewski PA, Vieira AR, Nishimura C, Ludwig B, Johnson M, O'Brien SE, et al (2003) Complete sequencing shows a role for MSX1 in non-syndromic cleft lip and palate. J Med Genet 40:399–407. https://doi.org/10.1136/jmg.40.6.399

[64] Mastroiacovo P, Maraschini A, Leoncini E, Mossey P, Bower C, Castilla EE, et al (2011) Prevalence at birth of cleft lip with or without cleft palate: Data from the International Perinatal Database of Typical Oral Clefts (IPDTOC). Cleft Palate-Craniofac J 48:66–81. https://doi.org/10.1597/09-217

[65] Vieira AR, Avila JR, Daack-Hirsch S, Dragan E, Félix TM,

Rahimov F, et al (2005) Medical Sequencing of Candidate Genes for Nonsyndromic Cleft Lip and Palate. PLoS Genet 1:e64. https://doi.org/10.1371/journal.pgen.0010064

[66] Rooryck C, Diaz-Font A, Osborn DPS, Chabchoub E, Hernandez-Hernandez V, Shamseldin H, et al (2011) Mutations in lectin complement pathway genes COLEC11 and MASP1 cause 3MC syndrome. Nat Genet 43:197–203. https://doi.org/10.1038/ng.757

[67] Jenkins D, Seelow D, Jehee FS, Perlyn CA, Alonso LG, Bueno DF, et al (2007) RAB23 mutations in carpenter syndrome imply an unexpected role for Hedgehog signaling in cranial-suture development and obesity. Am J Hum Genet 80:1162–70. https://doi.org/10.1086/518047

[68] Lines MA, Huang L, Schwartzentruber J, Douglas SL, Lynch DC, Beaulieu C, et al (2012) Haploinsufficiency of a spliceosomal GTPase encoded by EFTUD2 causes mandibulofacial dysostosis with microcephaly. Am J Hum Genet 90:369–77. https://doi.org/10.1016/j.ajhg.2011.12.023

[69] Siqueira JF, Rôças IN (2013) Microbiology and treatment of acute apical abscesses. Clin Microbiol Rev 26:255–73. https://doi.org/10.1128/CMR.00082-12

[70] Sancho LMM, Minamoto H, Fernandez A, Sennes LU, Jatene FB (1999) Descending necrotizing mediastinitis: A retrospective surgical experience. Eur J Cardiothorac Surg 16:200–5. https://doi.org/10.1016/s1010-7940(99)00168-2

[71] Sato FRL, Hajala FAC, Filho FWVF, Moreira RWF, de Moraes M (2009) Eight-Year Retrospective Study of Odontogenic Origin Infections in a Postgraduation Program on Oral and Maxillofacial Surgery. J Oral Maxillofac Surg 67:1092–7. https://doi.org/ 10.1016/j.joms.2008.09.008

[72] Brito TP, Hazboun IM, Fernandes FL, Bento LR, Zappelini CEM, Chone CT, et al (2017) Deep neck abscesses: study of 101 cases. Braz J Otorhinolaryngol 83:341–8. https://doi.org/10.1016/j.bjorl.2016.04.004

[73] Fernandes KS, Glick M, De Souza MS, Kokron CM, Gallottini M (2015) Association between immunologic parameters, glycemic control, and postextraction complications in patients with type 2 diabetes. J Am Dent Assoc 146:592–9. https://doi.org/10.1016/j.adaj.2015.02.014

[74] Moraes LC, Só MVR, Da Silva Dal Pizzol T, Ferreira MBC, Montagner F (2015) Distribution of genes related to antimicrobial resistance in different oral environments: A systematic review. J Endod 41:434–41. https://doi.org/10.1016/j.joen.2014.12.018

[75] Martins JR, Chagas OL, Velasques BD, Bobrowski ÂN, Correa MB, Torriani MA (2017) The Use of Antibiotics in Odontogenic Infections: What Is the Best Choice? A Systematic Review. J Oral Maxillofac Surg 75:2606.e1-2606.e11. https://doi.org/10.1016/j.joms.2017.08.017

[76] Antunes AA, De Santana Santos T, De Carvalho RWF, Avelar RL, Pereira CU, Pereira JC (2011) Brain abscess of odontogenic origin. J Craniofac Surg 22:2363–5. https://doi.org/10.1097/SCS.0b013e318231e585

[77] de Medeiros EHP, Pepato AO, Sverzut CE, Trivellato AE (2012) Orbital abscess during endodontic treatment: A case report. J Endod 38:1541–3. https://doi.org/10.1016/j.joen.2012.06.039

[78] Antunes AA, Avelar RL, De Melo WM, Pereira-Santos D, Frota R (2013) Extensive cervical necrotizing fasciitis of odontogenic origin. J Craniofac Surg 24(6). https://doi.org/10.1097/SCS.0b013e31829ad57b

[79] Martelli AJ, Martelli RAM, Martelli DRB, das Neves LT, Martelli Junior H (2021) The 100 most-cited papers in oral medicine and pathology. Braz Oral Res 35:1–14. https://doi.org/10.1590/1807-3107bor-2021.vol35.0020

[80] Hirsch JE. An index to quantify an individual's scientific research output. Proc Natl Acad Sci USA 102:16569–72. https://doi.org/10.1073/pnas.0507655102

[81] Shaw P, Lokhotiya K, Kumarasamy C, Sunil K, Suresh D, Shetty S, et al (2022) Mapping Research on miRNAs in Cancer: A Global Data Analysis and Bibliometric Profiling Analysis. Pathophysiology 29:66–80. https://doi.org/10.3390/pathophysiology29010007

[82] Anker MS, Hadzibegovic S, Lena A, Haverkamp W (2019) The difference in referencing in Web of Science, Scopus, and Google Scholar. ESC Heart Fail 6:1291. https://doi.org/10.1002/ehf2.12583

[83] Grillo R, Lucamba A, Sohal KS, Adebayo ET, Khemis M, Teixeira RG (2023) Evolution of African Oral and Maxillofacial Literature Through Years: A Bibliometric Analysis. J Maxillofac Oral Surg 1–8. https://doi.

org/10.1007/s12663-023-01941-4

[84] USA: US National Library of Medicine National Institute of Health. Principles of MEDLINE Subject Indexing [Internet]. U.S. National Library of Medicine; Available from: https://www.nlm.nih.gov/bsd/disted/meshtutorial/principlesofmedlinesubjectindexing/principles/index.html

[85] Baumann N (2016) How to use the medical subject headings (MeSH). Int J Clin Pract 70:171–4. https://doi.org/10.1111/ijcp.12767

[86] Mondal H, Mondal S, Mondal S (2018) How to choose title and keywords for manuscript according to medical subject headings. Indian J Vasc Endovasc Surg 5:141–4. https://doi.org/10.4103/ijves.ijves_15_18

[87] Grillo R (2021) Bibliometric trending analysis of complications related to facial non-surgical aesthetic procedures: a retrospective study. Prosthodontics 71:228–33. https://doi.org/10.5114/ps/140080

[88] Grillo R, Lopes T, Teixeira RG (2022). Top 50 covid and oral health articles: A 2021 altmetric analysis. J Oral Biol Craniofac Res 12:458–64. https://doi.org/10.1016/j.jobcr.2022.05.010

[89] Bozkurt AS (2023) Bibliometric Analysis of the Published Studies on the Kindling Model between 1980 and 2023. Eur J Ther 29:188–93. https://doi.org/10.58600/eurjther.20232902-396.y

How to Cite;

Grillo R, Aparecida Brozoski M, Lucamba A, Slusarenko da Silva Y, Meireles Borba A (2024) A Science Mapping Analysis of Brazilian Literature on Oral and Maxillofacial Surgery. 30(2)102-116. Eur J Ther. https://doi.org/10.58600/eurjther1999

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):117-124.
https://doi.org/10.58600/eurjther1943

Original Research

Findings on Sleep of Children with Cerebral Palsy and Their Mothers' Sleep and Emotional Intelligence

Numan Bulut [1], Bilge Nur Yardımcı-Lokmanoğlu [1], İpek Alemdaroğlu-Gürbüz [1], Selen Serel Arslan[1], Öznur Yılmaz [1]

[1] Hacettepe University, Faculty of Physical Therapy and Rehabilitation, Ankara, Türkiye

Received: 2023-11-23 **Accepted:** 2023-12-24 **Published Online:** 2023-12-26

Corresponding Author
Numan Bulut, PT, PhD, Assist Prof.
Address: Hacettepe University, Faculty of Physical Therapy and Rehabilitation, 06100, Samanpazarı, Altındağ, Ankara, Türkiye
E-mail: nmn60_90@hotmail.com

ABSTRACT

Objective: This study was aimed to explore (i) the sleep characteristics of children with cerebral palsy (CP), and the sleep and emotional intelligence results of their mothers, and (ii) the relationship between these parameters both with each other and with demographic characteristics of the children and their mothers.

Methods: Thirty-three children with CP and their mothers were included in this study. The functional level of children was evaluated with the Gross Motor Function Classification System (GMFCS), while sleep parameters with Child Sleep Habits Questionnaire-Abbreviated Form (CSHQ-AF). Sleep quality and emotional intelligence of mothers were evaluated by The Pittsburg Sleep Quality Index (PSQI) and Revised Schutte Emotional Intelligence Scale (RSEIS), successively.

Results: The highest percentage of children with CP participating in the study was at level 3 (GMFCS) with 24.24%. The mean sleep score of children with CP, according to CSHQ-AF, was 50.33 (SD: 9.38) points. Twenty-nine (87.9%) of children with CP had pediatric sleep problem while 17 (51.5%) of mothers had poor sleep quality. The total score of the mothers in the RSEIS was 149.54 (SD: 16.94). No relationship was found between sleep and emotional intelligence of mothers with sleep of children with CP ($p>0.05$).

Conclusion: The rate of sleep problems was found to be higher in children with CP compared to their mothers, as expected. The lack of relationship between sleep and emotional intelligence can be explained by the fact that both parameters can be affected by many factors.

Keywords: Cerebral Palsy, Mothers, Sleep, Emotional Intelligence

INTRODUCTION

Cerebral palsy (CP) is known as one of the most common causes of childhood disorders worldwide, although CP is seen in 2 to 3 per 1000 live births [1]. The definition of CP comprises persistent disorders of the development of movement, postural problems, activity restriction, and accompanied symptoms including secondary musculoskeletal problems and disturbances of sensation [2]. It has also been reported that sleep problems due to brain abnormalities, motor impairment, musculoskeletal problems, pain, behavioral problems, or epilepsy are more common in children with CP than in typically developing children; however, it is not always clear what the underlying causes of sleep problems are [3-10].

Sleep refers to a period of neurological and physiologic activity [11]. Newman et al. revealed that 44% of the children with CP whose Gross Motor Function Classification System (GMFCS) level are between I and V had clinically significant

sleep disorder, such as difficulty in initiating and maintaining sleep, sleep-related breathing disorders [12]. Additionally, it was also reported that children with spastic quadriplegia, those with dyskinetic CP, and those with severe visual impairment had more often difficulty in initiating and maintaining sleep; however, GMFCS level was not associated with the total sleep quality [12].

As sleep quality can be affected by several factors in children with CP, children' sleep problems affect mothers' sleep quality [10, 13]. Wayte et al. reported that sleep quality scores of children with CP were related to sleep quality scores of mothers [10]. Similar to this study, Lang et al. also reported that sleep quality in children with CP were related to caregiver sleep quality which in turn was related to the psychological health and well-being of caregiver [13]. As a result, it has been reported that caregivers may feel more stress, thus their quality of life may decrease, and their mental well-being may also be affected [14].

Emotional intelligence is defined as the ability of the natural capacity to think, use, communicate, identify, remember, learn, control, and know emotions [14]. Miguez-Torres et al. showed that the sleep duration was related to the quality of emotional intelligence ability [15], in addition to the relationship with problems in decision making and inhibitory control [16-20], which are components of emotional intelligence. The components of emotional intelligence, including stress management, were found to be related to sleep which regulates by the circadian rhythm [21]. Previous study was emphasized the circadian rhythm was also related to emotional regulation [21]. Emotional intelligence in mothers of children with CP may also be related to sleep which is affected by both their mood or stress and their children's sleep quality. However, when we look at the literature, no studies have been conducted on the sleep of children with CP and their mothers with mothers' emotional intelligence results together.

Main Points;

- Children with cerebral palsy have high risk for sleep problems although the causes of sleep problems are not always clear.
- Mothers of children with cerebral palsy have poor sleep quality, and this is not related to their emotional intelligence and sleep problems of children with cerebral palsy.
- The study highlights that sleep problems of both children with cerebral palsy and their mothers may depends on many internal and external factors such as pain, stress, or sleep environments.

This study aimed to (i) describe sleep of children with CP and their mothers, and mothers' emotional intelligence, and (ii) explore the relationship between these parameters each other and with demographic characteristics of participants.

MATERIALS AND METHODS

Design and Participants

This retrospective study was conducted in Faculty of Physical Therapy and Rehabilitation, Hacettepe University between January 2019 – September 2023. Ethical approval of this study was obtained from Health Science Research Ethics Board (SBA 23/249). Data were collected in accordance with the Declaration of Helsinki.

Children aged between 4-10 years with CP were included. Excluded from the study were children with co-morbidities and those who had undergone surgery in the previous six months. The inclusion criterion for mothers was having a child with CP, while the exclusion criteria were (i) having another person with other care needs at home, (ii) having an orthopedic, neurological, or psychological disorder, and (iii) using any medications that affect sleep.

Assessments

Demographic information and data on the children included in the study were obtained from archive files.

The level of motor activity and function: GMFCS was used to assess the clinical level of children with CP. The GMFCS is a system that assesses a child's independence in performing basic motor activities such as walking, climbing stairs, or moving with assistive equipment. In this system consisting of 5 different levels; Level 1 means that the child can walk indepedently and has a mild limitation in high-level functions, while Level 5 means that the child cannot move independently and is carried in a wheelchair by a career [22]. The Turkish version of the scale was found to have high reliability (ICC: 0.94) [23].

Sleep (for children): The sleep of the children were assessed using the Child Sleep Habits Questionnaire-Abbreviated Form

(CSHQ-AF). This questionnaire is used in children aged 4 to 10 years. It consists of 33 items with eight sub-items including parameters such as bedtime resistance, night wakings, parasomnias, and daytime sleepiness. Items are scored on a scale of 1 (rarely) - 3 (usually), with a score of 1 (rarely) given for a behavior occurring 0-1 times per week, 2 (sometimes) for 2-4 times per week, and 3 (usually) for 5-7 times per week [24]. However, certain items are scored in the reversed way. A threshold above 41 points of total score is considered to be of clinical significance [24]. Higher scores indicate a pediatric sleep disorder. The Turkish version of the questionnaire is validated (Cronbach alpha: 0.78) and reliable (ICC: 0.81) [25].

Sleep (for mothers): The Pittsburg Sleep Quality Index (PSQI) was preferred to examine the sleep quality of mothers of children with CP. The PSQI assesses the average sleep quality over the last month. The questionnaire consists of 19 questions and the 7 components [26]. Each component is scored on a 4-point Likert scale between 0-3 points, and the total score ranges between 0-21 points. A total score above five points indicates poor sleep quality [26]. The Turkish version of the questionnaire was found to have high internal consistency [27].

Emotional intelligence (for mothers): Mothers' emotional intelligence was determined with the Revised Schutte Emotional Intelligence Scale (RSEIS). Although the original form has 33 items, the revised version used in this study consists of 41 items. This scale comprises three factors: a) Optimism/Mood Regulation, b) Utilization of Emotions, and c) Appraisal of Emotions. 21 of the items are scored as forward-keyed while others are reverse-keyed [28]. Each item is scored with five point likert scale between 1-5 points [28]. RSEIS was found to be a valid (Cronbach's alpha= 0.82) and reliable (r=0.49) instrument for measuring emotional intelligence in the Turkish population [29].

Statistical Analysis

IBM SPSS Statistics 26 (Statistical Package for the Social Sciences) analysis program was used for statistical analyses. Kolmogorov-Smirnov tests were performed to evaluate whether the variables were parametrically distributed. Numerical variables were expressed as mean±standard deviation (mean (SD)) for parametric conditions, and median (interquartile range (IQR)) for non-parametric conditions. Ordinal and nominal values were expressed as number (n) and percentage (%). Independent Sample(s) T Test and Chi-square Test was performed for the comparison of numeric and nominal values. The relation between the variables were calculated using Pearson correlation coefficient under parametric conditions and Spearman correlation coefficient under non-parametric conditions. Correlation levels were accepted as weak (0.01-0.39); moderate (0.4-0.69); and strong (0.7-0.99) [30]. The value of statistical significance was set at $p<0.05$.

RESULTS

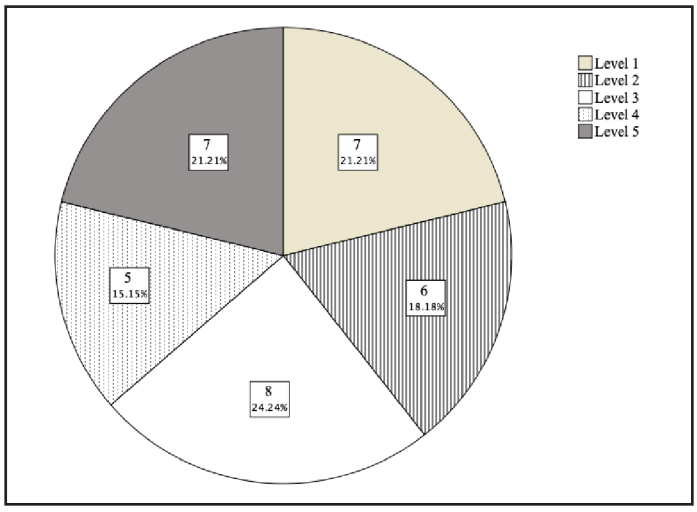
A total of 33 children with CP and their mothers participated in this study. Demographic characteristics of children and mothers are given in Table 1. Also, most of the mothers were housewives (n=29; 87.9%), and none of the mothers used alcohol.

The distribution of children with CP according to GMFCS is shown in Figure 1. There was no difference in sleep and emotional intelligence values between GMFCS levels ($p>0.05$).

Table 1. Clinical characteristics of children with Cerebral Palsy and their mothers (n=33).

	Children with Cerebral Palsy
Female - n (%)	13 (39.4)
Birth weight (kg) - median (IQR)	2.50 (1.30-3.16)
Gestational age (weeks) - median (IQR)	36.00 (32.50-39.00)
Age (years) - median (IQR)	8.00 (6.00-10.00)
Height (m) - median (IQR)	1.28 (1.10-1.35)
Weight (kg) - mean (SD)	25.73 (10.24)
Body mass index (kg/m²) - median (IQR)	15.50 (13.60-20.35)
Types of Cerebral Palsy	
Spastic - n (%)	27 (81.8)
Dyskinetic - n (%)	4 (12.1)
Ataxic - n (%)	2 (6.1)
Presence of visual impairment, n (%)	7 (21.2)
Presence of epilepsy, n (%)	0
	Mothers of Children
Age (years) - mean (SD)	36.24 (5.71)
Height (m) - mean (SD)	1.60 (5.39)
Weight (kg) - median (IQR)	68.00 (62.50-80.00)
Body mass index (kg/m²) - mean (SD)	27.34 (4.55)
The number of pregnancy - median (IQR)	2.00 (2.00-3.00)
Cigarette use (yes) - n (%)	5 (15.2)
Employment status (Employed) – n (%)	4 (12.1)

Figure 1. Distribution of the functional level of children according to the GMFCS



GMFCS: Gross Motor Functional Classfication System

The sleep parameters of both children and their mothers, and emotional intelligence of mothers are shown in Table 2. However, it was found that 87.9% (n=29) of the children with CP had pediatric sleep problems and 51.5% (n=17) of the mothers had poor sleep quality. 9.1% (n=3) of the mothers had a poor sleep quality while the absence of sleep problems in their child. There was no difference between sleep and emotional intelligence values in the groups with and without visual problems (p>0.05). It was determined that there was no relationship between sleep parameters and emotional intelligence (p>0.05). However, age of children was weakly related with PSQI (p=0.04, r=-0.35), and CSHQ-AF was moderately related with age of mothers (p=0.02, r=-0.40) and BMI of mothers (p=0.007, r=0.45) (Table 3).

Table 2. The results of sleep parameters and emotional intelligence children with Cerebral Palsy and their mothers (n=33).

	Children with Cerebral Palsy
CSHQ-AF - mean (SD)	50.33 (9.38)
	Mothers of Children
PSQI - median (IQR)	6.00 (4.00-8.50)
RSEIS	
Optimism/Mood Regulation - median (IQR)	80.00 (75.00-81.50)
Utilization of Emotions - mean (SD)	23.36 (4.45)
Appraisal of Emotions - mean (SD)	46.39 (9.60)
Total Score - mean (SD)	149.54 (16.94)

CSHQ-AF: Children Sleep Habit Questionnaire- Abbreviated Form, IQR: Inter-quartile range, PSQI: Pittsburg Sleep Quality Index, RSEIS: Revised Schutte Emotional Intelligence Scale, SD: Standart Deviation.

Table 3. Relationship between sleep parameters and emotional intelligence (n=33)

	Age (children)		**BMI (children)**		**Age (Mothers)**		**BMI (mothers)**		**CSHQ-AF**		**PSQI**		**RSEIS**	
	r	***p***	**r**	***p***	***r***	***p***	**r**	***p***	**r**	***p***	**r**	***p***	***r***	***p***
Age (children)			0.08	0.6	**0.40[b]**	**0.02**	-0.32	0.07	-0.15	0.4	**-0.35[b]**	**0.04**	-0.07	0.7
BMI (children)	0.08	0.6			0.02	0.9	-0.19	0.3	-0.12	0.5	-0.08	0.6	-0.16	0.3
Age (Mothers)	**0.40[b]**	**0.02**	0.02	0.9			-0.12	0.5	**-0.40[a]**	**0.02**	-0.05	0.8	-0.02	0.9
BMI (mothers)	-0.32	0.07	-0.19	0.3	-0.12	0.5			**0.45[a]**	**0.007**	-0.05	0.08	-0.35	0.05
CSHQ-AF	-0.15	0.4	-0.12	0.5	**-0.40[a]**	**0.02**	**0.45[a]**	**0.007**			-0.05	0.8	-0.33	0.06
PSQI	**-0.35[b]**	**0.04**	-0.08	0.6	-0.05	0.8	-0.05	0.08	-0.05	0.8			0.03	0.9
RSEIS	-0.07	0.7	-0.16	0.3	-0.02	0.9	-0.35	0.05	-0.33	0.06	0.03	0.9		

BMI: Body mass index, CSHQ-AF: Children Sleep Habit Questionnaire- Abbreviated Form, PSQI: Pittsburg Sleep Quality Index, RSEIS: Revised Schutte Emotional Intelligence Scale. [a] Pearson Correlation Coefficient, [b] Spearman's Correlation Coefficient.

Bold values indicate statistically significant at the $p < 0.05$ level

DISCUSSION

The results of our study provide further support on the claims children with CP and their mothers experience a high frequency of sleep problems. However, there was no relationship between sleep quality of children with CP and mothers' sleep quality, which was unexpected and contrary to the literature [10, 13]. In addition to these unexpected findings, the mothers' sleep quality was not related to their emotional intelligence results.

The rate of sleep problems in children with CP was determined to be 72.2% by Hulst et al. [31], 55% by Lang et al. [13], 44% by Newman et al. [12], and 20.7% by Horwood et al. [32], although it is difficult to identify the underlying mechanism of sleep problems in children with CP and to completely explain the relationship between CP and sleep problems. In this study, it was determined that children had a high rate of sleep problems and sleep was not affected by GMFCS level in parallel with the study of Newman et al [12]. It was found that sleep problems in children with CP were related to the having visual impairment [12, 13]. However, the relationship between the sleep problems and having epilepsy was controversial [12, 13]. Contrary to the literature, our study did not find a relationship with having visual impairment, and none of them had epilepsy. No relationship between sleep and emotional intelligence may be due to the fact that the quality of sleep depends on many internal and external factors, such as pain, stress, or sleep environments [32-34].

A systematic review in 2018 by Micsinszki et al. [35] reported that parents of children with developmental problems, including children with CP, had poorer sleep quality than typically developing children. In studies that included only children with CP the rate of sleep disorders was reported as 40% by Wayte et al. [10], and 71% by Lang et al. [13], which are in line with rate of present study. Recently, Hulst et al. [36] reported that only 13.6% mothers of children with CP satisfied about their own sleep. In addition to the child's physical problems, parents of children with CP had many concerns about safety and well-being of their child during sleep [36]. According to family statements, they wake up 10-15 times a night to monitor their child [36]. The mothers who had any orthopedic, neurological, or psychological disorder were not included in present study, and 9.1% of the mothers had a poor sleep quality despite the absence of sleep problems in their child. Children's sleep can be an important criterion for parents' sleep, but it is not the only criterion.

The sleep quality was related to depression, anxiety, stress, pain, and well-being [32-34]. However, our findings obtained in the relationship between the sleep quality and emotional intelligence show us that there was no relationship in mothers. In contrast to our study, previous studies tended to be the relationship between the sleep quality and emotional intelligence [15, 37, 38]. Miguez-Torres et al. [15] found that some subdomain of emotional intelligence was related to the sleep duration, and Bavafa et al. [38] revealed that there was relationship between emotional intelligence and sleep quality. Possible explanation for our findings may have been the emotional intelligence is a complex and complicated process, including self-awareness, managing emotions, motivating one-self, empathy, and handling relationships.

There are some limitations of the current study, including the sample size, which was result from the nature of the retrospective study. Another limitation was that we could not compare our findings with typically developing children. In addition, some characteristics information such as marital and educational status was missing and not included in the statistical analysis could have affected the results.

CONCLUSION

In conclusion, to our knowledge, the current study is the first study to examine the sleep quality in children with CP and their mothers with the emotional intelligence of the mothers. Most of the children with CP were having sleep problems in this study, while more than half of mothers had poor sleep quality. However, there were no relationship between each of them. Further studies are needed in which more detailed information can be collected prospectively and advanced analyzes can be performed.

Acknowledgements: None.

Informed Consent: None.

Conflicts of Interest: None of the authors report having a conflict of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical Approval: Ethical approval of this study was obtained from Hacettepe University Health Science Research Ethics Board (SBA 23/249).

Author Contributions: Idea/Concept: NB, BNYL; Design: İGA, SSA, OY; Control/Supervision: OY; Data collection and/or Processing: NB, BNYL; Analysis and/or interpretation: İGA, SSA; Literature review: NB, BNYL; Writing the Article: NB, BNYL; Critical Review: İGA, SSA, OY.

REFERENCES

[1] Cans C (2000) Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol 42:816-824. https://doi.org/10.1017/s0012162200001511

[2] Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, Jacobsson B, Damiano D (2005) Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol 47:571-576. https://doi.org/10.1111/j.1469-8749.2005.tb01195.x

[3] Horwood L, Li P, Mok E, Shevell M, Constantin E (2019) A systematic review and meta-analysis of the prevalence of sleep problems in children with cerebral palsy: how do children with cerebral palsy differ from each other and from typically developing children? Sleep Health 5:555-571. https://doi.org/10.1016/j.sleh.2019.08.006

[4] Adiga D, Gupta A, Khanna M, Taly AB, Thennarasu K (2014) Sleep disorders in children with cerebral palsy and its correlation with sleep disturbance in primary caregivers and other associated factors. Ann Indian Acad Neurol 17:473. https://doi.org/10.4103/0972-2327.144044

[5] Kotagal S, Gibbons VP, Stith JA (1994) Sleep abnormalities in patients with severe cerebral palsy. Dev Med Child Neurol 36:304-311. https://doi.org/10.1111/j.1469-8749.1994.tb11850.x

[6] Garcia J, Wical B, Wical W, Schaffer L, Wical T, Wendorf H, Roiko S (2016) Obstructive sleep apnea in children with cerebral palsy and epilepsy. Dev Med Child Neurol 58:1057-1062. https://doi.org/10.1111/dmcn.13091

[7] Lélis ALP, Cardoso MVL, Hall WA (2016) Sleep disorders in children with cerebral palsy: An integrative review. Sleep Med Rev 30:63-71

[8] Romeo DM, Brogna C, Quintiliani M, Baranello G, Pagliano E, Casalino T, Sacco A, Ricci D, Mallardi M, Musto E (2014) Sleep disorders in children with cerebral palsy: neurodevelopmental and behavioral correlates. Sleep Med. 15:213-218. https://doi.org/10.1016/j.smrv.2015.11.008

[9] Horwood L, Li P, Mok E, Oskoui M, Shevell M, Constantin E (2019) Behavioral difficulties, sleep problems, and nighttime pain in children with cerebral palsy. Res Dev Disabil 95:103500. https://doi.org/10.1016/j.ridd.2019.103500

[10] Wayte S, McCaughey E, Holley S, Annaz D, Hill CM (2012) Sleep problems in children with cerebral palsy and their relationship with maternal sleep and depression. Acta Paediatr 101:618-623. https://doi.org/10.1111/j.1651-2227.2012.02603.x

[11] Zee PC, Turek FW (1999) The Introduction to Sleep and Circadian Rhythms. 1 st ed. Regulation of Sleep and Circadian Rhythms, CRC Press. 133:1-17. https://doi.org/10.1201/9781420001211-4

[12] Newman CJ, O'Regan M, Hensey O (2006) Sleep disorders in children with cerebral palsy. Dev Med Child Neurol y 48:564-568. https://doi.org/10.1017/s0012162206001198

[13] Lang CP, Boucaut A, Guppy M, Johnston LM (2021) Children with cerebral palsy: A cross-sectional study of their sleep and their caregiver's sleep quality, psychological health and well-being. Child Care Health Dev 47:859-868. https://doi.org/10.1111/cch.12897

[14] Maqsood S, Naeem S, Bibi S, Tabassum MF (2023) Impact of Emotional Intelligence on Mother's Mental Health having Children with Cerebral Palsy: Mediating Role of Family Support. Int J Spec Educ 38(1).

[15] Miguez-Torres N, Martínez-Rodríguez A, Martínez-Olcina M, Miralles-Amorós L, Reche-García C (2021) Relationship between emotional intelligence, sleep quality and body mass index in emergency nurses. Healthcare 9(5):607. https://doi.org/10.3390/healthcare9050607

[16] Killgore WD, Balkin TJ, Wesensten NJ (2006) Impaired decision making following 49 h of sleep deprivation. J Sleep Res 15:7-13. https://doi.org/10.1111/j.1365-2869.2006.00487.x

[17] Demos K, Hart C, Sweet L, Mailloux K, Trautvetter J, Williams S, Wing R, McCaffery J (2016) Partial sleep deprivation impacts impulsive action but not impulsive

decision-making. Physiol Behav 164:214-219. https://doi.org/10.1016/j.physbeh.2016.06.003

[18] Heuer H, Kleinsorge T, Klein W, Kohlisch O (2004) Total sleep deprivation increases the costs of shifting between simple cognitive tasks. Acta Psychol 117:29-64. https://doi.org/10.1016/j.actpsy.2004.04.005

[19] Labelle MA, Dang-Vu TT, Petit D, Desautels A, Montplaisir J, Zadra A (2015) Sleep deprivation impairs inhibitory control during wakefulness in adult sleepwalkers. J Sleep Res 24:658-665. https://doi.org/10.1111/jsr.12315

[20] van Peer JM, Gladwin TE, Nieuwenhuys A (2019) Effects of threat and sleep deprivation on action tendencies and response inhibition. Emotion 19:1425. https://doi.org/10.1037/emo0000533.supp

[21] Gruber R, Casso J (2014) The interplay between sleep and emotion regulation: Conceptual framework empirical evidence and future directions. Curr Psychiatry Rep 16:500. https://doi.org/10.1007/s11920-014-0500-x

[22] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B (1997) Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 39:214-223. https://doi.org/10.1111/j.1469-8749.1997.tb07414.x

[23] El Ö, Baydar M, Berk H, Peker Ö, Koşay C, Demiral Y (2012) Interobserver reliability of the Turkish version of the expanded and revised gross motor function classification system. Disabil Rehabil 34:1030-1033. https://doi.org/10.3109/09638288.2011.632466

[24] Owens JA, Spirito A, McGuinn M (2000) The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 23(8):1043-1052. https://doi.org/10.1093/sleep/23.8.1d

[25] Fiş NP, Arman A, Ay P, Topuzoğlu A, Güler AS, Gökçe İmren S, Ersu R, Berkem M (2010) The validity and the reliability of Turkish Version of Children's Sleep Habits Questionnaire (Çocuk uyku alışkanlıkları anketinin Türkçe geçerliliği ve güvenilirliği). Anadolu Psikiyatri Derg 11:151-160 ([In Turkish])

[26] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193-213. https://doi.org/10.1016/0165-1781(89)90047-4

[27] Agargun M, Kara H, Anlar O (1996) The reliability and validity of Turkish version of Pittsburgh Sleep Quality Index (Pittsburgh Uyku Kalitesi İndeksi'nin Geçerliği ve Güvenirliği). Turk Psikiyatri Derg 7:107-115 ([In Turkish])

[28] Austin EJ, Saklofske DH, Huang SH, McKenney D (2004) Measurement of trait emotional intelligence: Testing and cross-validating a modified version of Schutte et al.'s (1998) measure. Pers Individ Differ 36:555-562. https://doi.org/10.1016/s0191-8869(03)00114-4

[29] Tatar A, Tok S, Saltukoğlu G (2011) Adaptation of the revised schutte emotional intelligence scale into Turkish and examination of its psychometric properties (Gözden geçirilmiş Schutte duygusal zeka ölçeğinin Türkçe'ye uyarlanması ve Psikometrik özelliklerinin incelenmesi). Klinik Psikofarmakol Bülteni 21:325-338. ([In Turkish])

[30] Akoglu H (2018) User's guide to correlation coefficients. Turk J Emerg Med 18:91-93. https://doi.org/10.1016/j.tjem.2018.08.001

[31] Hulst RY, Gorter JW, Voorman JM, Kolk E, Van Der Vossen S, Visser-Meily JM, Ketelaar M, Pillen S, Verschuren O (2021) Sleep problems in children with cerebral palsy and their parents. Dev Med Child Neurol 63:1344-1350. https://doi.org/10.1111/dmcn.15810

[32] Horwood L, Mok E, Li P, Oskoui M, Shevell M, Constantin E (2018) Prevalence of sleep problems and sleep-related characteristics in preschool-and school-aged children with cerebral palsy. Sleep Med 50:1-6. https://doi.org/10.1016/j.sleep.2018.05.008

[33] Scott AJ, Webb TL, Martyn-St James M, Rowse G, Weich S (2021) Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. Sleep Med Rev 60:101556. https://doi.org/10.1016/j.smrv.2021.101556

[34] Fadzil A (2021) Factors affecting the quality of sleep in children. Children 8(2):122. https://doi.org/10.3390/children8020122

[35] Micsinszki SK, Ballantyne M, Cleverley K, Green P, Stremler R (2018) Sleep outcomes for parents of children with neurodevelopmental disabilities: a

systematic review. J Fam Nurs 24(2):217-249. https://doi.org/10.1177/1074840718773381

[36] Hulst RY, Voorman JM, Pillen S, Ketelaar M, Visser-Meily JM, Verschuren O (2022) Parental perspectives on care for sleep in children with cerebral palsy: a wake-up call. Disabil Rehabil 44(3):458-467. https://doi.org/10.1080/09638288.2020.1770873

[37] Heidari H, Sharifshad F, Mohammadsalehi N, Mohammadbeigi A (2019) Association of Emotional Intelligence with Sleep Quality. Arch Occup Health 3(3):380-387. https://doi.org/10.18502/oh.v3i3i.1281

[38] Bavafa A, Fadaei M, Anbarani BS, Bameshghi M, Shekarian-Yazd F, Jaberghaderi N, Moeni K (2019) The Association between Emotional Intelligence and Sleep Quality Components in University Students. J Sleep Sci 4(1-2):37-43.

How to Cite;

Bulut N, Yardımcı-Lokmanoğlu BN, Alemdaroğlu-Gürbüz İ, Serel Arslan S, Yılmaz Ö (2024) Findings on Sleep of Children with Cerebral Palsy and Their Mothers' Sleep and Emotional Intelligence. 30(2):117-124. Eur J Ther. https://doi.org/10.58600/eurjther1943

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):125-135.
https://doi.org/10.58600/eurjther1907

Original Research

The Relationship Between Breast Volume and Thoracic Kyphosis Angle

Şenay Bengin Ertem [1], Ümit Ali Malçok [2]

[1] Department of Radiology, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Türkiye.
[2] Department of Neurosurgery, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Türkiye.

Received: 2023-10-23 **Accepted:** 2023-12/20 **Published Online:** 2023-12-20

Corresponding Author
Ümit Ali Malçok, MD, Associate Prof,
Address: Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Neurosurgery, 17100, Çanakkale, Türkiye.
E-mail: umalcok@gmail.com

ABSTRACT

Objective: It has been hypothesized that a disproportionate upper body weight caused by macromastia places abnormal stress on the spine, which may lead to skeletal abnormalities. To evaluate whether there is a relationship between breast volume and the thoracic kyphosis angle measured on thorax CT images.

Methods: A total of 448 female patients who underwent thoracic CT examinations were included in this study. Breast volume (ml), by using the "organ segmentation method"; thoracic kyphosis angles by using Cobb's method were made manually on the workstation.

Results: Mean right breast volume was 902.03 ± 376.47 (154.21 - 2366.20 ml), left breast volume was 911.01 ± 383.34 (167.93 - 2894.07 ml), total breast volume was 1810.09 ± 750.82 (354.39 - 5100.68 ml). The total breast volume ($p<0.001$) and thoracic kyphosis angle ($p=0.012$) in patients aged 50-69 years were significantly higher than those aged 17-29 years. Larger total breast volume [$p<0.001$] and thoracic kyphosis angle ($p<0.001$) values were associated with larger BMI intervals. A significant positive correlation was observed between the total breast volume and thoracic kyphosis angle ($r=0.771$, $p<0.001$).

Conclusion: Our results showed that the thoracic kyphosis angle significantly increased in parallel with a larger total breast volume, and that total breast volume was an independent risk factor for thoracic kyphosis angle. The manual organ segmentation method we used was found to be reliable and easy to apply, but time-consuming technique for calculating BV.

Keywords: Breast volume, thoracic kyphosis angle, organ segmentation technique, thorax computed tomography

INTRODUCTION

Women with a larger-than-normal breast volume (BV) experience cervical tension, head, back, and shoulder pain, and poor posture more often than women with normal or small breast volumes [1]. It has been hypothesized that a disproportionate upper body weight caused by macromastia places abnormal stress on the spine, which may lead to skeletal abnormalities [2]. Several studies have shown that high BV is one of the mechanisms leading to an increase in thoracic kyphosis and cervical lordosiss [3,4]. Improvements in pain, functional capacity, severity of additional symptoms, and thoracic kyphosis angle (TKA) after breast reduction surgery confirm these conclusions [3,5]. Furthermore, a cross-sectional study reported that women with large breasts had greater TKA and upper-trunk musculoskeletal pain than those with small breasts [1].

Although BV estimation is important for determining the amount of tissue to be removed before mastectomy and the approach to reconstructive surgery after mastectomy, there is still no standard method for measuring BV [6, 7]. Various techniques have been used for BV estimation, including anthropometric measurements, Archimedean procedure, Grossman-Rounder device, negative casting (plaster, paraffin, thermoplastic materials), 2D images such as mammography or ultrasound, 3D surface calculation, and Cavalieri principle [6-9].

Some of these methods have disadvantages such as being complex in terms of technical performance, causing discomfort to the patient or examiner, inadequate sensitivity, and high costs [7]. In existing studies assessing BV measurement methods, the participant count is either low or subjects only include certain groups (such as postmenopausesal patients with large breast). Therefore, a technique that can accurately measure BV in larger patient groups is needed.

The organ segmentation method using CT images is a technique developed for measuring organ volume. It has been used to measure the volume of intra-abdominal organs, such as the liver, spleen, and pancreas [10]. A few studies have used the same technique to measure breast volume [7, 11]. However, most of these studies were related to their use in breast reduction surgery.

Main Points;

- Our results showed that TKA was correlated with TBV and TBV was an independent risk factor associated with higher TKA
- TBV and TKA values in the 50-69 years age group were found to be significantly higher than those in the 17-29 years age group. But there was no significant correlation between age and TBV and TKA.
- Both TBV and TKA increased significantly as the BMI and weight increased.
- The Cobb angle method has subsequently been widely used in clinical practice to measure sagittal spine curves. We preferred the angle between T4 and T12, which is commonly used in TKA measurements.
- The manual organ segmentation method we used was found to be reliable and easy to apply, but time-consuming technique for calculating BV.

The aim of this study was to evaluate whether there is a relationship between BV and the TKA on thorax CT images.

MATERIALS AND METHODS

Study Design and Ethical Issues

This retrospective, single-center study was conducted at the Radiology Department of the University Hospital. Ethics committee approval was obtained (decision number: July 16, 2020, code:14-10) from the same location. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Since the study was conducted retrospectively, informed consent was not obtained from the participants.

Study Population

This study included 448 female patients who underwent thorax CT (TCT) examination at our Radiology Department from 2019 to 2020.

The exclusion criteria were age <17 years; impaired image quality due to artifacts; scoliosis; thoracic vertebral fracture; osteoporosis; presence of tumor or abscess at the level where TKA measurement would be made; having spinal, thoracic or breast surgery history; and having received radiotherapy at the site of measurement.

Data Collection, Imaging and Measuring Techniques

Patient age, height (cm), weight (kg), and TCT images were obtained from the hospital's medical record database. The body mass index (BMI) was calculated as weight/height² (kg/m²). Patients were divided into 7 groups according to age (17-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-100 years) and 3 groups according to BMI (<25, 25–30, ≥30) [12]. Thorax computed tomography examination was performed with a 320-detectors, 640-section Toshiba Aquillion One TSX-301C 2016 (Canon Medical Systems, Tokyo, Japan) tomography device with the following settings: kV 120, mA 50, rotation time 350 ms, slice thickness 5 mm, and slice interval 5 mm.

Measuring Breast Volume

Axial TCT images of 448 patients were evaluated to ensure that both the breasts were in the field of view. Coronal and sagittal reformat images were obtained from axial sections of the TCTs. Breast volume (ml) measurements were made manually at the workstation (Vitrea version 6.8.0]) by an experienced radiologist, using the "organ segmentation method" in accordance with the

manufacturer's recommended protocol. By selecting the tissues within the breast boundaries, volume measurements were performed for each breast (right and left) separately, and the total breast volume (TBV) was calculated automatically by the device (Figure 1).

Measuring Thoracic Kyphosis Angle

In the same session, TKAs were measured manually at the workstation (Vitrea version 6.8.0) on the sagittal plane of the TCT images in the bone window (W:2500, L:480) by an experienced radiologist and neurosurgeon as follows: First, straight lines were drawn in the sagittal plane, tangent to the upper end plate of the T4 vertebra, and the lower end plate of the T12 vertebra. Subsequently, two separate perpendicular lines that intersected these two lines were drawn. Finally, TKA was determined by measuring the acute angle at the intersection of the last two lines drawn (Cobb's angle) (Figure 2) [13].

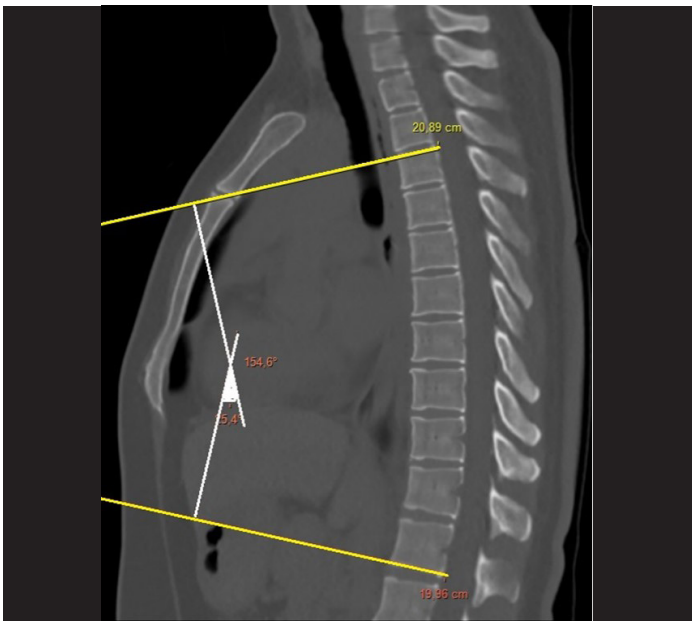


Figure 2. Thoracic kyphosis angle measurement technique on sagittal plane thorax CT image.

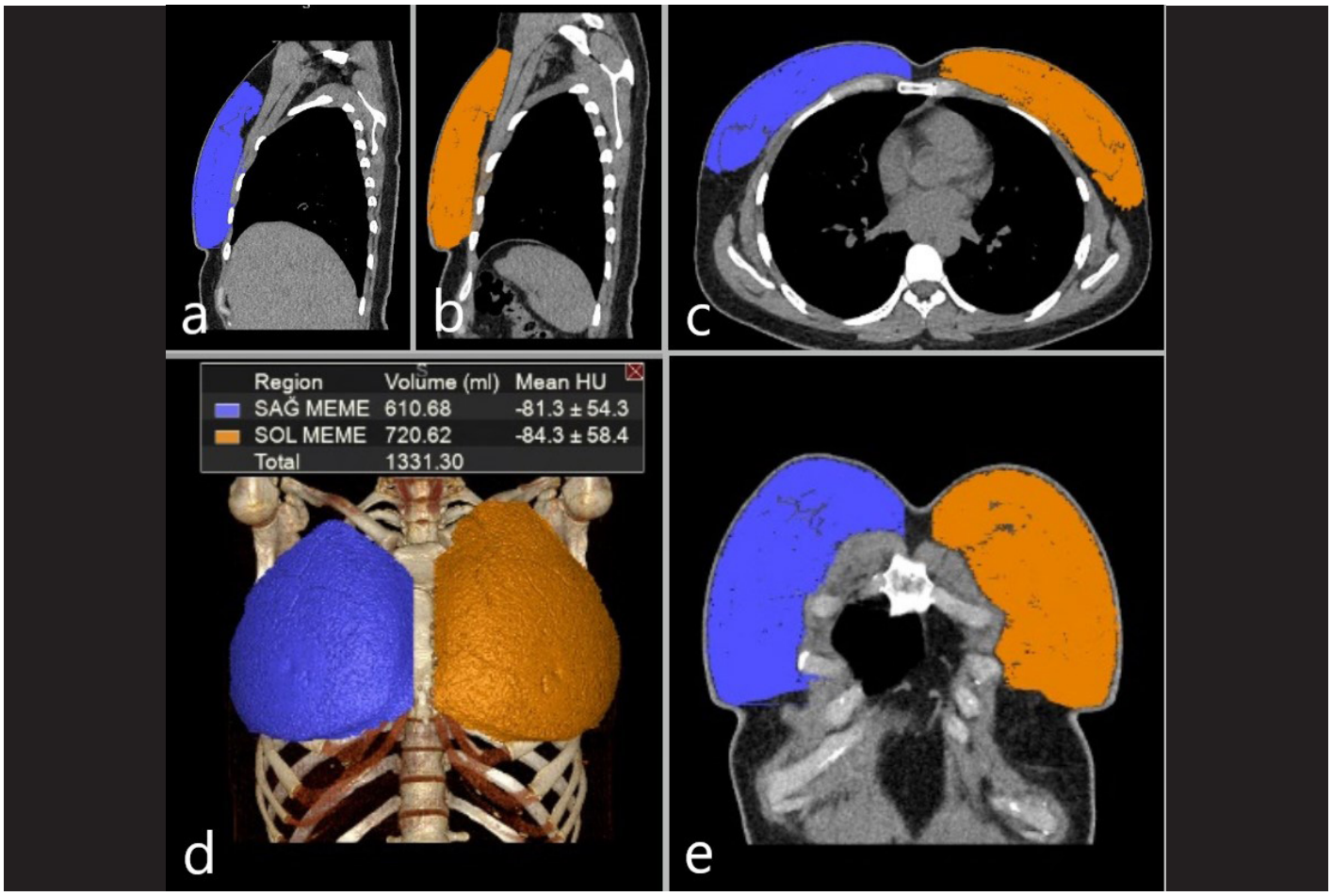


Figure 1. Sagittal (a, b), axial (c) 3-dimensional (d) and coronal (e) reformat images of breast volumes made with "organ segmentation method" on thorax CT images.

Statistical Analysis

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). For the normality check, histograms and Q-Q plots were employed. Continuous variables are described as mean ± standard deviation (minimum-maximum), and categorical variables are reported as frequency values (relative and absolute). Comparison of the right and left BVs was performed using the paired sample t-test. Comparisons between age and body mass index groups were performed using one-way analysis of variance (ANOVA). Pairwise corrections were performed using the Bonferroni method. Pearson correlation coefficients were calculated to evaluate the relationships between continuous variables. Multiple linear regression analysis was performed to determine significant factors associated with TKA. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

The mean age in the study group was 56.09±16.35 (17-91) years, and the mean BMI was 28.46±5.76 [16.00-56.93]. The distributions of 448 female patients age and BMI groups are shown in Table 1 (Table 1). Mean right BV was 902.03±376.47 (154.21-2366.20 ml), mean left BV was 911.01±383.34 (167.93-2894.07 ml), mean total BV (TBV) was 1810.09±750.82 (354.39-5100.68 ml). There was no significant difference between the right and left BV (p=0.104). The mean TKA was 29.98±9.14 (5.4-73.6) degrees.

The total breast volume (p<0.001) and TKA (p=0.012) of the patients in the 50-69 age range were significantly higher than the corresponding values in the 17-29 age group, while values in the other groups were similar. In addition, both TBV (p<0.001) and TKA (p<0.001) increased significantly with higher BMI intervals (Table 2).

According to the results of the Pearson correlation calculations, a significant positive correlation was observed between the TBV and TKA (r=0.771, p<0.001) (Figure 3). A significant positive correlation was observed between weight and TBV (r=0.524, p<0.001) and TKA (r=0.406, p<0.001). There was also a significant positive correlation between BMI and TBV (r=0.520, p<0.001) and TKA (r=0.405, p<0.001) (Table 3).

Table 1. Summary of patients' characteristics and measurements.

Age range	**Mean (%)**
17-29	37 (8.3%)
30-39	38 (8.5%)
40-49	71 (15.8%)
50-59	96 (21.4%)
60-69	109 (24.3%)
70-79	67 (15.0%)
80-100	30 (6.7%)
Mean Age ± sd (range)	56.09 ± 16.35 (17 - 91)
Mean Height ± sd, cm	160.54 ± 5.80 (145 - 185)
Mean Weight ± sd, kg	73.25 ± 14.67 (42 - 155)
Mean Body mass index ± sd, kg/m^2	28.46 ± 5.76 (16.00 - 56.93)
Body mass index range	**Mean (%)**
<25.0	128 (28.6%)
25.0-<30.0	157 (35.0%)
≥30.0	163 (36.4%)

Data are presented as the mean ± standard deviation (minimum - maximum) for continuous variables. and as frequency (percentage) for categorical variables.

Table 2. Distribution of total breast volume and thoracic kyphosis angles according to age and body mass index.

	Total breast volume, ml	**Thoracic kyphosis angle**
Age		
17-29	1469.48 ± 652.09 ^{a}	26.11 ± 7.58 ^{a}
30-39	1719.78 ± 724.06 ^{ab}	28.83 ± 8.51 ^{ab}
40-49	1661.59 ± 638.21 ^{ab}	29.37 ± 7.89 ^{ab}
50-59	2036.07 ± 701.00 ^{b}	31.58 ± 8.85 ^{b}
60-69	1938.98 ± 830.74 ^{b}	31.45 ± 9.69 ^{b}
70-79	1776.85 ± 815.14 ^{ab}	30.00 ± 10.60 ^{ab}
80-100	1578.87 ± 561.28 ^{ab}	27.15 ± 8.06 ^{ab}
p	**<0.001**	**0.012**
Body mass index, kg/m^2		
<25	1269.36 ± 572.52 ^{a}	24.96 ± 7.88 ^{a}
25 to <30	1831.73 ± 658.01 ^{b}	30.00 ± 8.21 ^{b}
≥30.0	2213.88 ± 697.16 ^{c}	33.91 ± 9.02 ^{c}
p	**<0.001**	**<0.001**

Data are presented as mean ± standard deviation. The same letters denote a lack of statistically significant differences between groups.

Multiple linear regression analysis was performed to determine the significant risk factors associated with higher TKA rates. We found that a large TBV (p<0.001) was a significant risk factor for higher TKA after adjusting for age, height, weight, and body mass index. Other variables included in the model, such as age (P=0.876), height (P=0.966), weight (P=0.993), and BMI (P=0.998) were found to be non-significant (Table 4).

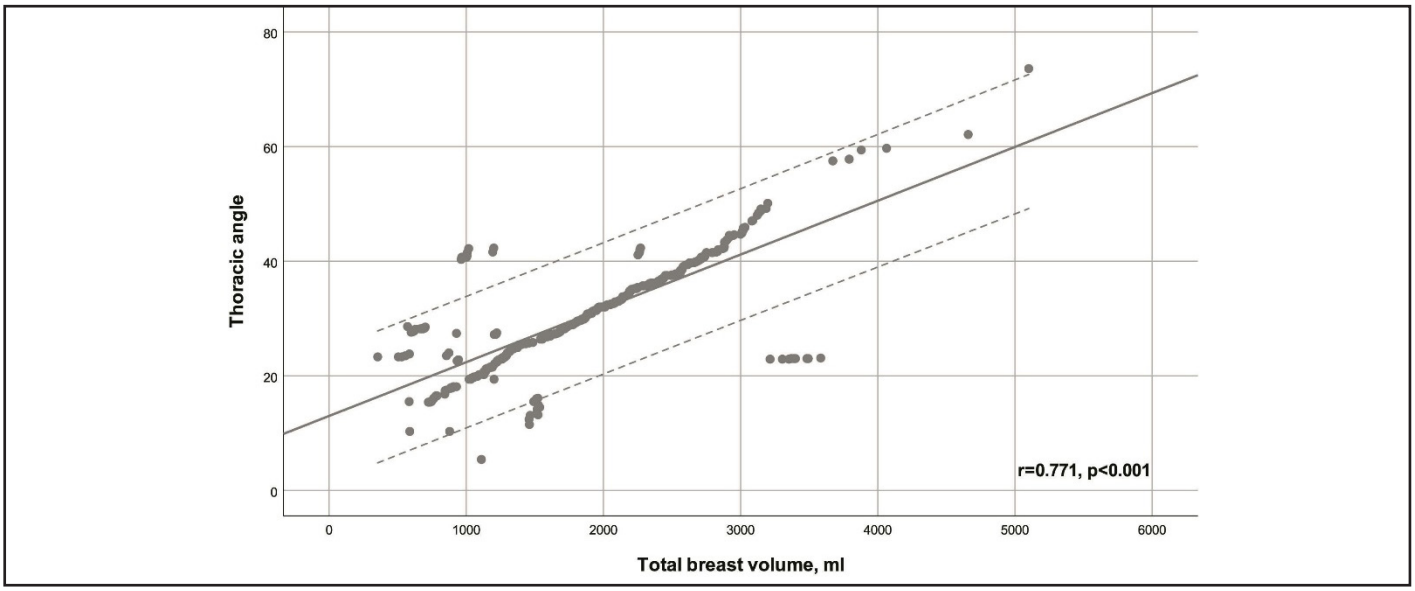


Figure 3. Scatter plot of total breast volume and thoracic kyphosis angle.

Table 3. Correlations between breast volume, thoracic kyphosis angle and patients characteristics.

		Total breast volume, ml	Thoracic kyphosis angle
Total breast volume, ml	r	-	**0.771**
	p	-	**<0.001**
Age	r	0.089	0.076
	p	0.060	0.110
Height, cm	r	0.012	0.003
	p	0.796	0.955
Weight, kg	r	**0.524**	**0.406**
	p	**<0.001**	**<0.001**
Body mass index, kg/m^2	r	**0.520**	**0.405**
	p	**<0.001**	**<0.001**

r: Pearson correlation coefficient

Table 4. Risk factors of the high thoracic kyphosis angle, multiple linear regression analysis.

	Unstandardized β	Standard Error	Standardized β	t	p	95.0% Confidence Interval for β	
(Constant)	14.341	36.803		0.390	0.697	-57.989	86.672
Age	0.003	0.018	0.005	0.157	0.876	-0.033	0.039
Height, cm	-0.010	0.229	-0.006	-0.043	0.966	-0.461	0.441
Weight, kg	0.002	0.252	0.004	0.009	0.993	-0.493	0.497
Body mass index, kg/m^2	-0.002	0.643	-0.001	-0.003	0.998	-1.266	1.262
Total breast volume, ml	0.009	0.000	0.770	21.486	**<0.001**	0.009	0.010

Dependent variable: Thoracic kyphosis angle; Adjusted R^2=0.590; F=129.769; p<0.001

DISCUSSION

In our study, TBV and TKA values in the 50-69 years age group were found to be significantly higher than those in the 17-29 years age group, but there was no significant correlation between age and TBV and TKA. In addition, both TBV and TKA increased significantly as the BMI and weight increased. Our study has an advantage over the literature in that the number of participants in the study population is relatively high, regardless of age and breast size.

Excessive BV causes biomechanical disorders such as back pain, avoidance of physical activity, and biopsychological problems such as cosmetic dissatisfaction [4, 14, 15]. In the present study, we showed a relationship between TBV and TKA, which may be associated with the development of back pain. In the correlation analysis, we found that a larger TBV was associated with a higher TKA, indicating an increased kyphosis angle. Multiple linear regression analysis showed that TBV was independently associated with higher TKA regardless of other factors. Notably, both weight and BMI were positively correlated with TBV and TKA.

Previous studies have shown that abnormal increases in BV that force the thoracic spine anteriorly are involved in the deterioration associated with sagital vertebral aksis (SVA). The increased load due to the large BV in the front side of the body can shift the body's center of gravity in the same direction [14, 16, 17]. Fındıkçıoğlu et al., showed that women with large breasts according to cup sizes had significantly greater TKA (measured by lateral radiography) than women with small breasts [3]. Similarly, in a cross-sectional study that included 300 women between the ages of 18-82, BV was measured using a hand-held three-dimensional scanner, and the participants were divided into four groups: small, medium, large and hypertrophic according to BV. TKA was measured using a flexicurve ruler. Although the hypertrophic group had the highest TKA value, breast size did not have a significant effect on TKA [5]. In a recent study from Türkiye, the BV of 60 women was measured using the Grossman-Rounder device. The cervical lordosis, thoracic kyphosis and lumbar lordotic Cobb's angles were calculated. The average cervical lordosis angle was significantly higher in patients with larger breasts than in those with smaller breasts [4].

In another studies, found that a large BV is not only a cosmetic but also a functional problem and can lead to pathological conditions such as increased cervical lordosis and thoracic kyphosis and increased or decreased lumbar lordosis. They also reported that reduction mammoplasty can correct pathological angulation of the vertebral column [18-20].

Sanal et al. used a technique similar to the BV calculation method used in our study. They retrospectively screened patients who had undergone TCT for various reasons, and calculated TBV by adding the volumes of each breast separately calculated from the 3D breast reconstruction images obtained on the CT workstation [11]. By examining the midsagittal planes of the same CT images containing the 1st thoracic to 1st lumbar levels, they determined the degree of degeneration at each spinal level using the Kellgren-Lawrence degeneration scale. They found that both the total degeneration grade and total number of involved levels were significantly higher in women with large breasts than in those with normal and small breasts.

Thoracic kyphosis tends to increase with aging [21]. After the fourth decade of life, the kyphotic angle generally begins to worsen rapidly in women than in men [21,22]. Age related hyperkyphosis often occurs in older ages and is characterized by excessive forward curvature of the thoracic spine [23]. Currently, there is no well-defined threshold that distinguishes normal kyphosis from hyperkyphosis. The cut-off value for the hyperkyphosis angle has generally been used at a higher value such as greater than 40 degree or 50 degree in the literature [23-28]. The exact etiology of thoracic hyperkyphosis and its progression over time have not yet been determined. However, studies have examined various risk factors such as osteoporosis, vertebral fractures, degenerative changes, decreased mobility, reduced proprioception, spinal extansor musculature, and even heredity [29-32]. Osteoporosis is a systemic musculoskeletal disease that results in a decrease in bone mass and deterioration in bone microstructure. It causes bone fragility and an increase in the possibility of fractures [33]. It has been reported that 70% of all bone fractures in adults aged 45 and over and one –third of vertebral fractures in women the age of 65 are related to osteoporosis [34]. Postural kyphosis, one of the leading consequences of osteoporosis, develops due to vertebral fractures and causes physical and psychological damage [35]. Hyperkyphotic posture not only increases postural back pain, but also increases the risk of falls and therefore the risk of bone fractures [35,36]. Our study was conducted retrospectively. Since patient datas were obtained from our hospital's medical record database; bone densitometry results were not available

for each patient. Therefore, we could not examine the effect of osteoporosis on the TKA angle.

The Cobb angle method was originally proposed to evaluate the severity of scoliosis. However, it has subsequently been widely used in clinical practice to measure sagittal spine curves [37]. In this study, we chose to measure TKA using the Cobb angle method because it provides information about the anatomy of the vertebrae and spinal alignment. In addition, high inter- and intra-observer reliability has been defined for the use of the Cobb angle with well-trained inspectors. Owing to the superposition of the shoulder joints and bones, it is difficult to accurately assess the region from the fourth thoracic vertebra to cranial vertebra. Therefore, we preferred the angle between T4 and T12, which is commonly used in TKA measurements [13]. We obtained results consistent with those of previous studies. Thoracic kyphosis was positively correlated with TBV. Considering that age, weight, height and BMI may also affect TKA, we performed regression analysis and determined that TBV was an independent risk factor for TKA.

Many factors such as breast shape, the complex anatomy of the breast region, consistency, weight fluctuation, menstrual and hormonal effects, and position of the breast on the chest wall can affect the results of BV measurement; therefore, it is difficult to determine a standard BV measurement method [6]. In addition, because most of these methods cannot adequately measure the tissue lateral to the pectoral folds and/or the breast facing the chest wall, the results are often unreliable [7]. In addition to the advantages of most of the methods used to measure BV, there are also disadvantages, such as difficulty in implementation, costs, and not always being acceptable for patients [38]. The formula-related problems of anthropomorphic measurements, the inaccuracy of the Grossman-Roudner device for larger breasts, and the fact that the water displacement technique is reliable in medium or large breasts are specific disadvantages of previously reported methods [39-41].

It is difficult to automatically estimate breast volume because the breast consists of tissues of different densities, such as glands, fat, and skin [7, 42]. Along with technological developments, advances have been made in imaging systems and the three-dimensional detailing of these images [43, 44]. Today there are modern MRI, CT, mammography (MG), and ultrasound (US) devices containing special software that can automatically and accurately estimate the breast volume and benign or malignant mass volumes in the breast [7, 45- 50]. Magnetic resonance imaging (MRI) has excellent soft tissue resolution, is radiation-free, offers multiplanar and multi-sequence imaging; but is expensive and time consuming [51]. Computed tomography imaging (CT) has high spatial and intensity resolution. But it causes large amounts of radiation exposure and use of contrast agents that have negative side effects [52]. Mammography (MG) is the main diagnostic method in breast cancer screening and is the only imaging method that contributing to reducing breast cancer- related mortality [53]. But there is still radiation exposure in MG, although not as much as CT. Ultrasound (US) has advantages of being widespread, easily accessible, economical, easy to apply and does not contain radiation as CT or MG. It is considered the preferred imaging method for breast cancer [48,54]. But, volume measurement with two-dimensional ultrasound images is difficult; therefore 3D ultrasound (ABUS) which can perform automatic volume measurement of breast sould be used [49,55]. However, since automatic volume measurement softwares are expensive and not available on every devices, limits their clinical applications.

Studies have shown that the volume of various organs, such as the spleen [56], liver [57], and abdominal adipose tissue [58], can be measured with CT- and MRI-assisted manual organ segmentation. To the best of our knowledge, there are few publications in the literature on manual BV measurement utilizing the “organ segmentation method” over axial sections and coronal-sagittal reformat images in multislice CT. We preferred this method for TBV because it is objective and easily measurable. The comparison of these values with TKA values (measured using the objective Cobb method), allowed for an accurate assessment of the relationships between breast size and thoracic kyphosis.

Our study has some limitations. The retrospective and single-center design of our study limited the addition of new data and the generalizability of the results. The fact that the proposed BV measurement method requires CT imaging means both radiation exposure and additional cost. In addition, the manual measurement of BV with organ segmentation requires a relatively long time.

In conclusion, our results showed that TKA was correlated with TBV and TBV was an independent risk factor associated with higher TKA. It was observed that the increase in TBV and TKA values was especially evident in the 50-69 age group. The

manual organ segmentation method we used was found to be reliable and easy to apply, but time-consuming technique for calculating BV.

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

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval: Ethical approval for the study was granted by the Clinical Research Ethical Committee of Çanakkale Onsekiz Mart University (Approval number: 2020-07-16/14-10).

ŞB Ertem and *ÜA Malçok*: Contributed significantly to understanding and designing or obtaining data, or analyzing and interpreting data, drafting the manuscript or critically reviewing it for important intellectual content, and approving the final version to be published. They also agree to be responsible for all aspects of the work if questions arise regarding the accuracy or completeness of the work.

REFERENCES

[1] McGhee DE, Coltman KA, Riddiford-Harland DL, Steele JR (2018) Upper torso pain and musculoskeletal structure and function in women with and without large breasts: A cross sectional study. Clin Biomech. 51:99-104. https://doi.org/10.1016/j.clinbiomech.2017.12.009

[2] Elowitz EH (2014) Does Reduction Mammaplasty Revert Skeletal Disturbances in the Vertebral Column of Patients With Macromastia? A Preliminary Study. Aesthetic Plast Surg. 38(1):113-4. https://doi.org/10.1007/s00266-013-0215-0

[3] Fındıkcıoğlu K, Fındıkcıoğlu F, Bulam H, Sezgin B, Ozmen S (2013) The impact of breast reduction surgery on the vertebral column. Ann Plast Surg. 70(6):639-42. https://doi.org/10.1097/sap.0b013e31823fac41

[4] Tunçkale T, Gürdal SÖ, Çalışkan T, Topçu B, Yüksel MO (2021) The impact of various breast sizes of women on vertebral column and spinopelvic parameters. Turk Neurosurg. 31(5):699-703. https://doi.org/10.5137/1019-5149.jtn.30936-20.2

[5] Coltman CE, Steele JR, McGhee DE (2019) Effect of breast size on upper torso musculoskeletal structure and function: a cross-sectional study. Plast Reconstr Surg. 143(3):686-95. https://doi.org/10.1097/prs.0000000000005319

[6] Kovacs L, Eder M, Hollweck R, Zimmermann A, Settles M, Schneider A, Endlich M, Mueller A, Schwenzer- Zimmerer A, Papadopulos NA, Biemer E (2007) Comparison between breast volume measurement using 3D surface imaging and classical techniques. The Breast. 16(2):137-45. https://doi.org/10.1016/j.breast.2006.08.001

[7] Erić M, Anderla A, Stefanović D, Drapšin M (2014) Breast volume estimation from systematic series of CT scans using the Cavalieri principle and 3D reconstruction. Int Surg. 12(9):912-7. https://doi.org/10.1016/j.ijsu.2014.07.018

[8] Lee WY, Kim MJ, Lew DH, Song SY, Lee DW (2016) Three-dimensional surface imaging is an effective tool for measuring breast volume: a validation study. Arch Plast Surg. 43(5):430-7. https://doi.org/10.5999/aps.2016.43.5.430

[9] Choppin SB, Wheat JS, Gee M, Goyal A (2016) The accuracy of breast volume measurement methods: a systematic review. The Breast. 28:121-9. https://doi.org/10.1016/j.breast.2016.05.010

[10] Ma J, Zhang Y, Gu S, Zhu C, Ge C, Zhang Y, An X, Wang C, Wang Q, Liu X, Cao S, Zhang Q, Liu S, Wang Y, Li Y, He J,Yang X (2021) Abdomen CT-1K: Is abdominal organ segmentation a solved problem?. IEEE Trans. Pattern Anal Mach Intell. 27:1-19. https://doi.org/10.1109/tpami.2021.3100536

[11] Sanal B, Korkmaz M, Nas OF, Can F, Hacikurt K (2017) The effect of gigantomasty on vertebral degeneration: a computed tomography study. J Back Musculoskelet Rehabil. 30(5):1031-5. https://doi.org/10.3233/bmr-169600

[12] Quesada O, Lauzon M, Buttle R, Wei J, Suppogu N, Kelsey SF, Reis SE, Shaw LJ, Sopko G, Handberg E, Pepine CJ, Merz CNB (2022) Body weight and physical fitness in women with ischaemic heart disease: does physical fitness contribute to our understanding of the obesity paradox in women? Eur J Prev Cardiol. 4;zvac046. https://doi.org/10.1093/eurjpc/zwac046

[13] Koelé MC, Lems WF, Willems HC (2020) The clinical relevance of hyperkyphosis: A narrative review. Front Endocrinol [Lausanne]. 11:5. https://doi.org/10.3389/fendo.2020.00005

[14] Kruse M, Thoreson O (2021) The prevalence of diagnosed specific back pain in primary health care in Region Västra Götaland: a register study of 1.7 million inhabitants. Prim Health Care Res Dev. 22:e37. https://doi.org/10.1017/s1463423621000426

[15] Schinkel-Ivy A, Drake JDM (2016) Breast size impacts spine motion and postural muscle activation. J Back Musculoskelet Rehabil. 29(4):741-8. https://doi.org/10.3233/bmr-160680

[16] Shimizu M, Kobayashi T, Chiba H, Senoo I, Ito H, Matsukura K, Saito S (2020) Adult spinal deformity and its relationship with height loss: a 34-year longitudinal cohort study. BMC Musculoskelet Disord. 21(1):1-7. https://doi.org/10.1186/s12891-020-03464-2

[17] Oxland TR (2016) Fundamental biomechanics of the spine-what we have learned in the past 25 years and future directions. J Biomech. 49(6):817-32. https://doi.org/10.1016/j.jbiomech.2015.10.035

[18] Fındıkcıoğlu K, Fındıkcıoğlu F, Özmen S, Güçlü T (2007) The impact of breast size on the vertebral column: a radiologic study. Aesthetic Plast Surg. 31(1):23-7. https://doi.org/10.1007/s00266-006-0178-5

[19] Berberoğlu Ö, Temel M, Türkmen A (2015) Effects of reduction mammaplasty operations on the spinal column: clinical and radiological response. Aesthetic Plast Surg. 39 (4):514-22. https://doi.org/10.1007/s00266-015-0516-6

[20] Karabekmez FE, Gökkaya A, Işık C, Sağlam I, Efeoğlu FB, Görgü M (2014) Does reduction mammaplasty revert skeletal disturbances in the vertebral column of patiensts with macromastia? A preliminary study. Aesthetic Plast Surg. 38(1):104-12. https://doi.org/10.1007/s00266-013-0194-1

[21] Fon GT, Pitt MJ, Thies AC Jr. Toracic kyphosis: range in normal subjects. Am J Roentgenol 134:979-83 https://doi.org/10.2214/ajr.134.5.979

[22] Ensrud KE, Black DM, Harris F, Ettinger B, Cummings SR (1997) Correlates of kyphosis in older women. The fracture intervention trial research group. J Am Geriatr Soc 45:682-7 https://doi.org/10.1111/j.1532-5415.1997.tb01470.x

[23] Katzma WB, Wanek L, Shepherd JA, Sellmeyer DE (2010). Age- related hyperkyphosis: its causes, consequences, and management. J Orthop Sports Phys Ther 40(6): 352-60 https://doi.org/10.2519%2Fjospt.2010.3099

[24] Roghani T, Zavieh MK, Manshadi FD (2017) Age-related hyperkyphosis: update of its potential cuses and clinical impacts- narrative review. Aging Clin Exp Res 29: 567-77 https://doi.org/10.1007/s40520-016-0617-3

[25] McDaniels-Davidson C, Davis A, Wing D, Macera C, Lindsay SP, Schousboe JT, Nichols JF and Kado DM (2017) Kyphosis and incidental falls among community-dwelling older adults. Osteporos Int 29:163-9 https://doi.org/10.1007/s00198-017-4253-3

[26] van der Jagt-Willems HC, de Groot MH, van Campen JP, Lamoth CJ, Lems WF (2015) Associations between vertebral fractures, increased thoracic kyphosis, a flexed posture and falls in older adults: a prospective cohort study. BMC Geriatr. 15:34 https://doi.org/10.1186/s12877-015-0018-z

[27] Kado DM, Miller- Martinez D, Lui LY, Cawthon P, Katzman WB, Hillier TA, Fink AH (2014) Hyperkyphosis, kyphosis progression, and risk of non-spine fractures in older community dwelling women: the study of osteoporotic fractures (SOF). J Bone Miner Res. 29: 2210-6 https://doi.org/10.1002/jbmr.2251

[28] Sinaki M, Brey RH, Hughes CA, Larson DR, Kaufman KR (2005) Balance disorder and increased risk of falls in osteoporosis and kyphosis: significance of kyphotic posture and muscle strength. Osteoporos İnt. 16:1004-10 https://doi.org/ 10.1007/s00198-004-1791-2

[29] Milne JS, Lauder IJ (1976) The relationship of kyphosis to the shape of vertebral bodies. Ann Hum Biol 3:173-9 https://doi.org/10.1080/03014467600001281

[30] Anderson DE, D'Agostino JM, Bruno AG, Demissie S, Kiel DP, Bouxsein ML (2013) Variations of CT- based trunk muscle attenuation by age, sex, and specific muscle. J Gerontol A Biol Sci Med Sci 68:317-23 https://doi.org/10.1093/gerona/gls168

[31] Kamel HK (2003) Sarcopenia and aging. Nutr Rev 61:157-67 https://doi.org/10.1301/nr.2003.may.157-167

[32] Van der Klift M, De Laet CE, McCloskey EV, Hofman A, Pols HA (2002) The incidence of vertebral fractures in men and women: Rotterdam Study. J Bone Miner Res 17: 1051-6 https://doi.org/10.1359/jbmr.2002.17.6.1051

[33] Bonner FJ, Lindsay R (2005). Osteoporosis. İn: Delisa JA (ed) Physical medicine and rehabilitation, 4th edn. Lippincott Wiliams and Wilkins, Philadelphia, pp 699-719.

[34] Hall SE, Criddle RA, Comito TL, Price RL (1999). A case-control study of quality of life and functional impairement in women with long-standing vertebral osteoporotic fracture. Osteoporos Int 9(6): 508-15 http://dx.doi.org/10.1007/s001980050178

[35] Sarıdoğan ME (2005) Osteoporoz Epidemiyolojisi. Gökçe Kutsal Y (ed) Osteoporoz, Ankara, pp 5-36.

[36] Sinaki M (1998) Musculoskeletal challenges of osteoporosis. Aging 10(3): 249-62 https://doi.org/10.1007/bf03339659

[37] Gölpınar M, Komut E (2022) The reliability of the projection area per length squared for measuring lumbar lordosis an lateral radiographs: A comparison with Cobb Method. Eur J Ther. 28(4):285-91. https://doi.org/10.58600/eurjther-28-4-0091

[38] Hussain Z, Roberts N, Whitehouse GH, Garcia-Finana M, Percy D (1999) Estimation of breast volume and its variation during the menstrual cycle using MRI and stereology. BJR. 72(855):236-45. https://doi.org/10.1259/bjr.72.855.10396212

[39] Bulstrode N, Bellamy E, Shrotria S (2001) Breast volume assessment: comparing five different techniques. The Breast. 10(2):117-23. https://doi.org/10.1054/brst.2000.0196

[40] Kayar R, Civelek S, Cobanoglu M, Gungor O, Catal H, Emiroglu M (2011) Five methods of breast volume measurement: a comparative study of measurements of specimen volume in 30 mastectomy cases. Breast Cancer: Basic and Clinical Research. 5:43-52. https://doi.org/10.4137/bcbcr.s6128

[41] Sigurdson LJ, Kirkland SA (2006) Breast volume determination in breast hypertrophy: an accurate method using two anthropomorphic measurements. Plast Reconstr Surg. 118(2):313-20. https://doi.org/10.1097/01.prs.0000227627.75771.5c

[42] Yip JM, Mouratova N, Jeffery RM, Veitch DE, Woodman RJ, Dean NR (2012) Accurate assessment of breast volume: a study comparing the volumetric gold standard [direct water displacement measurement of mastectomy specimen] with a 3D laser scanning technique. Ann Plast Surg. 68(2):135-41. https://doi.org/10.1097/sap.0b013e31820ebdd0

[43] Ratib O, Valentino DJ, McCoy MJ, Balbona JA, Amato CL, Boots K (2000) Computer-aided design and modeling of workstations and radiology reading rooms for the new millennium. Radiographics. 20(6):1807-16. https://doi.org/10.1148/radiographics.20.6.g00nv191807

[44] Lenchik L, Heacock L, Weaver AA, Boutin RD, Cook TS, Itri J, Cristopher GF, Gullapalli RP, Lee J, Zagurovskaya M, Redson T, Godwin K, Nicholson J, Narayana PA (2019) Automated segmentation of tissues using CT and MRI: a systematic review. Acad Radiol. 26(12):1695-706. https://doi.org/10.1016/j.acra.2019.07.006

[45] Ortiz CG, Martel AL (2012) Automatic atlas-based segmentation of the breast in MRI for 3D breast volume computation. Med Phys. 39(10):5835-48. https://doi.org/10.1118/1.4748504

[46] Kim YS, Cho HG, Kim J, Park SJ, Kim HJ, Lee SE, Yang JD, Kim WH, Lee JS (2022) Prediction of implant size based on breast volume using mammography with fully automated measurements and brest MRI. Ann. Surg. Oncol 29(12): 7845-54. https:// doi.org/10.1245/s10434-022-11972-9

[47] Nara M, Fujioka T, Mori M, Agura T, Tateishi U (2022) Prediction of breast cancer risk by automated volumetric breast density measurement. Jpn J Radiol. 41(1): 54-62. https://doi.org/10.1007/s11604-022-013-y

[48] Ma JJ, Meng S, Dang SJ, Wang JZ, Yuan Q, Yang Q, Song CX (2022) Evaluation of a new method of calculating breast tumor volume based on automated breast ultrasound. Front Oncol. 13:12:895575. https://doi.org/10.3389/fonc.2022.895575.eCollection 2022

[49] Lagendijk M, Vos EL, Ramlakhan KP, Verhoef C, Koning AHJ, Lankeren WV, Koppert LB (2018) Breast and tumour volume measurements in breast cancer patients using 3-D automated breast volume scanner images. World J Surg.

42(7): 2087-93 https://doi.org/10.1007/s00268-017-4432-6

[50] Schmachtenberg C, Fischer T, Hamm B, Bick U (2017) Diagnostic performance of automated breast volume scanning (ABVS) compared to handheld ultrasonography with breast MRI as the gold standard. Acad Radiol. 24(8):954-61 https://doi.org/10.1016/j.acra.2017.01.021

[51] Kim JS, Bae K, Lee EJ, Bang M (2021) Mammography with a fully automated breast volumetric software as a novel method for estimating the preoperative breast volüme prior to mastectomy. Ann Surg Treat Res. 100(6):313-19 https://doi.org/10.4174/astr.2021.100.6.313

[52] Li H, Yao L, Jin P, Hu L, Li x, Gua T, Yang K (2018) MRI and PET-CT for evaluation of the pathological response to neoadjuvant chemotherapy in breast cancer: A systematic review and meta- analysis. Breast 40:106-15 https://doi.org/10.1016/j.breast.2018.04.018

[53] Li J, Gao W, Yu B, Wang F, Wang L (2018) Multi-slice spiral CT evaluation of breast cancer chemotherapy and correlation between CT results and breast cancer specifik gene1. J BUON 23(2):378-83

[54] Dobruch-Sobczak K, Piotrkowska- Wroblewska H, Klimonda Z, Roszkowska- Purska K, Litniewski (2019) J Ultrasound echogenity reveals the response of breat cancer to chemotherapy. Clin Imaging 55:41-6 https://doi.org/10.1038%2Fs41598-021-82141-3

[55] Vourtis A (2019) Three-dimensional automated breast ultrasound: Technical aspects and first results. Diagn Interv Imaging 100:579-92 https://doi.org/10.1016/j.diii.2019.03.012

[56] Xu Z, Gertz AL, Burke RP, Bansal N, Kang H, Landman BA, Abramson RG (2016) Improving spleen volume estimation via computer-assisted segmentation on clinically acquired CT scans. Acad Radiol. 23(10):1214-20. https://doi.org/10.1016/j.acra.2016.05.015

[57] Gotra A, Sivakumaran L, Chartrand G, Vu K-N, Vandenbroucke-Menu F, Kauffmann C, Kadoury S, Gallix B, de Guise JA, Tang A (2017) Liver segmentation: indications, techniques and future directions. Insights into Imaging. 8(4):377-92. https://doi.org/10.1007%2Fs13244-017-0558-1

[58] Hu HH, Nayak KS, Goran MI (2011) Assessment of abdominal adipose tissue and organ fat content by magnetic resonance imaging. Obes Rev. 12(5):e504-15. https://doi.org/10.1111/j.1467-789x.2010.00824.x

How to Cite;

Ertem ŞB, Malçok ÜA (2024) The Relationship Between Breast Volume and Thoracic Kyphosis Angle. 30(2):125-135. Eur J Ther. https://doi.org/10.58600/eurjther1907

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):136-144.
https://doi.org/10.58600/eurjther1925

Original Research

Investigation of the Effect of Tinnitus and Hearing Loss on Hippocampus Volume

Hadi Sasani [1], Mazhar Ozkan [2], Tolga Ersozlu [3]

[1] Tekirdag Namik Kemal University, Faculty of Medicine, Department of Radiology, Tekirdag, Türkiye
[2] Tekirdag Namik Kemal University, Faculty of Medicine, Department of Anatomy, Tekirdag, Türkiye
[3] Tekirdag Namik Kemal University, Faculty of Medicine, Department of Otolaryngology, Tekirdag, Türkiye

Received: 2023-11-10 **Accepted:** 2024-02-24 **Published Online:** 2024-02-25

Corresponding Author
Hadi Sasani, MD
Address: Tekirdag Namik Kemal University, Faculty of Medicine, Department of Radiology, 59030, Tekirdag, Türkiye
E-mail: hsasani@nku.edu.tr

ABSTRACT

Objective: This study aims to compare hippocampal changes with a correlation of audiological testing results in patients suffering from tinnitus.

Methods: Patients diagnosed with tinnitus in the university hospital between February 2021 and March 2022 were prospectively included in the study by performing magnetic resonance imaging. The volume was determined by manually tracing the hippocampus' margins on the images using the Vitrea2® workstation (Canon Medical Systems Vital Images, Minnesota, USA). Statistics were used to assess the correlation between the parameters of the hearing test.

Results: The distribution of the patient group (21 males, 19 females) and control group (15 males, 15 females) was uniform, and the mean ages of the two groups were 50.23±12.09 and 32.30±7.97, respectively. Significant statistical differences existed in the mean ages of the groups ($p<0.05$). Bilateral hippocampal volumes, right bone, and air conduction all differed significantly ($p<0.05$). The median values in the patient group were as follows: right HC 2620 mm3 (range 1600-3610), left HC 2450 mm3 (range 1610-3990), right air conduction 20 dB (range 10-61), left air 21 dB (range 11-65), and right bone 13.5 dB (range 8-49). Age was positively correlated with bilateral measurements of air and bone hearing levels (p 0.05; right air r=0.513, right bone r=0.438, left air r=0.589, left bone r=0.487). Between the 30-39 and 60-69 age groups, there was a significant difference in bone and air conduction levels ($p<0.05$).

Conclusion: In this study, it was found that the hippocampus volumes of healthy hearing people with tinnitus complaints were significantly higher in MRI examinations compared to the control group. In addition, in cases of tinnitus accompanied by bone conduction hearing loss, hippocampus volumes were found to be less than those of tinnitus alone, but not less than in the control group. It is suggested that chronic acoustic stimulation caused by tinnitus causes an increase in hippocampus volume and that problems in sensorineural integrity prevent this increase.

Keywords: Hearing loss, Hippocampus, Magnetic resonance imaging, Tinnitus, Volume

INTRODUCTION

Tinnitus is one of the most prevalent hearing disorders defined by the perception of a sound, such as a voice or noise, when there is no external sound origin. It is experienced by 17% of the general population and 33% of the elderly [1, 2]. An estimated 1% of the adult population suffers from tinnitus annually, of

which a severe form affects 2% of individuals and all adults experience tinnitus. There is no evidence that the prevalence of tinnitus varies between the sexes; nevertheless, it does increase with age (10 percent of young adults, 14 percent of middle-aged people, and 24 percent of the elderly) [3]. Tinnitus is a social challenge in aging populations.

Symptoms can be acute (within <3 months) or chronic (typically <12 months). It appears to be linked to hearing loss in many cases, as both symptoms frequently coexist. Approximately ninety percent of chronic tinnitus sufferers also have hearing loss. High-frequency hearing loss is frequently correlated with high-pitched tinnitus [1, 4, 5].

Several factors, including age, medications, head or neck trauma, otological problems, and general medical conditions (hypertension, cardiovascular disease, and Meniere's disease), have been implicated in the development of tinnitus. Nevertheless, exposure to loud noises is believed to be the primary cause of hearing loss [1].

Numerous studies have established a close association between tinnitus and both maladaptive neuroplasticity and attention-cycle disorder. According to functional neuroimaging studies, several regions beyond the central auditory system, including the frontal cortex, parahippocampus, insula, cerebellum, and thalamus, have been implicated in tinnitus perception and accompanying suffering. Also, recent studies have found that subcortical nuclei such as the amygdala, thalamus, hippocampus, insula, and basal ganglia exert a significant influence on tinnitus [6-10].

Functional imaging research has identified specific regions within the limbic system (hippocampus) and central auditory pathway (auditory cortex, medial geniculate body) that exhibit activity in patients experiencing somatic tinnitus when they adjust the volume of the phantom sound by moving their face, jaw, or upper torso. Somatic tinnitus appears to arise from somatosensory system invasion of deafened auditory cortical areas. It has also been demonstrated that tinnitus sufferers have a considerable loss in hippocampus gray matter. It has also been demonstrated that in the tinnitus group, subcortical and cortical auditory areas, as well as sound detection regions (posterior insula, hippocampus), respond with decreased, rather than increased, blood oxygenation level-dependent (BOLD) activity [4, 11].

Main Points:

- Tinnitus patients had significant hippocampal changes compared to non-tinnitus patients.
- Tinnitus caused a significant increase in hippocampal volume.
- Hearing loss reduces hippocampal volume, which rises with tinnitus.

The importance of the hippocampus in learning, memory formation, and spatial navigation has been the subject of much research [12]. Nonetheless, because it receives information from the thalamus and auditory cortex, the hippocampal region is also intimately linked to the auditory system [13]. Due to these connections, the hippocampus can perform vital functions linked to auditory processing, such as differentiating sounds, integrating auditory data with other sensory inputs, and creating memories associated with auditory events [14]. According to research, the hippocampus is involved in the creation of episodic memories that are related to specific auditory cues [15]. Numerous cognitive deficiencies, such as issues with memory formation, spatial navigation, and auditory information processing, can result from hippocampal dysfunction. Volumetric changes in the hippocampus and its subdivisions, which play an important role in the formation and retrieval of memories, have been associated with epilepsy, Alzheimer's disease, and other disorders [16]. For these reasons, the hippocampal region seems important for auditory and cognitive activities.

Magnetic resonance imaging (MRI), which has a very important place in soft tissue examination, is one of the primary tools used to examine the brain in the diagnosis and monitoring of various neurological and psychiatric diseases. MRI, which enables detailed examination and measurement of structures of different sizes in the brain with different sequences and examination options, provides clinicians with highly accurate and reliable information in monitoring the progression of diseases and monitoring their response to treatment. In this context, MRI-based measurement methods are of great importance for clinical and research purposes in brain diseases [17].

This study aims to investigate the correlation of clinical and audiological data and radiological findings in patients diagnosed with tinnitus and compare hippocampal volumetric changes in tinnitus.

MATERIALS AND METHODS

Ethical Consideration

The non-interventional clinical research ethics committee of the medical faculty approved the study protocol (a prospective case-control study, permission number: 2021.141.05.14). All patients reviewed and signed the informed consent form. The people participating in the study were treated in accordance with the 1964 Declaration of Helsinki and its amendments.

Study Population

Patients aged between 18-65 years and diagnosed with tinnitus between February 2021 and March 2022 were prospectively included in the study by performing MRI.

Patients were categorized into groups including: 1) control group (n=30), without tinnitus and/or hearing loss (0-25 decibels hearing level; dBHL), 2) tinnitus group (n=25), without hearing loss (0-25 dBHL), and 3) mild-to-moderate hearing loss associating tinnitus group (n=15, 26-60 dBHL).

Hippocampus (HC) volumes and hearing test metrics, including bilateral assessments of air and bone conduction, were compared between groups.

Inclusion and Exclusion Criteria

Patients aged 18-65 years, who had audiometric tests and MRI of optimum quality, were included in the study. Patients with previous surgery, trauma history, and malignancy were excluded.

The study subjects comprised individuals who presented with sensorineural hearing loss and an air-bone gap of less than 10 dB.

Image Ocquisition

MR images were obtained using T1-weighted imaging (WI), T2-WI, FLAIR, and postcontrast-T1-WI 3D Cube sequences on a 1.5 Tesla device (GE Healthcare Signa, Philips Ingenia) using a receive-only, eight-channel, phased-array head-neck coil.

Scan Parameters

- 3D Cube T1-WI parameters: TR (repetition time), 600 ms; TE (effective echo time) 29 ms; flip angle 8; matrix size 250x250; 1 mm slice thickness; NEX 1 and 250 mm FOV.
- 3D Cube FLAIR parameters: TR 4800 ms; TE 306 ms; TI (inversion time), 1660 ms; flip angle 90; echo-train length 125; matrix size 250x250; slice thickness 1 mm; FOV 250 mm and NEX 1.
- 3D Cube T2-WI parameters: TR 2800 ms; TE 275 ms; flip angle 40; matrix size 250x250; slice thickness 1 mm; FOV 250 mm and NEX 1.
- 3D Cube Postcontrast T1-WI: The same parameters used as T1-WI. MRI contrast material (Gadoterate meglumine, 0.1 mmol/kg, intravenous injection rate 2-3 ml/sec) was used for evaluation.

Postcontrast T1-WI MR images were employed in the assessment and reconstruction of the 3D hippocampus volume (Figure 1).

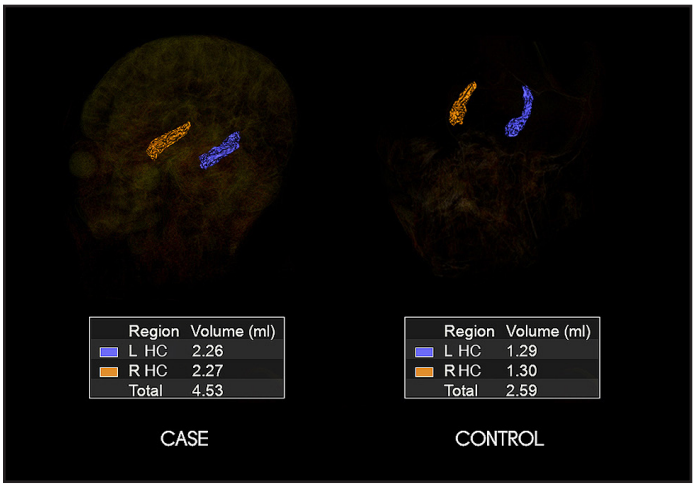


Figure 1. 3D reconstruction images show bilateral hippocampal volumes of case and control groups (HC: hippocampus).

Measurement and Imaging Analysis

The volume and segmentation were determined by manually tracing both hippocampus margins on the MR images with the Vitrea2 ® workstation (Canon Medical Systems Vital Images, Minnesota, USA). Volume and segmentation were determined by manual tracing of both hippocampus edges on MR images with the Vitrea2 ® workstation (Canon Medical Systems Vital Images, Minnesota, USA). The segmentation and measurement procedures were performed by a highly experienced radiologist and an anatomist in accordance with the scientific method based on mutual consultation and current studies in the literature.

The selection process for segmenting the anatomical borders of the hippocampus followed the methodology outlined by McHugh et al. [18] (Figure 2). In the presence of mammillary bodies in the coronal slice, which served as a demarcation line between the amygdala and the hippocampus, the anterior boundary of the

hippocampus was delineated. Defined at the section where the fornix appeared as a continuous tract, the posterior demarcation was established. The inferior horn of the lateral ventricle was encompassed within the gray matter-described superior border of the hippocampus. By means of the collateral white matter of the parahippocampal gyrus, the inferior border was developed. The segmentation process additionally included the subiculum and uncal sulcus.

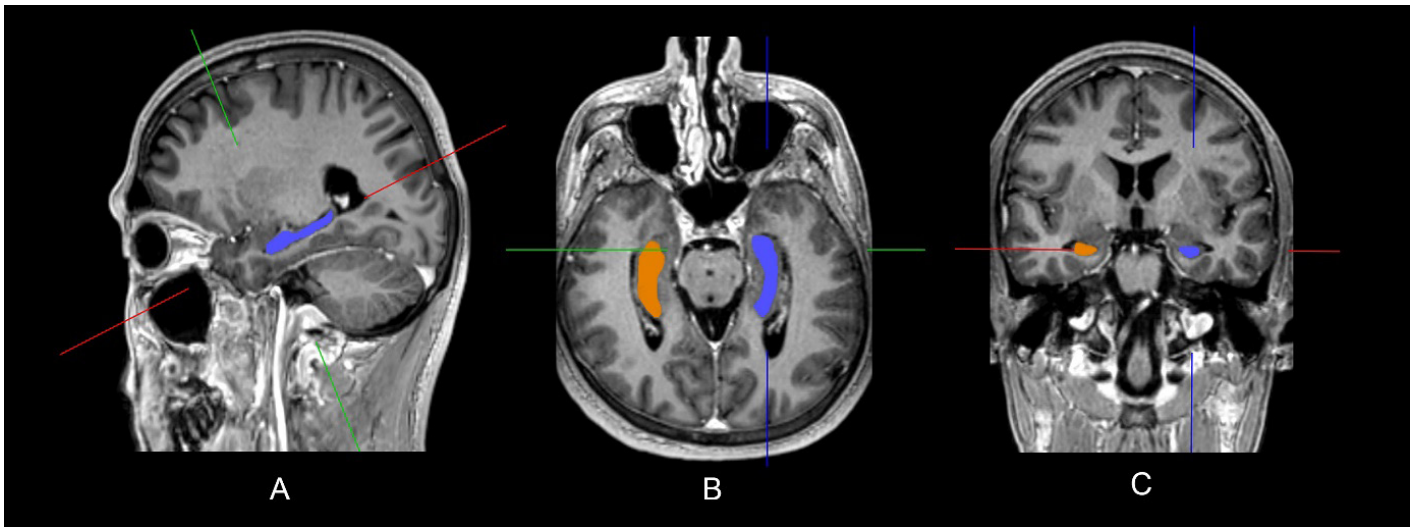


Figure 2. Multiplan demonstration of determined hippocampus borders in the long axis on the MR images.

Pure Tone Audiometry (PTA)

All participants underwent PTA as well. The same audiometrist conducted the operation in accordance with international standards using a two-channel audiometer (Interacoustics A/S, Denmark). For each ear, thresholds for frequencies ranging from 250 Hz to 8 kHz were examined. The average PTA thresholds were calculated from threshold levels of 500, 100, and 2000 Hz. A diagnosis of auditory dysfunction was made for individuals whose hearing threshold exceeded 25 dBHL [19].

Statistical Evaluation

The statistical analysis was conducted utilizing version 18.0 of SPSS. To determine whether the data were normally distributed, the Kolmogorov-Smirnov normality test was applied. In the process of evaluation, parametric or non-parametric tests were employed. In order to analyze demographic data, including marital status, age, and gender, descriptive tests were utilized. To compare groups with normally distributed data, the independent sample T-test was applied; for non-normally distributed data, the Mann-Whitney U test was utilized; and for categorical data, the chi-square test was applied. The correlation study utilized the Pearson test to assess the distribution of normally distributed data and Spearman's rho test to investigate data that was not normally distributed. P was set at a level of statistical significance below 0.05.

Statement

The authors employed a paraphrasing technology (QuillBot AI) to paraphrase the text while writing this paper. After utilizing this tool/service, the authors examined and modified the text as needed and accepted full responsibility for the publication's content.

RESULTS

The gender, age, hippocampal volume (HV), and hearing test results of the participants in the study are summarized in Table 1. The difference in mean age between the groups was statistically significant ($p<0.05$). HVs and hearing test metrics, including bilateral assessments of air and bone conduction, were compared between groups. Bilateral HVs and mean air-bone metrics differed significantly ($p< 0.05$).

Age was positively correlated with bilateral measurements of air and bone hearing levels ($p< 0.05$; right air $r=0.513$, right bone $r=0.438$, left air $r=0.589$, left bone $r=0.487$). Between the 30-39 and 60-69 age groups, there was a significant difference in bone and air hearing metrics ($p<0.05$, Figure 3).

A statistically significant difference was found between the control group (0-25 dBHL) and patients with tinnitus – without hearing loss (cases, 0-25 dBHL), and patients with tinnitus and

hearing loss (26-60 dBHL) in the comparison of air level and bilateral HVs ($p<0.05$, Figure 4).

There was a statistically significant difference between the control group (0-25 dB) and the patients with tinnitus without hearing loss (cases, 0-25 dBHL) in the comparison of bone level metric and both HV ($p<0.01$). In the comparison of the control group (0-25 dBHL) and patients with tinnitus and hearing loss (26-60 dBHL), the bone level metric and only the right HV were found to be statistically significant ($p<0.01$, Figure 4).

Although HVs increased compared to the control group, in bone level metrics HVs showed a decrease among the tinnitus groups (Figure 4). In the patient group with hearing loss, the air-bone gap was 6.5 dBHL on average.

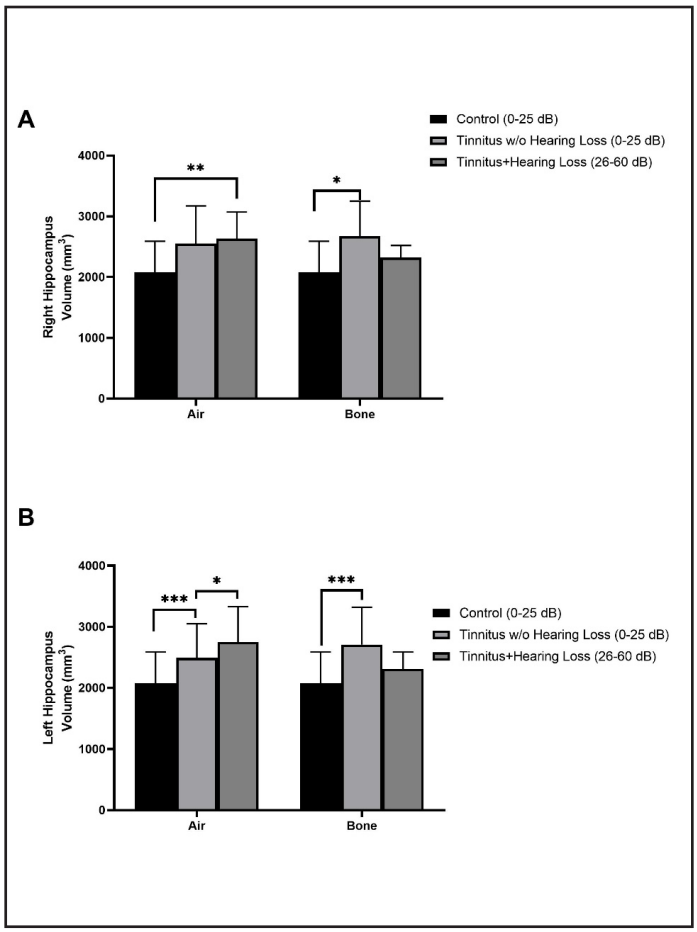


Figure 4. Hippocampal volume changes in the control group and tinnitus patients based on hearing loss groupings with air and bone conduction (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$).

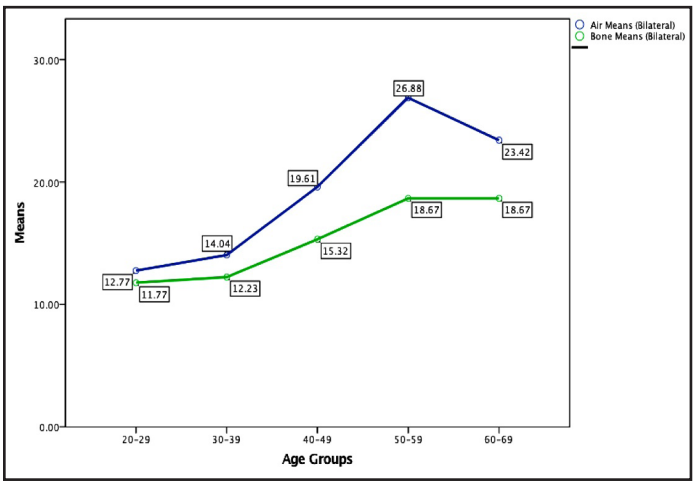


Figure 3. A significant difference in bone and air hearing metrics between the 30-39 and 60-69 age groups ($p<0.05$).

DISCUSSION

Tinnitus has a significant negative impact on patients' lives (emotional distress, cognitive dysfunction, social withdrawal, and impaired work performance) [20, 21], and the disease's causes and treatments are still unknown [22]. However, neurological approaches to the etiology of tinnitus have expanded the scope of tinnitus research [23]. The integrity of the complete hearing system, from the external ear to the auditory brain, is evaluated using air conduction testing. Bone conduction testing evaluates the sensorineural structures' integrity (cochlea, eighth nerve, brainstem nuclei, and relays to the auditory cortex). The integration of these two assessments enables the doctor to classify the patient's hearing as being within the expected range by utilizing essential physiological data [24].

The hippocampus, which is located in the temporal lobe of the central nervous system where hearing is processed, is assumed to play a role in the processing of auditory input, episodic memory, spatial navigation, and their reflection on actions [25, 26]. Noise exposure and tinnitus, for example, have been found to have an effect on hippocampal development and function [27]. Hearing loss and dementia are also investigated in the context of the hippocampus-auditory process link [28].

Tinnitus patients' left hippocampus was shown to be smaller than the control group paired for hearing loss [29]. Hippocampal surface area, on the other hand, was adversely connected negatively correlated with tinnitus handicap inventory scores which is specifically designed to evaluate the effect of tinnitus

in daily life and to document the results of tinnitus treatment by Newman et al. [7]. The right and left hippocampus volumes in both the patient and control groups were found to be the same in our investigation, and the difference between the two sides identified in prior studies was not seen in the current study.

The increased connection between the hippocampus and auditory cortex is related to louder tinnitus percepts and longer tinnitus duration in resting-state fMRI studies [8, 30]. It appears that, as compared to the control group, the left hippocampus is a key essential structure in chronic tinnitus patients [31].

In the study conducted by Tae et al. [7], a non-significant increase in left hippocampus volume was observed in patients with tinnitus (n=53) compared to the age and sex-matched control (n=52) group (3.67±0.46 ml and 3.57±0.47 ml, respectively), while a very small non-significant decrease in right hippocampus volume was observed (3.80±0.50 ml and 3.84±0.55 ml, respectively). Another study found that tinnitus increased the volume of the hippocampus and amygdala while hearing loss had no effect on the volume of either region. However, it has been noted that the duration and severity of tinnitus have no effect on this volumetric change. It is stated that the lateralization is primarily on the right side [32]. As a result of the region of interest analysis conducted in another study, a significant decrease in gray matter concentration in the left hippocampus was reported [6]. In the current study, both hippocampi volumes were shown to be higher in patients with tinnitus than in the control group. This also demonstrates that the HVs may show variation depending on the region and country. The findings of this study revealed that HVs were higher in the tinnitus-only group compared to control group patients, but HVs were lower in the tinnitus group with hearing loss. We suggest that chronic acoustic stimulation caused by tinnitus causes an increase in hippocampus volume and that problems in sensorineural integrity prevent this increase. The review by Zhang et al (2022) discusses possible mechanisms that may support this hypothesis and is recommended for those who want to have detailed information [33].

In the comparison with the literature, the mean HVs showed variation between 3076 ± 472 mm^3 (minimum) and 3573 ± 630 mm^3 (maximum) (Supplementary Table 1). The mean HV in the current study was 2304 ± 599 mm^3 which shows the variation in HV according to the regions and populations.

Tinnitus is exacerbated by age, which causes cortical thinning and the most significant changes in the frontal and temporal cortices (hippocampal areas) and deeper structures (putamen, thalamus, nucleus accumbens). Aging causes changes in many brain areas that aren't directly related to age-related sensory degeneration (presbycusis, presbyopia) [34, 35]. After average hearing loss was taken into account, it was discovered that age had a negative link with the gray matter volume of the bilateral amygdalae, hippocampi, nucleus accumbens, and thalami. Hearing loss was substantially associated with bilateral nucleus accumbens and thalamus volume, but not with amygdala or hippocampus volume [36]. In the current study, tinnitus showed a positive correlation with increasing age.

Table 1. Shows the age of participants, hippocampus volume, and hearing test metrics.

Parameters	Subgroups	Control	Tinnitus without Hearing Loss	Tinnitus with Hearing Loss
Age (years)	All	32.30±7.98	47.12±12.47	53.33±8.67
Gender	Male	15	13	8
	Female	15	12	7
Bone conduction (dB)	Right	11.53 ± 1.69	11.28±2.44	24.47±10.58
	Left	11.70 ± 1.78	12.04±2.30	24.67±12.86
Air conduction (dB)	Right	11.73 ± 1.66	14.68±3.95	35.80±12.97
	Left	11.73 ± 1.61	16.64±4.83	36.80±13.30

Mean values are provided.

Limitations

The limitations in the current study can be listed as being a single-center study, the number of patients admitted during the study period is limited, and low voluntary participation in the study is low. Another issue with our study is that the total volume measurement values we acquired from the MR imaging system and the software we utilized for the measurement were low in comparison to other studies in the literature. The reason for this is assumed to be connected with slice thickness and post-processing, which can be corrected by a variety of formulas. To retain the data's authenticity, the results obtained from measurements taken under identical conditions were compared. There is no reason to be concerned about the reliability and accuracy of our data in the present situation.

CONCLUSION

In conclusion, tinnitus induced a substantial increase in bilateral hippocampi volume, and the hearing loss that accompanies tinnitus generated a less significant increase in patients suffering from tinnitus alone compared to the control group. Future research should look into whether the hippocampus volume increase, which we believe is caused by tinnitus, regresses with the emergence of hearing loss, or whether these two factors, which occur concurrently, restrict the increase in volume.

Acknowledgments: None.

Conflict of interest: No conflicts of interest are disclosed by the authors.

Acknowledgments: None.

Conflicts of interest statement and funding: The authors declare no competing interests.

Institutional ethics review committee's approval: Tekirdag Namık Kemal University, Faculty of Medicine, Non-interventional clinical research ethics committee, Approval No: 2021.141.05.14.

Authorship Contributions: HS: Conceptualization, Design, Supervision, Materials, Data collection and processing, Analysis and/or Interpretation, Literature review, Writing, Critical Review. MO: Analysis and/or Interpretation, Literature review, Writing. TE: Conceptualization, Design, Materials, Data collection and processing, Critical Review.

REFERENCES

[1] Baguley D, McFerran D, Hall D (2013) Tinnitus. Lancet. 382(9904):1600-1607. https://doi.org/10.1016/S0140-6736(13)60142-7

[2] Bhatt JM, Lin HW, Bhattacharyya N (2016) Tinnitus Epidemiology: Prevalence, Severity, Exposures and Treatment Patterns In The United States. JAMA Otolaryngol Head Neck Surg. 142(10):959-965. https://doi.org/10.1001/jamaoto.2016.1700

[3] Jarach CM, Lugo A, Scala M, van den Brandt PA, Cederroth CR, Odone A, et al (2022) Global prevalence and incidence of tinnitus: A systematic review and meta-analysis. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2022.2189

[4] Salvi R, Langguth B, Kraus S, Landgrebe M, Allman B, Ding D, et al (2011) Tinnitus and Hearing Loss and Changes in Hippocampus. Semin Hear. 32(2):203-211. https://doi.org/10.1055/s-0031-1277243

[5] Sereda M, Hall DA, Bosnyak DJ, Edmondson-Jones M, Roberts LE, Adjamian P, et al (2011) Re-examining the relationship between audiometric profile and tinnitus pitch. Int J Audiol. 50(5):303-312. https://doi.org/10.3109/14992027.2010.551221

[6] Landgrebe M, Langguth B, Rosengarth K, Braun S, Koch A, Kleinjung T, et al (2009) Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. Neuroimage. 46(1):213-218. https://doi.org/10.1016/j.neuroimage.2009.01.069

[7] Tae WS, Yakunina N, Lee WH, Ryu YJ, Ham HK, Pyun SB, et al (2018) Changes in the regional shape and volume of subcortical nuclei in patients with tinnitus comorbid with mild hearing loss. Neuroradiology. 60(11):1203-1211. https://doi.org/10.1007/s00234-018-2093-2

[8] Chen YC, Wang F, Wang J, Bo F, Xia W, Gu JP, et al (2017) Resting-State Brain Abnormalities in Chronic Subjective Tinnitus: A Meta-Analysis. Front Hum Neurosci. 11:22. https://doi.org/:10.3389/fnhum.2017.00022

[9] Leaver AM, Seydell-Greenwald A, Rauschecker JP (2016) Auditory-limbic interactions in chronic tinnitus: Challenges for neuroimaging research. Hear Res. 334:49-57. https://doi.org/10.1016/j.heares.2015.08.005

[10] Chen YC, Xia W, Chen H, Feng Y, Xu JJ, Gu JP, et al (2017) Tinnitus distress is linked to enhanced resting-state functional connectivity from the limbic system to the auditory cortex. Hum Brain Mapp. 38(5):2384-2397. https://doi.org/10.1002/hbm.23525

[11] Hofmeier B, Wolpert S, Aldamer ES, Walter M, Thiericke J, Braun C, et al (2018) Reduced sound-evoked and resting-state BOLD fMRI connectivity in tinnitus. Neuroimage Clin. 20:637-649. https://doi.org/10.1016/j.nicl.2018.08.029

[12] Eichenbaum H, Cohen NJ (2004) From conditioning to conscious recollection: Memory systems of the brain. Oxford Psychology Series (Online Ed). https://doi.org/10.1093/acprof:oso/9780195178043.001.0001

[13] Teki S, Kumar S, von Kriegstein K, Stewart L, Lyness CR, Moore BC, et al (2012) Navigating the auditory scene: an expert role for the hippocampus. J Neurosci. 32(35):12251-12257. https://doi.org/10.1523/jneurosci.0082-12.2012

[14] Jacobs J, Kahana MJ, Ekstrom AD, Fried I (2007) Brain oscillations control timing of single-neuron activity in humans. J Neurosci. 27(14):3839-3844. https://doi.org/10.1523/JNEUROSCI.4636-06.2007

[15] Moser E, Moser MB, Andersen P (1993) Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. J Neurosci. 13(9):3916-3925. https://doi.org/10.1016/j.neuroscience.2015.07.084

[16] Bartsch T, Wulff P (2015) The hippocampus in aging and disease: from plasticity to vulnerability. J Neurosci. 309:1-16. https://doi.org/10.1016/j.neuroscience.2015.07.084

[17] Mueller SG, Weiner MW (2009) Selective effect of age, Apo E4, and Alzheimer's disease on hippocampal subfields. Hippocampus. 19(6):558-564. https://doi.org/10.1002/hipo.20614

[18] McHugh TL, Saykin AJ, Wishart HA, Flashman LA, Cleavinger HB, Rabin LA, et al (2007) Hippocampal volume and shape analysis in an older adult population. Clin Neuropsychol. 21(1):130-145. https://doi.org/10.1080/13854040601064534

[19] ASHA. Degree of Hearing Loss (2023) https://www.asha.org/public/hearing/Degree-of-Hearing-Loss/

[20] Schlee W, Schoisswohl S, Staudinger S, Schiller A, Lehner A, Langguth B, et al (2021) Towards a unification of treatments and interventions for tinnitus patients: The EU research and innovation action UNITI. Prog Brain Res. 260:441-451. https://doi.org/10.1016/bs.pbr.2020.12.005.

[21] Hoekstra CE, Wesdorp FM, van Zanten GA (2014) Socio-demographic, health, and tinnitus related variables affecting tinnitus severity. Ear Hear. 35(5):544-554. https://doi.org/10.1097/AUD.0000000000000045

[22] Maes IHL, Cima RFF, Vlaeyen JW, Anteunis LJC, Joore MA (2013) Tinnitus: A Cost Study. Ear Hear. 34(4):508-514. https://doi.org/10.1097/AUD.0b013e31827d113a

[23] Eggermont JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci. 27:676-682. https://doi.org/10.1016/j.tins.2004.08.010

[24] Turner JS JR (1990). The Ear and Auditory System. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 126. Available from: https://www.ncbi.nlm.nih.gov/books/NBK231/

[25] Billig AJ, Lad M, Sedley W, Griffiths TD (2022) The hearing hippocampus. Prog Neurobiol. 218:102326. https://doi.org/10.1016/j.pneurobio.2022.102326

[26] Knierim JJ (2015) The hippocampus. Curr Biol. 25(23):R1116-R1121. https://doi.org/10.1016/j.cub.2015.10.049

[27] Zhang L, Wu C, Martel DT, West M, Sutton MA, Shore SE (2019) Remodeling of cholinergic input to the hippocampus after noise exposure and tinnitus induction in Guinea pigs. Hippocampus. 29(8):669-682. https://doi.org/10.1002/hipo.23058

[28] Griffiths TD, Lad M, Kumar S, Holmes E, McMurray B, Maguire EA, et al (2020) How can hearing loss cause dementia? Neuron. 108(3):401-412. https://doi.org/10.1016/j.neuron.2020.08.003

[29] Boyen K, Langers DR, de Kleine E, van Dijk P (2013) Gray matter in the brain: differences associated with tinnitus and hearing loss. Hear Res. 295:67-78. https://doi.org/10.1016/j.heares.2012.02.010

[30] Ueyama T, Donishi T, Ukai S, Ikeda Y, Hotomi M,

Yamanaka N, et al (2013) Brain regions responsible for tinnitus distress and loudness: a resting-state FMRI study. PloS One. 8(6):e67778. https://doi.org/10.1371/journal.pone.0067778

[31] Lan L, Chen YC, Shang S, Lu L, Xu JJ, Yin X, et al (2022) Topological features of limbic dysfunction in chronicity of tinnitus with intact hearing: New hypothesis for 'noise-cancellation'mechanism. Prog Neuropsychopharmacol Biol Psychiatry. 113:110459. https://doi.org/10.1016/j.pnpbp.2021.110459

[32] Profant O, Škoch A, Tintěra J, Svobodová V, Kuchárová D, Svobodová Burianová J, et al (2020) The Influence of Aging, Hearing, and Tinnitus on the Morphology of Cortical Gray Matter, Amygdala, and Hippocampus. Front Aging Neurosci. 12:553461. https://doi.org/10.3389/fnagi.2020.553461

[33] Zhang L, Wang J, Sun H, Feng G, Gao Z (2022) Interactions between the hippocampus and the auditory pathway. Neurobiol Learn Mem. 189:107589. https://doi.org/10.1016/j.nlm.2022.107589

[34] Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB, Alzheimer's Disease Neuroimaging Initiative (2014) What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol. 117:20-40. https://doi.org/10.1016/j.pneurobio.2014.02.004

[35] Lin FR, Ferrucci L, Metter EJ, An Y, Zonderman AB, Resnick SM (2011) Hearing loss and cognition in the Baltimore Longitudinal Study of Aging. Neuropsychology. 25(6):763-770. https://doi.org/10.1037/a0024238

[36] Yoo HB, de Ridder D, Vanneste S (2016) The Importance of Aging in Gray Matter Changes Within Tinnitus Patients Shown in Cortical Thickness, Surface Area and Volume. Brain Topogr. 29(6):885-896. https://doi.org/10.1007/s10548-016-0511-5

How to Cite;

Sasani H, Ozkan M, Ersozlu T (2024) Investigation of the Effect of Tinnitus and Hearing Loss on Hippocampus Volume. 30(2):136-144. Eur J Ther. https://doi.org/10.58600/eurjther1925

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):145-150.
https://doi.org/10.58600/eurjther1977

Original Research

Can Appendiceal Neoplasms Be Predicted in Patients with Presumed Acute Appendicitis?

Şevki Pedük [1]

[1] Department of Surgical Oncology, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Türkiye

Received: 2023-12-23 **Accepted**: 2024-02-06 **Published Online**: 2024-02-07

Corresponding Author
Şevki Pedük, M.D.
Address: Department of Surgical Oncology, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Türkiye
E-mail: hagariii@gmail.com

ABSTRACT

Objective: The detection of malignancy in the final pathology report of patients undergoing surgery for acute appendicitis is a nasty surprise for both the patient and the clinician. To improve the management of this situation, we analyzed clues for predicting possible neoplasms.

Methods: We analyzed in detail the data of patients operated on in our department with a preliminary diagnosis of acute appendicitis over 42 months. The group whose final pathology was reported as primary appendiceal neoplasm was compared with the acute appendicitis group.

Results: Appendiceal neoplasm was detected in 16 patients (1%). Half of these were mucinous epithelial neoplasms. Neuroendocrine tumors (18.7%) were the second most common neoplasm. According to the logistic regression model, low hemoglobin level ($p<0.01$) and low Alvarado score (p:0.02) were the two most valuable factors in the prediction of primary appendiceal neoplasms. Laboratory findings of high neutrophil/lymphocyte ratio ($p<0.01$) and plastron formation on imaging (p:0.03) were more common in the neoplasm group. Advanced age, comorbidity, immunosuppression and inflammatory bowel diseases (IBD) were other characteristics of the neoplasm group.

Conclusions: Appendiceal neoplasms should always be considered in anemic patients with relatively low Alvarado scores.

Keywords: Appendicitis, Appendectomy, Appendiceal Neoplasms, Appendiceal Tumor

INTRODUCTION

Primary appendiceal neoplasms are a rare condition that is usually encountered incidentally in around 1% of appendectomies performed for acute appendicitis, and this rate may be as high as 1.7% in some studies from the United States [1,2]. The lifetime incidence of acute appendicitis is around 8%, which increases the importance of incidental appendiceal neoplasms [3].

Although it is known that symptomatic appendiceal cancer cases present with signs of acute appendicitis, patients presenting with nonspecific findings constitute the group with a more advanced stage and worse prognosis [4]. Appendiceal neoplasms may have a wide histological diversity and highly variable biological behavior. The most common neoplasms are mucinous epithelial lesions, followed by neuroendocrine tumors and non-mucinous epithelial neoplasms [5]. As in the stomach and colon, signet ring cell carcinoma has a more aggressive biological behavior and fortunately represents a smaller group. Goblet cell carcinoma is known to be more aggressive than malignant carcinoid but has a better prognosis than colonic-type cancers. Lymphoma, sarcoma and nerve sheath tumors constitute a very rare non-epithelial group [6].

It may be useful to consider some parameters when planning interval appendectomy in cases of plastron appendicitis, which is especially common in elderly patients, to prevent the progression of possible neoplasms [7]. At the same time, inadequate patient information about the results of histologic examination after appendectomy may bring some legal problems. Therefore, we aimed to present this retrospective study to improve the approach to patients with suspected neoplastic lesions before appendectomy and to increase awareness of this issue.

MATERIALS AND METHODS

The study was conducted on the data of patients operated with a preliminary diagnosis of acute appendicitis in Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital. Patients signed an informed consent form regarding the use of medical records and ethics committee approval was obtained from the same center. Biological and demographic information, imaging and laboratory results were collected from the hospital information management system and operative findings were analyzed from patient files. Patients receiving systemic chemotherapy for malignancy, pregnant patients and the population younger than 18 years were excluded. Patients who underwent surgery for a different cause of acute abdomen but were found to have appendicitis as the primary focus were also excluded. The study included 1598 patients who underwent surgery in the 42 months between September 2019 and February 2023.

Duration of symptoms, American Society of Anesthesiologists score (ASA), immunosuppression status and Alvarado scores were also questioned. Patients with primary appendiceal neoplasia (neoplasm group) and patients with appendicitis (appendicitis group) were compared in terms of independent variables. The neoplasm group was divided into epithelial tumors and neuroendocrine tumors. Epithelial lesions were classified as mucinous and non-mucinous.

Main Points:

- In patients with a prediagnosis of acute appendicitis, the rate of neoplasm detection in the final pathology is approximately 1%.
- The fact that it is the most common acute abdomen surgery performed worldwide increases the importance of this rate.
- Since preoperative prediction of this condition may change both the operative strategy and the treatment plan, a number of parameters were analysed.
- Appendiceal neoplasm should be considered and managed accordingly, especially in anaemic patients with low Alvarado score

Statistical Analysis

Data distribution was tested by Shapiro-Wilk analysis. Pearson chi-square test was used for categorical variables and the Mann-Whitney U test for continuous variables. The logistic regression method was used for predictive value analysis. Cut-off values were calculated by the receiver operating characteristic curve (ROC). $P \leq 0.05$ was considered statistically significant. All analyses were performed with SPSS version 22 for Windows software.

RESULTS

The median age of the 1598 patients included in the study was 25 years (18-82). According to Tabachnick, nonparametric tests were used for age and other data that did not show normal distribution and are emphasized with * in the tables [8]. Of the total patients, 646 were female (40.4%). There was a total of 11 patients with severe life-threatening conditions such as sepsis, newly diagnosed myocardial infarction or other serious life-threatening conditions (ASA 4). The mean body mass index was 26.8. Symptom duration at presentation ranged from 12 to 72 hours. Severe heart failure, uncontrolled diabetes, chronic renal failure, chronic lung parenchymal disease or neurologic problems were considered as comorbidities. The number of patients receiving treatment for inflammatory bowel disease was 9 (0.56%) and the number of patients receiving high-dose steroids and other immunosuppressants for different reasons was 26 (1.6%). Biological data are summarized in Table 1 and laboratory and imaging findings are summarized in Table 2.

The appendiceal neoplasm was detected in only 16 patients, and its rate among all appendectomies is around 1%. Mucinous type adenoma or adenocarcinoma was detected in 8 of them (50%). The neuroendocrine tumor was observed in three patients (18.7%), colonic type adenocarcinoma was observed in two patients (12.5%), and signet ring cell carcinoma, goblet cell carcinoma and lymphoma were detected in one patient each (6.2%). Patients with appendiceal neoplasm were relatively older ($p<0.01$). In parallel, higher ASA scores and body mass indexes in the neoplasm group and more comorbidities in this

group were thought to be associated with advanced age. It was statistically significant that inflammatory bowel diseases and immunosuppressed patients were more common in the neoplasm group (p:0.003, p:0.02, respectively). Weak immunity, especially in association with intestinal inflammation, was thought to be a facilitator for appendiceal neoplasms. Gender seemed to be insignificant in terms of appendiceal neoplasms. Smoking habits and the duration of appendicitis-specific symptoms did not provide any clue for appendiceal neoplasms. A lower Alvarado score (6.5-7.1) was statistically significant for tumor patients. The most striking imaging finding was that plastron formation was more common in the neoplasm group (p:0.03). Although the mean appendix diameter (mm) was higher, it was below the statistical significance level (12.6-11.8). When the laboratory findings were analyzed, higher neutrophil count versus lower lymphocyte count suggested that the neutrophil/lymphocyte ratio could give an idea about appendiceal neoplasms.

Table 1. Demographic and biological characteristics between the two groups

Biological features	Neoplasm	Appendicitis	P value
Age*	45	25	**<0.01**
Sex Male	11(68.8%)	941(59.5%)	0.45
BMI	26.9	25.2	**0.05**
ASA score	2(1-4)	2(1-4)	**0.02**
Smoker	6(37.5%)	398(25.2%)	0.19
Comorbidity	8(50%)	178(11.3%)	**<0.01**
IBD	2(12.5%)	7(0.4%)	**0.003**
Immunosuppression	2(12.5%)	24(1.5%)	**0.02**
Alvarado score	6.5	7.1	**0.04**
DoS*	20.5	22.4	0.13

Chi-Square , Student's t-test, *Mann Whitney-U

BMI: body mass index; ASA: American Society of Anesthesiologists; IBD: inflamatory bowel disease; Dos: duration of symptoms

Table 2. Radiologic and laboratory differences between the two groups

Imaging & Laboratory	Neoplasm	Appendicitis	P value
DoA(mm)	12.6	11.8	0.17
Appendicolith	4(25%)	466(29.5%)	0.79
Plastron	2(12.5%)	28(1.8%)	**0.03**
Abscess	1(6.3%)	79(5%)	0.56
Phlegmon	2(12.5%)	94(5.9%)	0.24
IAF	3(18.8%)	206(13%)	0.35
WBC($\times10^9$/L)	14.2	13.1	**0.04**
Lymphocyte($\times10^9$/L)	1.6	1.9	**0.01**
Neutrophil($\times10^9$/L)	12	11.2	0.1
Hemoglobin(g/dL)	12.2	13.9	**<0.01**
Platelet* ($\times1000/\mu L$)	248.8	303.8	**0.05**
NLR	7.7	6.2	**<0.01**
PLR*	160	155.8	0.43

Chi-Square , Student's t-test, *Mann Whitney-U

DoA: diameter of appendix; IAF: intra abdominal fluid; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio

When the independent variables that differed between the neoplasm group and the appendicitis group were examined by logistic regression analysis, it was seen that a low hemogram value was the most reliable indicator in predicting neoplasm ($p<0.01$). It was determined that each 1-point decrease in the Alvarado score increased the probability of neoplasm by 0.4 times (p:0.02) (Table 3). Roc curves for both parameters were shown in Figure 1 (area under the curve for hemoglobin 0.83, for Alvarado score 0.65). The cut-off value for hemoglobin was 13.45 g/dL and for Alvarado score was 6.5.

Table 3. Impact of variables on prediction of appendiceal neoplasms

Variables	Exp(B)	95% C.I. for EXP(B)		P value
		Lower	Upper	
Age	1.040	0.981	1.103	0.19
BMI	1.072	0.908	1.266	0.41
ASA score	1.392	0.503	3.853	0.52
Comorbidity	0.484	0.104	2.247	0.35
IBD	0.246	0.011	5.495	0.37
Immunosuppression	0.540	0.015	19.603	0.73
Alvarado score	0.415	0.190	.906	**0.02**
Plastron	0.188	0.010	3.541	0.26
WBC	2.371	0.587	9.574	0.22
Lymphocyte	0.949	0.033	26.968	0.97
Neutrophil	0.502	0.088	2.869	0.43

Hemoglobin	0.530	0.376	.746	**0.00**
Platelet	0.999	0.995	1.003	0.54
NLR	1.260	0.409	3.878	0.68

Logistic regression analysis(enter method)

BMI: body mass index; ASA: American Society of Anesthesiologists; IBD: inflamatory bowel disease; WBC: white blood cell; NLR: neutrophil/lymphocyte ratio

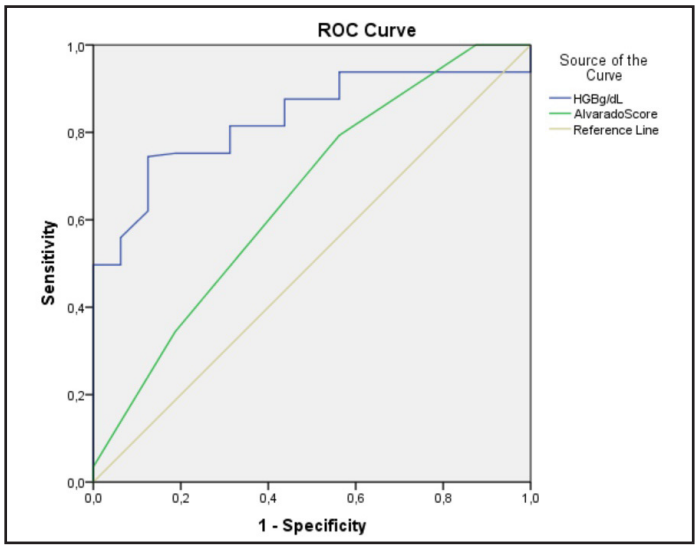


Figure 1. ROC analysis of two important parameters in the prediction of appendiceal neoplasms.

DISCUSSION

Since appendectomy is one of the most frequently performed emergency operations both in our country and worldwide, we believe that it deserves a special approach in terms of follow-up and outcomes [9]. If some predictive factors for appendiceal neoplasms can be determined preoperatively, the surgical technique and follow-up strategy can be appropriately developed. For resection to be performed by oncological principles, preparations such as preparation of erythrocyte suspension in the preoperative period, informing the patient, obtaining appropriate surgical consent and preparing the necessary surgical materials are required. In this way, the need for repeat surgery can be eliminated. Even if an appendiceal neoplasm is not detected intraoperatively, the presence of possible risk factors will keep in mind that the case may not be a simple appendicitis, so that close follow-up of the final pathology report may prevent advanced disease [10].

When patients who were operated on for more than 4 years were carefully analyzed, it was observed that the group in which appendiceal neoplasms were detected consisted of significantly older patients, which is in line with the literature [11, 12]. Increasing body mass index and the high incidence of comorbidities can be considered as a result of advanced patient age, although they are not directly related to the neoplasm.

Although female gender has been considered a risk factor for appendix malignancy in some studies [13], the general opinion in the literature is that gender is not a determinant [14]. In our study, gender was not a significant variable. The significantly lower Alvarado score in the neoplasm group (p:0.04) may be because pain migration is a symptom specific to acute appendicitis. Studies are emphasizing this situation [12]. Inflammatory bowel diseases (p:0.003) and immunosuppression (p:0.02) were found to be two different parameters that were more common in the appendiceal neoplasm group. In the literature, there are articles stating that the association of inflammatory bowel diseases and appendiceal carcinoids has no special significance [15], and there are also authors claiming that this is not a simple coincidence [16]. Although the increased risk of colon adenocarcinoma due to long-term epithelial inflammation has been emphasized, no consensus has been reached for isolated tumors of the appendix [17, 18]. Based on the data from our study, we suggest that weak immunity may constitute a risk for appendiceal neoplasms and that colonic inflammation further increases this risk.

When preoperative imaging features and perioperative findings were considered, it was found that only plastron formation was significantly higher in appendiceal neoplasms (12.5% - 5.9% p:0.02). It was found that this condition was described as a suspicious mass in some publications in the literature, while focal dilatation of the appendix was emphasized in others [12, 19]. In laboratory results, the mean total white blood cell count (WBC) was slightly higher in neoplasm patients, while lymphocytosis was more prominent in patients with acute appendicitis (p:0.01). Considering the publications that consider relatively low WBC as an independent predictor of appendiceal tumor [20], low hemoglobin value and high NLR ratio were considered to be more valuable parameters (p<0.001).

Limitations

The only limitation of the study was the lack of a standardized description of the plastron formation during perioperative evaluation, which was compensated by careful CT examination and comparison.

CONCLUSION

As a result of both the biological characteristics of the patients and laboratory findings, hemoglobin value was found to be the most valuable finding as a neoplasm predictor. It should be kept in mind that the operation of anemic patients with relatively low Alvarado scores under more optimal conditions will make undeniable contributions to improving the prognosis of the disease.

Funding: No grants or support were received in the development of the study.

Acknowledgment: We would like to thank the staff of general surgery, radiology and pathology departments of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital

REFERENCES

[1] Shaib WL, Assi R, Shamseddine A, Alese OB, Staley C 3rd, Memis B, Adsay V, Bekaii-Saab T, El-Rayes BF (2016) Appendiceal Mucinous Neoplasms: Diagnosis and Management. Oncologist 9:1107-1116. https://doi.org/10.1634/theoncologist.2017-0081

[2] Connor SJ, Hanna GB, Frizelle FA (1998) Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum 41:75–80. https://doi.org/10.1007/BF02236899

[3] Carpenter SG, Chapital AB, Merritt MV, Johnson DJ (2012) Increased risk of neoplasm in appendicitis treated with interval appendectomy: single-institution experience and literature review. Am Surg 78:339-43

[4] Bardakci M, Demirtas Esmer D, Hafızoğlu E, Karakaş H, Bal Ö, Algın E, Akıncı MB, Yalçın B (2023) Clinical Presentation and Prognostic Factors of Primary Appendiceal Malignancies: A retrospective evaluation. Adnan Menderes University Journal of Faculty of Health Sciences 7:296-304. https://doi.org/10.46237/amusbfd.1098489

[5] McCusker ME, Coté TR, Clegg LX, Sobin LH (2002). Primary malignant neoplasms of the appendix: A population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer 94:3307-3312. https://doi.org/10.1002/cncr.10589

[6] Zakka K, Williamson S, Jiang R, Reid MD, Alese OB, Shaib WL, Wu C, Behera M, El-Rayes BF, Akce M (2021) Is adjuvant chemotherapy beneficial for stage II-III goblet cell carcinoid/goblet cell adenocarcinoma of the appendix? Surg Oncol 36:120-129. https://doi.org/10.1016/j.suronc.2020.12.003

[7] Son J, Park YJ, Lee SR, Kim HO, Jung KU (2020) Increased Risk of Neoplasms in Adult Patients Undergoing Interval Appendectomy. Ann Coloproctol 36:311-315. https://doi.org/10.3393/ac.2019.10.15.1

[8] Tabachnick BG, Fidell LS (2007) Experimental designs using ANOVA (Vol. 724). Belmont, CA: Thomson/Brooks/Cole

[9] Turan Ü, Kılavuz H, Irkorucu O (2022) Emergency Right Hemicolectomy for Pericecal Masses Mimicking Acute Appendicitis: Surgeon's Fearful Dilemma. Eur J Ther 28:142-145. https://doi.org/10.54614/eurjther.2021.0090

[10] Kelly KJ (2015) Management of Appendix Cancer. Clin Colon Rectal Surg. 28:247-55. https://doi.org/10.1055/s-0035-1564433

[11] Addiss DG, Shaffer N, Fowler BS, Tauxe RV (1990) The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 132:910–25. https://doi.org/10.1093/oxfordjournals.aje.a115734

[12] Loftus TJ, Raymond SL, Sarosi GA Jr, Croft CA, Smith RS, Efron PA, Moore FA, Brakenridge SC, Mohr AM, Jordan JR (2017) Predicting appendiceal tumors among patients with appendicitis. J Trauma Acute Care Surg. 82:771-775. https://doi.org/10.1097/TA.0000000000001378

[13] Sadot E, Keidar A, Shapiro R, Wasserberg N (2013) Laparoscopic accuracy in prediction of appendiceal pathology: oncologic and inflammatory aspects. Am J Surg. 206:805-9. https://doi.org/10.1016/j.amjsurg.2013.05.002

[14] Yıldırım E, Kegin M, Özdemir M, Bektaş S, Pelen Z, Er M (2022) Neoplasms of the appendix: Single institution and ten-year experiences results. Ulus Travma Acil Cerrahi Derg. 28:352-360. https://doi.org/10.14744/tjtes.2021.86032

[15] Greenstein AJ, Balasubramanian S, Harpaz N, Rizwan M, Sachar DB (1997) Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. Am J Gastroenterol. 92:682-5

[16] Le Marc'hadour F, Bost F, Peoc'h M, Roux JJ, Pasquier D, Pasquier B (1994) Carcinoid tumour complicating inflammatory bowel disease. A study of two cases with review of the literature. Pathol Res Pract. 190:1185-92. https://doi.org/10.1016/S0344-0338(11)80445-0

[17] Da Silva JIA, Caetano C, da Rocha AMS, Lamas NJ, Lago P, Pedroto IMTC (2020) A rare cecal subepithelial tumor in a Crohn´s Disease patient. Autops Case Rep. 8;11:e2020211. https://doi.org/10.4322/acr.2020.211

[18] Nehme F, Schneider A, Hamid F (2019) Appendiceal Adenocarcinoma Associated With Ulcerative Colitis. ACG Case Rep J. 25;6:e00255. https://doi.org/10.14309/crj.0000000000000255

[19] Marotta B, Chaudhry S, McNaught A, Quereshy F, Vajpeyi R, Chetty R, Ghai S (2019) Predicting Underlying Neoplasms in Appendiceal Mucoceles at CT: Focal Versus Diffuse Luminal Dilatation. AJR Am J Roentgenol. 213:343-348. https://doi.org/10.2214/AJR.18.20562

[20] Koç MA, Çelik SU (2023) Evaluation of factors predicting appendiceal tumoral lesions in patients undergoing appendectomy for acute appendicitis. Ulus Travma Acil Cerrahi Derg. 29:358-363. https://doi.org/10.14744/tjtes.2023.34833

How to Cite;

Pedük Ş (2024) Can Appendiceal Neoplasms Be Predicted in Patients with Presumed Acute Appendicitis?. 30(2):145-150. Eur J Ther. https://doi.org/10.58600/eurjther1977

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):151-159.
https://doi.org/10.58600/eurjther1957

Original Research

Global Publication Trends and Research Hotspots of the Gastric Neuroendocrine Neoplasms: A Bibliometric Analysis of the Current Situation

Hüseyin Köseoğlu [1], Muhammed Kaya [1], İbrahim Durak [1], Tolga Düzenli [1], Mustafa Kaymazlı [2], Mesut Sezikli [1]

[1] Department of Gastroenterology, Hitit University, Faculty of Medicine, Çorum, Türkiye
[2] Department of Gastroenterology, Hitit University, Erol Olçok Education and Research Hospital, Çorum, Türkiye

Received: 2023-12-14 **Accepted:** 2024-01-26 **Published Online:** 2024-01-29

Corresponding Author
Hüseyin Köseoğlu, Assoc. Prof., MD
Address: Hitit University, Faculty of Medicine, Department of Gastroenterology, Çepni, 19040, Çorum, Türkiye
E-mail: huseyinko@yahoo.com

ABSTRACT

Objective: Gastric neuroendocrine neoplasms (gNENs) are uncommon tumors, with growing understandings about the disease. Bibliometric analyzes have the advantage of visually depicting the dynamic evaluation of scientific knowledge of a specific topic. The aim of this study was to perform and report bibliometric analysis of gNENs, which was not formerly studied in the literature.

Methods: Articles published between 1980 and 2022 within the database of Web of Science Core Collection were included in this bibliometric analysis. Vosviewer package program and Datawrapper were used for bibliometric data interpretation.

Results: A total of 2270 articles about gNENs was detected with 63240 citations and an H index of 103. A remarkable increase was detected among the articles for years. Research have focused on gastroenterology and hepatology, endocrinology and metabolism, oncology, general medicine, pathology and surgery areas. Norwegian University of Science Technology was the leading institution about gNENs literature. Modlin IM, had the highest number of articles and citations among the authors. United States, Japan and Italy were the top three countries with the most published articles.

Conclusion: This bibliometric study provides an engrossing, insightful conclusion to the research and development trajectory in gNENs with a future perspective.

Keywords: neuroendocrine neoplasms, bibliometric, publication trends, research hotspots

INTRODUCTION

Gastric neuroendocrine neoplasms (gNENs) are uncommon tumors of the stomach, which are derived from enterochromaffin-like cells of the gastric mucosa [1]. While gNENs were called as carcinoids in the historical process, it was later classified according to different features and finally gNENs were classified as gastric neuroendorine tumors (gNETs) and gastric neuroendocrine carcinoma (gNEC) according to the tumor grade [2,3]. gNENs are seen uncommonly and represent 5%-23% of all digestive NENs, but the overall incidence of g-NENs increases with time [3,4]. A study showed that the incidence of g-NENs increased from 0.309 to 6.149 per 1000000 persons in 40 years [5]. Changes in disease frequency and classification over years, made gNEN a target subject for studies. Formerly g-NENs were classified as three distinct subtypes, but a newly defined fourth type is also present [6,7]. It is essential to discriminate between types of g-NENs, because the prognosis, managing and treatment differ between these types. Treatment options for g-NENs are follow-up without excision, endoscopic resection, surgical resection or medical treatment depending on the tumor subtype, lesion size and number, disease extent and the differentiation of the tumor [1,3,8]. Recently, new data on new subgroups are

emerging, as well as changes in treatment and follow-up are present. Therefore, more studies about gNENs are expected in the literature.

Bibliometric was defined by Pritchard, as 'the application of mathematical and statistical methods to books and other media of communication' in 1969 and it was further defined as 'the quantitative analysis of the bibliographic features of a body of literature' by Hawkins [9,10]. Bibliometric analysis may also be defined as the measurement of all aspects related to the publication and reading of books and documents and bibliometric research are very popular in various areas in recent years [11,12]. It has the advantage of keeping abreast with the latest advances of interest within a particular scientific topic or area. Although the history of bibliometrics are quite old, it has become increasingly popular in recent years, especially in the field of medical sciences [13] To date bibliometric analyzes were performed for various gastrointestinal diseases, but a bibliometric analysis of gNENs is lacking. The aim of this study was to perform and report bibliometric analysis of gNENs, for the first time in the literature to the best of our knowledge. The objective of our study was to perform a bibliometric analysis about gNENs and we aimed to fill the gap on this subject. We believe that this study will serve as a guide for future researches about gNENs, save time to concentrate on more critical points, and make a notable contribution by directing gNENs research.

Main Points:

- The study aims to fill a gap in the literature by providing insights into publication trends, research hotspots, influential authors, institutions, and countries contributing to the field of gNENs.
- The analysis revealed a steady increase in both the number of publications and citations over the years, highlighting the growing interest and research activity in the field of gNENs. It also identified leading journals, authors, and institutions contributing to gNENs research globally.
- Additionally, correlations between publicaetion numbers and economic indicators like GDP and HDI are explored. The study concludes that bibliometric analysis serves as a valuable tool for understanding the evolving landscape of research on gNENs and guiding future studies in the field

MATERIALS AND METHODS

The search in the Web of Science Core Collection database was performed on 19.02.2023. The words "gastric neuroendocrine" or "gastric carcinoid" were used for analyze without using any exclusion criteria in all fields. No filtering was used while the search, and publications which were published between 1980 and 2022 were included in the search. Because including 2023 would cause misinterpretation, it was not included in the analysis. The numerical statistics of the publications were examined with the performance analyzes using Web of Science. The Web of Science website allows searching with certain keywords through the articles and journals indexed in the database, and the results obtained can be evaluated by analyzing characteristics such as authors, years, countries, journals in which they are published, subject headings and citations.

After the numerical statistics were extracted, visual network maps of the articles about gNENs were obtained using the Vosviewer package program (Version 1.6.17, Leiden University's Center for Science and Technology Studies). The obtained citation analyzes, co-citation and co-authorship analyzes, visual network maps of keyword analysis and the features and links of the researches were presented. The VOSviewer package program is one of the prominent analysis programs with its user-friendly interface in terms of visual mapping of bibliometric networks. With this program, downloaded data from the Web of Science website can be used to create visual maps. The networks which were detected through this program included countries, journals, institutions, authors or individual publications. Countries of origin were identified according to the first authors' affiliation. Citation numbers, keywords bibliographic matching, co-citation and co-authorship relationships can be used for the creation of these Networks [14]. Additionally, "https://app.datawrapper.de" website was used for the world map image. This website offers a free-to-use application that allows obtaining regional and worldwide maps in a wide variety of fields, from health to meteorology, and presenting visual data on these maps.

Correlation analysis between the number of articles produced by the countries and their economic and development indicators of GDP (gross domestic product), GDP PPP (purchasing power parity) and GDP per capita (data was obtained from the World Bank Group website - 2021 data) [15], and HDI (Human Development Index) (data was obtained from the United Nations Development Programme Human Development Report 2021-2022) [16] were analyzed using the Spearman correlation

coefficient. GDP is the sum of the value of all goods and services produced in a country in a given year. GDP PPP is the adjusted version of this value in order to evaluate the real purchasing power by taking into account the price differences of goods and services between countries [15]. GDP per capita is the production value of goods and services per capita obtained by dividing GDP data by the country's population [15]. HDI, on the other hand, is used as a more advanced welfare level calculation tool by including citizens' statistics such as life expectancy at birth, literacy rate, and education period in addition to the economic data of the countries [16].

A citation can be defined as a reference to an article identifying the document in which it may be found. Citation per publication was calculated by dividing the total citation to the total publications in a particular journal. The articles are divided into four groups according to their impact factor. Q1 (first quartile) represents the top 25% journals according to the impact factor for a specific subject category, Q2 the top 25% between 50%, Q3 the top 50% between 75% and Q4 lists the last 25% part according to the impact factor. The H index is defined as the number of articles (*h*) that have received at least *h* citations.

RESULTS

Publications between 1980 and 2022 were analyzed and 3269 manuscripts were found. After exclusion of reviews, 2270 articles were included for analysis. Annual productivity and citation counts increased by year gradually especially after 2010, with a slight decrease in 2022 (Figure 1).

The most popular journals by the number of articles published are given in Table 1. World Journal of Gastroenterology, Scandinavian Journal of Gastroenterology, American Journal of Surgical Pathology, Journal of Clinical Endocrinology Metabolism and Digestion published 49, 39, 30, 30 and 28 articles, respectively. The highest total citation count among journals was detected in Cancer Journal with a total citation count of 4229 (citation per document:162.65). Among the 2270 articles, 2027 items were published in journals which are indexed in Science Citation Index Expanded.

The top three authors were Modlin IM (55 articles), Waldum HL (52 articles) and Bordi C (36 articles), whereas other productive authors and citation numbers are presented in Table 2. Norwegian University of Science Technology (70 article), Yale University (62 article), National Institutes of Health USA (50 article), Uppsala University (49 article) and University of California (47 article) were the most prolific institutions.

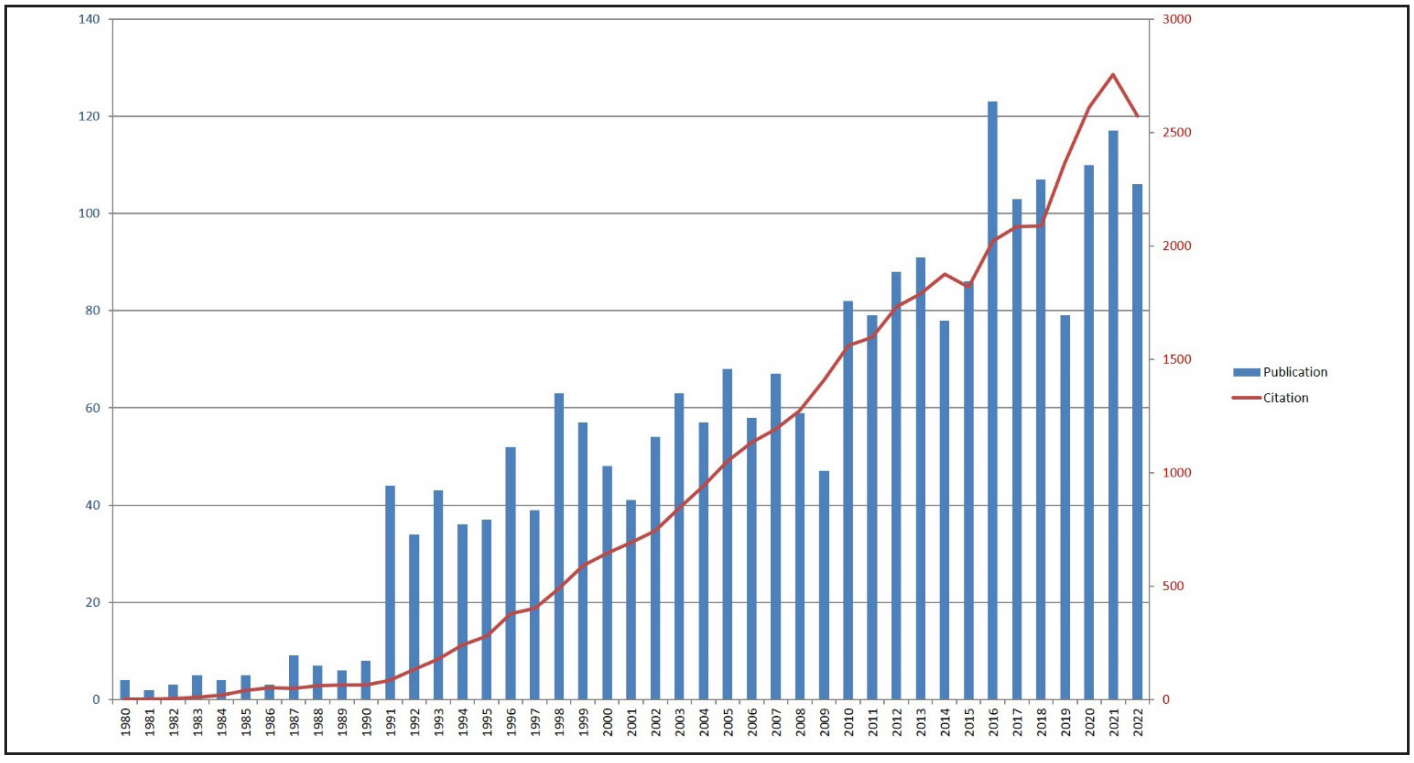


Figure 1. Annual article number and citation counts according to years from 1980 to 2022.

Table 1. Most popular journals according to the number of articles published and citation data.

Journals	Q	Publication	Citation	Citation per publication
World Journal of Gastroenterology	Q2	49	1048	21.39
Scandinavian Journal of Gastroenterology	Q4	39	1180	30.26
American Journal of Surgical Pathology	Q1	30	1792	59.73
Journal of Clinical Endocrinology Metabolism	Q1	30	2454	81.80
Digestion	Q3	28	945	33.75
Cancer	Q1	26	4229	162.65
Hepato Gastroenterology*		25	472	18.88
Medicine	Q3	23	259	11.26
Alimentary Pharmacology Therapeutics	Q1	21	787	37.48
Neuroendocrinology	Q2	21	1096	52.19
Regulatory Peptides**		21	541	25.76
Digestive Diseases and Sciences	Q3	20	559	27.95
Gastrointestinal Endoscopy	Q1	20	1864	93.20

* Hepato-Gastroenterology has been discontinued. ** Regulatory Peptides was incorporated into peptides.

Table 2. Most productive authors and their citation numbers.

Authors	Publication	Citation	Citation per publication
Modlin IM	55	4166	75.75
Waldum HL	52	1914	36.81
Bordi C	36	1978	54.94
Kidd M	36	3790	105.28
Sandvik AK	29	811	27.97
Fossmark R	27	657	24.33
Rindi G	25	2170	86.80
Solcia E	25	2237	89.48
Ahlman H	23	921	40.04
Jensen RT	23	1719	74.74
Qvigstad G	22	759	34.50
Capella C	21	1640	78.09
Delle Fave G	20	1149	57.45
Nilsson O	20	740	37.00
Huang CM	18	187	10.39
Wangberg B	18	629	34.94
Annibale B	17	532	31.29
Azzoni C	17	978	57.53
Li P	17	178	10.47
Varro A	17	508	29.88

Most of the articles were produced from the United States (586 articles), Japan (349 articles), Italy (230 articles), PR China (225 articles), Germany (178 articles), Sweden (118 articles), England (104 articles), South Korea (84 articles), Norway (78 articles) and France (70 articles) (Figure 2). Among the top 25 countries with the highest publication counts, highest citation per article numbers were achieved in Australia, Canada, France and Netherlands, respectively. Of the most prolific countries, only 3 countries had a GDP per capita level below 10000 dollars, whereas others had high GDP per capita values. The mean GDP per capita value was 43788 dollars among the top 25 countries. The correlation analysis between publication numbers and GDP, GDP PPP, GDP per capita and HDI showed that publication numbers increase with increased GDP, GDP PPP, GDP per capita and HDI (r: 0.811, 0.674, 0.521 and 0.516, respectively. $p<0.001$ for all parameters).

The total citation number of articles about gNENs was 63240, with an H index of 103. The average citation per item was calculated as 27.86. The most cited manuscript about gNENs was "A 5-decade analysis of 13,715 carcinoid tumors" which was written by Modlin IM in 2003 [17].

The top five indexed keywords except the term "neuroendocrine tumor" were: stomach, gastric cancer, carcinoid, immunohistochemistry and gastrin. Scientometric network analysis of the keywords is presented in Figure 3.

The citation network analysis included 30 countries with over 10 articles and 10 citations, which had the highest connection rates, and the network analysis is given in Figure 4. Similarly, the citation network analysis of institutions and authors with more than 5 articles and 5 citations are shown in Figure 5.

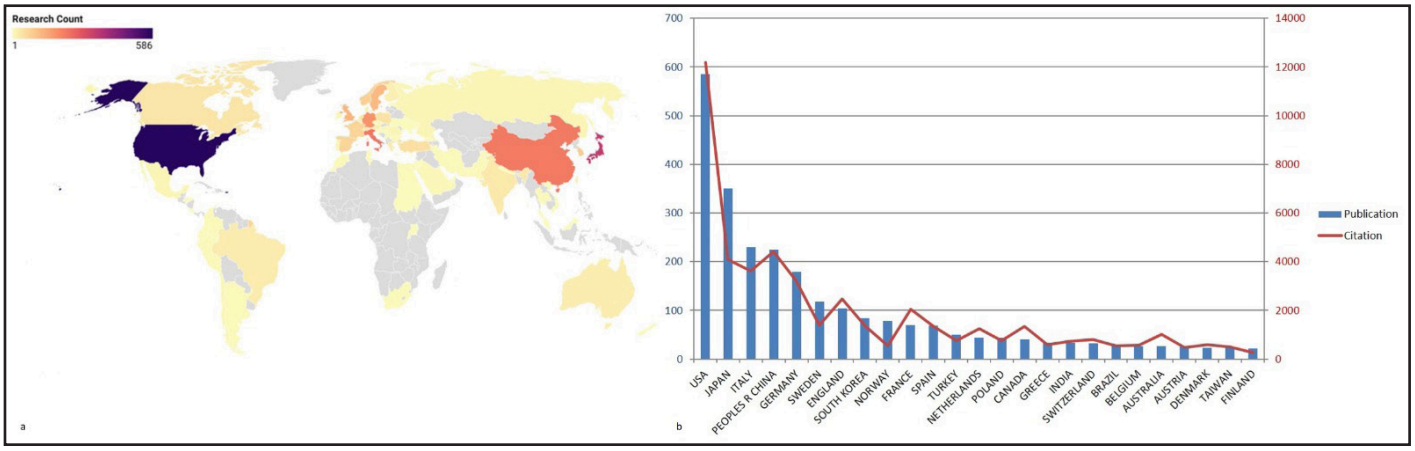


Figure 2. The most prolific countries in the field of gastric neuroendocrine tumors. a) The countries are shown in the world map, b) Top 25 countries according their publication number and citation counts of these countries.

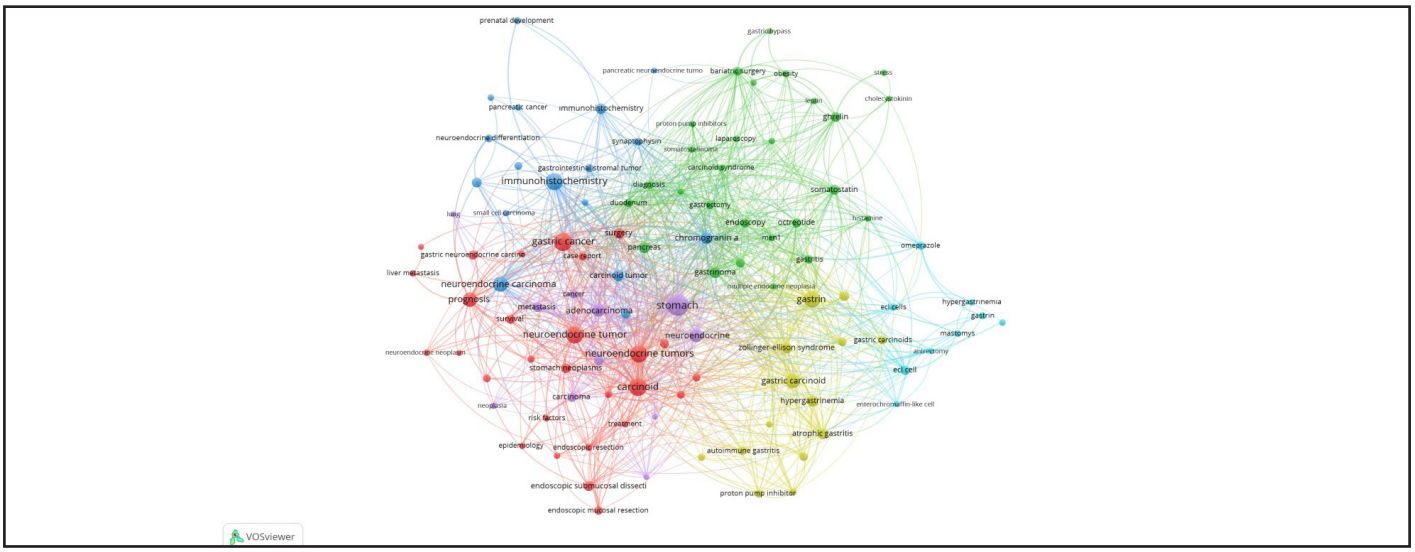


Figure 3. Scientometric network analysis of the mentioned keywords in articles about gastric neuroendocrine neoplasia.

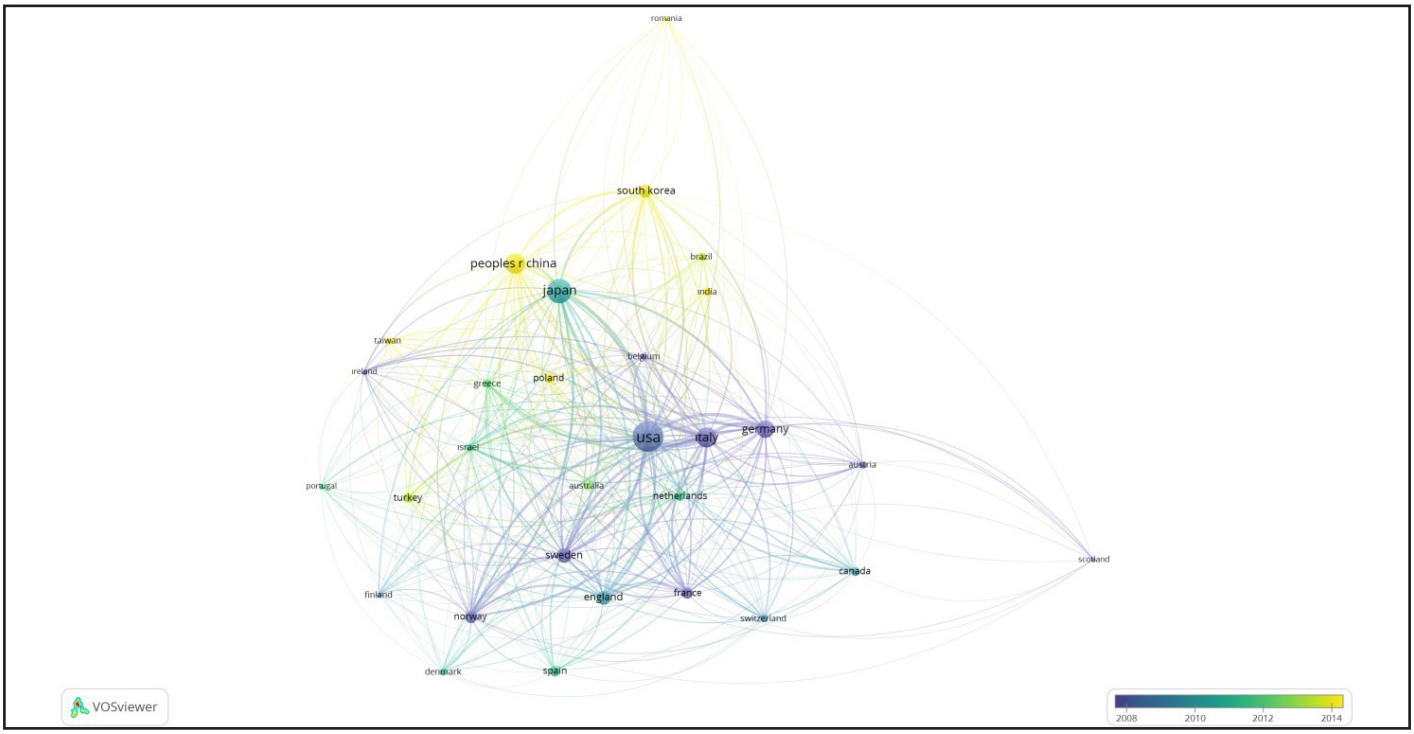


Figure 4. The citation network analysis including 30 countries with over 10 articles and 10 citations, which had the highest connection rates. Lighter colors indicate more recent studies.

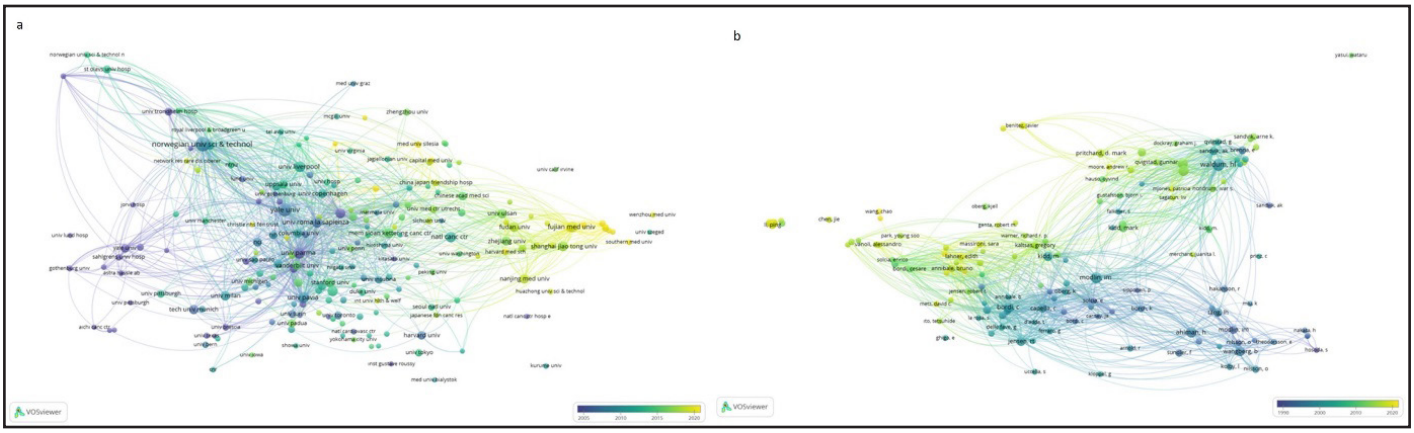


Figure 5. The citation network analysis of institutions and authors with more than 5 articles and 5 citations. Lighter colors indicate more recent studies.

DISCUSSION

Bibliometric analysis, which is a computer-based procedure in which all available publications on a subject are analyzed, benefits future studies by providing guidance based on previous data [18]. Bibliometric analysis, which is a computer-based procedure in which all available publications on a subject are analyzed, benefits future studies by providing guidance based on previous data [17]. Bibliometric analyses can be used by current researchers to save time. In this study, leading countries, organizations, authors, journals, hotspots, and trends in gNENs research were identified through a search of the Web of Science Core Collection database and VOSviewer to produce a thorough summary of the progress of gNENs research over the last 40 years. To the best of our knowledge, this study is the first bibliometric analysis of the existing gNENs literature.

Although the existence of gNENs was established more than a century ago, many new studies on the subject are being published, and ongoing scientific development in this area continues. In particular, the nomenclature, classification, treatment, and follow-up options for patients with gNENs are of great interest [3]. This data is supported by our analysis, which showed an increase in the number of articles and citations over the years. The number of citations is the basis of bibliometric analysis, and a relatively high number of citations per item was seen in our analysis [19]. The article most often cited was a large epidemiology series that included NENs written by Modlin IM [17]. Modlin IM was also found to be the most productive author, having published the most articles (55 articles) gNENs.

Most of the journals publishing articles on gNENs were indexed in Science Citation İndex Expanded. The top ten most popular journals were found to have high impact factors of Q1 (first quartile), representing the top 25% of journals, or Q2, representing the top 25% to 50%. The high number of Q1 and Q2 journals shows that there is considerable interest in the study of gNENs. Among the 11 most popular currently publishing journals, six belong to the category of gastroenterology and hepatology, two to endocrinology and metabolism, and one each to general medicine, oncology and pathology, and surgery. The fact that studies on gNENs have been published in journals from diverse categories shows the breadth of interest in the topic. The World Journal of Gastroenterology published the most articles on gNENs, which may be the result of its weekly publishing schedule. The journal most often cited was Cancer, which is a Q1 journal in the field of oncology.

The countries found to be leading in the publication of studies on gNENs were the United States, Japan, Italy, China, and Germany. The highest citation-per-article values were achieved in Australia, Canada, and France. Among the top 25 countries with the highest number of articles published, 16 are located in Europe, 5 in Asia, 2 in North America, 1 in South America, and 1 in Australia. No country in Africa placed in the top 25 countries. Publication counts were found to positively correlate with GDP and HDI. It is a fact that high income level creates more opportunity for further research. Another issue is that upper gastrointestinal endoscopy, which is the diagnostic method of gNENs, is an invasive method with relatively higher cost. Easy access to endoscopic facilities in higher income countries may be another reason for higher numbers of articles.

This study also determined the institutions with the greatest levels of production and their network analyses. The Norwegian University of Science Technology was the leading institution in the field of gNENs articles. Among the five highest-producing institutions, three are located in the United States and one each in Norway and Sweden.

Limitations

We have to mention some limitations of the study. Probably some articles may be missed during the search of the articles, because their titles or keywords did not comprise the selected keywords. Our study contained articles which are indexed in Web of Science Core Collection and other indexes were not searched. But Web of Science was used because it is the most reliable database indexing high quality journals with high impact factors. Although not containing other indexes we think that Web of Science would be sufficient for this analysis because we performed this bibliometric analysis with a satisfactory number of articles (2270 articles). Another limitation is that the countries were determined according to the first author, but some articles may have international cooperation. These limitations do not hinder our bibliometric results on the topic of gNENs, which is not formerly published in the literature.

CONCLUSION

This study examines global research trends on gastric neuroendocrine neoplasms (gNENs) from 1980 to 2022, revealing a rise in publications. The United States, Japan, and Italy are leading contributors, with the Norwegian University of Science Technology as a prominent institution. Prolific authors include Modlin IM, and high-impact journals in gastroenterology feature prominently. The analysis suggests a positive link between research output and economic indicators. Despite limitations, this study offers valuable insights for guiding future research on gNENs.

Acknowledgments: None.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: The study was not funded by any organization or person.

Informed Consent: Informed consent was not taken because the study did not involve human participants.

Ethical Approval: Ethical Approval was not taken because the study did not involve human participants.

Author Contributions: Conception: Hüseyin Köseoğlu; Muhammed Kaya - Design: Hüseyin Köseoğlu; Muhammed Kaya; İbrahim Durak - Supervision: Hüseyin Köseoğlu; Tolga Düzenli; Mustafa Kaymazlı; Mesut Sezikli; - Fundings: None - Materials: Muhammed Kaya; İbrahim Durak; Tolga Düzenli - Data Collection and/or Processing: Muhammed Kaya; İbrahim Durak; Tolga Düzenli - Analysis and/or Interpretation: Hüseyin Köseoğlu; Muhammed Kaya - Literature: Mustafa Kaymazlı; Mesut Sezikli - Review: Mustafa Kaymazlı; Mesut Sezikli - Writing: Hüseyin Köseoğlu; Muhammed Kaya; İbrahim Durak - Critical Review: Hüseyin Köseoğlu; Tolga Düzenli; Mustafa Kaymazlı; Mesut Sezikli.

REFERENCES

[1] Delle Fave G, O'Toole D, Sundin A, et al; Vienna Consensus Conference participants. (2016) ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology 103: 119-124. https://doi.org/10.1159/000443168

[2] Rindi G, Klimstra DS, Abedi-Ardekani B, et al. (2018) A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 31:1770-1786. https://doi.org/10.1038/s41379-018-0110-y

[3] Köseoğlu H, Duzenli T, Sezikli M. (2021) Gastric neuroendocrine neoplasms: A review. World J Clin Cases 9:7973-7985. https://dx.doi.org/10.12998/wjcc.v9.i27.7973

[4] Yang Z, Wang W, Lu J, et al. (2018) Gastric Neuroendocrine Tumors (G-Nets): Incidence, Prognosis and Recent Trend Toward Improved Survival. Cell Physiol Biochem 45:389-396. https://doi.org/10.1159/000486915

[5] Hu P, Bai J, Liu M, et al. (2020) Trends of incidence and prognosis of gastric neuroendocrine neoplasms: a study based on SEER and our multicenter research. Gastric Cancer 23:591-599. https://doi.org/10.3390/cancers15082202

[6] Rindi G, Luinetti O, Cornaggia M, et al. (1993) Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology 104:994-1006. https://doi.org/10.1016/0016-5085(93)90266-F

[7] Ahmed M. (2020) Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol 12:791-807. https://dx.doi.org/10.4251/wjgo.v12.i8.791

[8] Kunz PL, Reidy-Lagunes D, Anthony LB, et al; North American Neuroendocrine Tumor Society. (2013) Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 42:557-577. https://doi.org/10.1097/mpa.0b013e31828e34a4

[9] Pritchard A. (1969). Statistical bibliography or bibliometrics? Journal of Documentation 25:348–349.

[10] Hawkins DT (2001). Bibliometrics of electronic journals in information science. Information Research: An International Electronic Journal 7: 120.

[11] Rousseau R. (2014). Library science: forgotten founder of bibliometrics. Nature 510:218. http://doi.org/10.1038/510218e

[12] Kaya AE. (2023) Global scientific outputs of psychiatric malpractice publications: A bibliometric approach from 1980 to 2022. Journal of Contemporary Medicine 13:503-508. https://doi.org/10.16899/jcm.1275093

[13] Kokol P, Blažun Vošner H, Završnik J. (2021) Application of bibliometrics in medicine: a historical bibliometrics analysis. Health Info Libr J 38(2):125-138. https://doi.org/10.1111/hir.12295

[14] Van Eck N, Waltman L. (2010) Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 84:523-538. https://doi.org/10.1007/s11192-009-0146-3

[15] World Bank. International Comparison Program database. https://data.worldbank.org/indicator/NY.GDP.MKTP.CD. Accessed 01.04.2023.

[16] United Nations Development Programme. Human Development Report 2021-2022. https://hdr.undp.org/data-center/country-insights#/ranks. Accessed 01.04.2023.

[17] Modlin IM, Lye KD, Kidd M. (2003) A 5-decade analysis of 13,715 carcinoid tumors. Cancer 97:934-959. https://doi.org/10.1002/cncr.11105

[18] Donthu N, Kumar S, Mukherjee D, et al. (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

[19] Patience GS, Patience CA, Blais B, et al. (2017) Citation analysis of scientific categories. Heliyon 3:e00300. https://doi.org/10.1016/j.heliyon.2017.e00300

How to Cite;

Köseoğlu H, Kaya M, Durak I, Düzenli T, Kaymazlı M, Sezikli M (2024) Global Publication Trends and Research Hotspots of The Gastric Neuroendocrine Neoplasms: A Bibliometric Analysis of The Current Situation. 30(2):151-159. Eur J Ther. https://doi.org/10.58600/eurjther1957

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):160-169.
https://doi.org/10.58600/eurjther1927

Original Research

Protective Effect of Pomegranate Juice on Lead Acetate-Induced Liver Toxicity in Male Rats

Hıdır Pekmez [1,*], Ebru Annaç [2], Özgür Bulmuş [3], Büşra Zencirci [4], Merve Aydın [1], Ali Aydın [4]

[1] Department of Anatomy, Faculty of Medicine, Malatya Turgut Özal University, Malatya, Türkiye
[2] Department of Histology and Embryology, Faculty of Medicine, Adıyaman University, Adıyaman, Türkiye
[3] Department of Physiology, Faculty of Medicine, Balıkesir University, Balıkesir, Türkiye
[4] Department of Anatomy, Faculty of Medicine, Adıyaman University, Adıyaman, Türkiye

Received: 2023-11-10 **Accepted**: 2023-12-26 **Published Online**: 2023-12-27

Corresponding Author
Hıdır Pekmez, Associate Professor
Address: Department of Anatomy, Faculty of Medicine, Malatya Turgut *Özal* University, Malatya, Türkiye
E-mail: hidir.pekmez@ozal.edu.tr

ABSTRACT

Objective: Lead has been reported to cause oxidative stress in liver tissues and cause histopathological changes. Studies have shown that pomegranate juice has antioxidant properties that prevent oxidative stress. In this study, the harmful effects of lead acetate on rat liver tissue and the efficacy of pomegranate juice against these effects were investigated.

Methods: 28 male Wistar albino rats were divided into four groups: control, lead acetate (50 mL/kg), pomegranate juice (1 mL/kg), and lead acetate + pomegranate juice (50 mL/kg+1 mL/kg). Lead acetate and pomegranate juice were administered orally.

Results: When compared with the control group, it was seen that the lead acetate had an increase in the malondialdehyde level and a decrease in reduced Glutathione, Glutathione S-transferase, and Carboxylesterases. Group lead acetate + pomegranate juice had a reduction in malondialdehyde level and an increase in Glutathione, Glutathione S-transferase, and Carboxylesterases compared with the group lead acetate. The lead level of group lead acetate + pomegranate juice decreased compared to the group lead acetate. Cellular degeneration and irregular hepatic cords were observed in group lead acetate's liver tissue, and the negative changes were lost in group lead acetate + pomegranate juice.

Conclusion: It was observed that pomegranate juice had a protective effect against liver toxicity caused by lead acetate.

Keywords: Antioxidant, Lead acetate, Liver, Pomegranate juice, Oxidative stress

INTRODUCTION

Today, industrial activities cause an increase in environmental waste, such as heavy metals. Lead (Pb), one of these heavy metals, spreads to the biosphere in developing and industrialized societies due to its essential role in industry, causing high environmental exposure. Pb can enter the body through water, food, and breathing air, and can accumulate in the tissues causing toxic effects. The most common ways of exposure are through consumption followed by inhalation. For this reason, Pb poisoning is amongst the most common heavy metal poisonings. Due to slow Pb excretion, even at low doses, living organisms can experience physiological, biochemical, and behavioral disorders as a result of Pb accumulation in their tissues. Pb has been reported in studies that cause neurological, immunological, renal, hepatic, and hematological disorders [1-3]. In the antioxidant system, Pb binds to sulfhydryl groups and

is replaced by essential cofactors, copper and zinc. Nearly 90% of Pb is found in blood and bone, while the rest is found in the liver and kidneys [4, 5]. In many studies, lipid peroxidation due to Pb poisoning; has been reported to cause inhibition of the antioxidant system by causing the release of reactive oxygen species and free radicals. Accordingly, Pb has been reported to cause oxidative stress in liver tissues and cause histopathological changes [6].

Pomegranate (*Punica granatum L.*) is a fruit of nutritious and therapeutic value, which has been widely used in the past. Its medicinal properties are related to the existence of polyphenols (Ellagitannins, flavonoids, phenolic acids, stilbenes, tannins, and anthocyanins) with free radical scavenging properties. Pomegranate has been reported in studies with anti-carcinogenic, cardioprotective, antihyperlipidemic, anti-inflammatory, and antioxidant effects [7, 8].

Tissues produce free oxygen radicals and antioxidants in a regulated manner. Excessive production of free radicals leads to the formation of harmful substances like malondialdehyde (MDA). Antioxidant defense systems develop against its harmful effects when overproducing free oxygen radicals. Antioxidant defense systems show their impact by eliminating the detrimental effects of radicals. Glutathione (GSH) and Glutathione S-transferase (GST) are important antioxidants [9]. Carboxylesterases (Ces) are a member of esterases and catalyses the hydrolysis of amides, esters, and thioesters. The enzymatic process of converting esters into carboxylic acid and hydroxylated products has been identified in various tissues, including the liver [10].

The discovery of natural products and new substances has gained significant importance in treating diseases and toxic substances that threaten human health. Pomegranate and pomegranate juice (PJ), which contain phytochemicals that significantly increase bioactivity, have also been the subject of recent studies [11]. In addition, it has been reported in experimental studies that PJ has a histological and biochemical hepatoprotective effect by reducing oxidative stress and inflammation [12-14]. Studies have shown that consuming pomegranate juice can help prevent non-alcoholic fatty liver disease and inhibit the development of unhealthy lipid profiles. Including pomegranate juice in the diet of individuals at risk of fatty liver and high cholesterol can be beneficial [15]. We conducted a study using light microscopy and biochemical analysis to investigate the impact of lead acetate (LA) on rat liver tissue and the potential protective effect of PJ on these changes. Therefore, in this study, the effects of PJ on MDA, GSH, GST, Ces, element levels, and histopathological parameters in rat liver tissues exposed to LA were investigated.

Main Points:

- A decrease in the liver function of the rats was observed as a result of the administration of LA, according to the findings of our research.
- Our research suggests that consuming PJ may alleviate the negative effects of LA-induced oxidative stress.

MATERIALS AND METHODS

Animals

The research was carried out in the Animal Experiment Center of Fırat University. Ethics committee approval was obtained by Fırat University Animal Experiments Local Ethics Committee with the 2018/04 protocol number and 09 decision number. 28 adult Wistar albino 200-250 g male rats were used in the research. The animals were divided into four groups, and experimental procedures were applied. Rats were housed at 22 ± 2^0C room temperature, 12 hours light, and 12 hours dark-light cycle, as feed and water ad-libitum.

PJ Preparation

In our study, pomegranate grown in the Adıyaman region was used. After the pomegranates were washed and dried, their juice was obtained by pulling them out of the blender. PJ was kept at -20°C until used.

Chemical Content of PJ

The chemical composition of pomegranate grown in the Adıyaman region was investigated. The content of PJ was anthocyanin 137.1 mg/L, phenolic acid 490.75 mg/kg, ellagic acid 175 mg/100g, total flavonoids 63 mg/kg, and total antioxidants 1530 mg/kg [16].

The Study Groups and Applications

Twenty-eight male Wistar albino rats were randomly divided into control groups, LA, PJ and LA+PJ (n=7 in each group). The cages were left untouched for a week prior to the start of the experiment to allow for adaptation.

Control group: Rats were given distilled water for 30 days without any additional procedures conducted throughout the investigation.

LA group: 500 ppm Pb dissolved in acetic acid was mixed into drinking water per liter. Rats were administered 50 mL/kg of Pb through oral gavage per animal daily for 30 days, from a stock solution.

PJ group: PJ were given 1 mL/kg of PJ every two days for 30 days through oral gavage [16].

Oral gavage was applied to the rats at the same time each day. No complications resulted from these applications. The rats were sacrificed by intraperitoneal injections of xylazine hydrochloride and ketamine hydrochloride after the 30-day study period. The liver tissue samples were divided into two sections for the biochemical analysis and histopathological examination. One half of the samples were stored at a temperature of -80 °C, while the other half was fixed in 10% formaldehyde.

Preparation of Tissue Homogenates

Tissue samples of the liver in cooled potassium phosphate buffer (0.1 M, pH 7.4; 0.15M KCl, 1.0 mM EDTA, 1.0 mM DTT) were homogenized with the device of the Homogenizer (Heidolph 2021). Five hundred microliters of homogenate were reserved for use in MDA analysis. The remaining homogenates were centrifuged for 20 minutes at +4 °C (Hettich 460 R), 16.000 x g, and supernatants (S16) were taken into Eppendorf tubes for measurements of biomarkers other than MDA.

Determination of Liver MDA Level

MDA levels in liver tissue samples were determined using the technique established by Placer et al. [17]. A solution of 0.375% thiobarbituric acid and 15% trichloroacetic acid in 0.25 N hydrochloric acid was used. MDA reacts with thiobarbituric acid to form a pink-colored compound. The absorbance of the samples was read spectrophotometrically (ThermoTM Varioskan Flash, Finland) at 532 nm. In the study, MDA levels were shown as nmol/mg protein. This study was carried out on Thermo-3001 UV/VIS device with Microplate Attachment.

Determination of Liver Reduced GSH Activity

GSH analysis in liver tissues was performed at 412 nm using the Sedlak and Lindsay method on a Thermo-3001 UV/VIS device with Microplate Attachment [18]. Tissues were precipitated with 50% TCA (Trichloroacetic acid) and centrifuged at 1000xg for 5 minutes. 0.5 ml was taken from the supernatant in Eppendorf tubes removed from the centrifuge, and 2 ml Tris EDTA buffer (0.2 M, pH: 8.9) and 0.1 ml 0.01 M 5,5'-dithio-bis-2 nitrobenzoic acid were added. This mixture was left at room temperature for 5 minutes and absorbance values were measured at 412 nm on the device. GSH levels were expressed as nmol/mg protein.

Determination of Liver GST Activity

The examination of GST activity involved the preparation of a solution comprising 10 µL of supernatant, 100 µL of GSH, and 100 µL of phosphate buffer (0.1 M, pH 6.5). Following this, a solution of 20 mM 1-chloro-2,4 dinitrobenzene was prepared as a substrate, utilizing 96% ethanol, and subsequently transferred into the designated microplate wells. The microplates were placed within the reader system, and the corresponding alterations in absorbance were diligently recorded at 344 nm for a duration of 2 minutes, with a temperature of 25°C maintained throughout the process. Specific GST activity was determined from the nmol/min/mg protein type [19].

Determination of Liver Ces

For the analysis of Ces activity, 26 mM of nitrophenol acetates were utilized as a substrate, which was prepared in 96% ethanol. The reaction solution, consisting of a mixture of 5 µL of sample and 250 µL of 50 M Mtrizma buffer (pH, 7.4), was incubated for 3 minutes at 25°C. To initiate the reaction, 5 µL of the substrate was added and monitored for 2 minutes at 25 °C, with readings taken at 405 nm. Ces activity was expressed as nmol/min/mg protein [20].

Determination of Total Protein

The protein amount was measured as standard using bovine serum albumin (0–1.4 mg BSA/mL) [20].

Determination of Liver Element Concentrations

Liver Pb, iron (Fe), manganese (Mn), zinc (Zn), calcium (Ca), and copper (Cu) levels were measured at Adıyaman University Central Research Laboratory. NexION 350 inductively coupled plasma mass spectrometry (ICP-MS, Perkin Elmer, MA, USA) was used [21]. The measurements were conducted in parts per billion (ppb) unit.

Histopathological Evaluation

To perform histopathological analysis, liver samples taken were divided into 10% formaldehyde solution by dividing into

separate groups. Following a week of fixation, paraffin blocks were prepared in accordance with standard histological tissue protocol. Subsequently, 5-micron thick sections were extracted from the paraffin blocks. The stained sections were evaluated using images captured by the Carl Zeiss brand Axiocam ERc5 model digital camera attached to a microscope for histopathological analysis.

Statistical Analysis

All statistical calculations were made using SPSS 22.0 program. The results have been calculated and presented as mean ± SEM. One-way analysis of variance (ANOVA) was used for the statistical evaluation of the groups, and the Tukey-HSD test was used to identify the significant groups.

RESULTS

MDA, Reduced GSH, GST, and Ces Levels in the Liver

Liver tissue biochemical parameter levels are given in Table 1. Our study observed no statistically significant difference between the control group's MDA level and the PJ group ($p > 0.05$). It was determined that there was an increase in the LA group's MDA level compared to the control group ($p < 0.001$). In contrast, the LA+PJ group MDA level increased compared to the control group ($p < 0.001$), and it was observed that the LA+PJ group MDA level reduced compared to the LA group ($p < 0.01$). Furthermore, GSH level of LA group decreased compared to other groups ($p < 0.001$; $p < 0.01$).

It was observed that the GST enzyme activity level decreased in the LA group compared to the control group ($p < 0.01$). In comparison to the LA group, the GST enzyme activity level of the PJ group was decreased ($p < 0.05$). In addition, there was a partial increase in the LA+PJ group GST enzyme activity level compared to the LA group. In comparison to the control group, the activity level of Ces enzyme was observed to decrease in the LA group ($p < 0.001$). On the other hand, PJ and LA+PJ groups Ces enzyme activity levels were increased compared to the LA group ($p < 0.01$).

Findings on the Liver Element Analysis

The results of our study indicate that there was no statistically significant difference in the level of Pb between the control group and the groups that consumed PJ ($p > 0.05$). However, it was observed that the group that received Pb showed a significant increase in Pb levels when compared to the control group ($p < 0.001$). Also, LA+PJ group showed an increase in Pb levels in comparison to the control group ($p < 0.001$). However, the Pb levels decreased in LA+PJ group when compared to the LA group ($p < 0.01$) (Table 2).

There was no significant difference in Fe level between the groups ($p > 0.05$). A significant decrease was found in the Mn level in the LA group compared to the control group ($p < 0.05$). While the Zn level decreased in the LA group compared to the control ($p < 0.001$), it increased in the PJ ($p < 0.01$) and LA+PJ groups compared to the LA group ($p < 0.05$). Upon conducting an analysis on the levels of Ca, it has been observed that there is a significant increase in the PJ group in comparison to the LA group ($p < 0.01$). Also, there was no significant difference in Cu levels between the groups ($p > 0.05$).

Table 1. Biochemical parameters in the rat hepatic tissues

Parameters	Control	LA group	PJ group	LA+PJ group
MDA (nmol/mg protein)	8.37±0.47	20.5±0.95^{c}	10.3±0.47^{z}	15.1±1.1^{cy}
GSH (nmol/mg protein)	97.8±2.80	59.9±1.44^{c}	73.8±1.50^{cy}	77.6±2.02^{cz}
GST (nmol/min/mg protein)	60.3±1.89	45.7±1.71^{b}	55.5±3.27^{x}	52.7±1.60
Ces (nmol/min/mg protein)	1.90±0.06	1.30±0.04^{c}	1.62±0.05^{y}	1.61±0.07^{y}

Values are expressed as means ± SEM; n=7 for each treatment group.
Comparison with group control. a: $p < 0.05$, b: $p < 0.01$, c: $p < 0.001$
Comparison with group LA. x: $p < 0.05$, y: $p < 0.01$, z: $p < 0.001$

Table 2. Element concentrations in the rat hepatic tissues

Parameters	Control	LA group	PJ group	LA+PJ group
Pb (ppb)	80.07±2.04	1337.21±35,56^{c}	86.22±4.39^{z}	287.37±20.22^{cz}
Fe	145095.99±5556.20	162619.31±4478.40	159101.43±6338,39	161356.43±5609.52
Mn	3265.83±166.51	2605.15±50.82^{a}	2971.49±100.98	2910.13±165.71
Zn	33504.42±1197.89	26729.02±30997^{c}	31798.02±897.79^{y}	31207.61±556.24^{x}
Ca	117905.01±2933.38	108197.37±3356.26	130237.61±5137.38^{y}	122698.83±3082.36
Cu	4160.26±243.01	3899.98±232.56	4247.64±52.59	4444.85±271.49

Values are expressed as means ± SEM; n=7 for each treatment group.
Comparison with group control. a: $p < 0.05$, b: $p < 0.01$, c: $p < 0.001$
Comparison with group LA. x: $p < 0.05$, y: $p < 0.01$, z: $p < 0.001$

Histologic Analysis of Liver Tissue

After analysing tissue sections belonging to both the control and PJ groups using hematoxylen eosin, it was observed that the hepatocyte cords extending from v. centralis to the periphery in the middle of the liver lobule, as well as the sinusoids located between these cords, appeared to be regular and consistent (Figures 1 AI and BI). The monitoring of polygonal-shaped liver cells revealed that the cytoplasms of hepatocytes exhibited an acidophilic staining feature that varied in density in accordance with cell activity levels. The nuclei of these cells were centrally located and characterized as large, round, and euchromatic. Additionally, some hepatocytes displayed a bi-nucleus and exhibited normal structural features (Figures 1 AII and BII). To assess the connective tissue density, we utilized Masson's triple staining method on liver tissues from both the control group and the group that received PJ. Our analysis revealed the presence of dense connective tissue around the v. centralis and periportal area (Figures 1 AIII and BIII). The observed density of mast cells in the connective tissue surrounding the vessel was within the average range (Figures 1 AIV and BIV).

Upon examination of rat liver tissues from the group treated with LA, a disruption in the arrangement of hepatocyte cords was observed around the vena centralis, resulting in an altered liver structure. At slight magnification, the lobule's structure and boundaries were indistinguishable. These findings may have significant implications in understanding the effects of LA on liver function (Figure 1 CI). It is of significance to note that in the enlarged views of the same group, the cytoplasmic boundaries of the hepatocytes composing the parenchyma are indistinguishable, the polygonal shapes are absent, and the variations in size and degenerative changes between the cells are eliminated. Certain regions of these cells exhibit a dark pyknotic core (Figure 1 CII). To evaluate the connective tissue density within the rat liver tissues of the LA group, Masson's triple staining method was employed. The results revealed the presence of non-dense connective tissue surrounding the v. centralis and periportal area, which was consistent with the control and PJ groups. Furthermore, the examination of this group revealed notable dilatation observations in the structures of the v. centralis, portal vein, and sinusoid (Figure 1 CIII). The study observed a significant increase in mast cell density within the vascular connective tissue, as compared to both the control and PJ groups (Figure 1 CIV).

When the sections of rat liver tissues belonging to the LA and PJ treated groups are examined with H.E, hepatocytes form parenchyma in slight magnification, similar to control and PJ groups. It has been noted that there exists a stable structure surrounding the v. centralis (Figure 1 DI). It was noted that the hepatocytes, the primary cells of the liver parenchyma, possess a consistent structure and maintain their acidophilic properties even in instances of significant enlargement within the same group. It was observed that the presence of hepatocytes degenerated in places among hepatocytes still continues, but their density decreases (Figure 1 DII). With the triple painting method of Masson, it was observed that the connective tissue density in the v. centralis and periportal areas was similar to in all other groups (Figure 1 DIII). The density of mast cells was slightly lower in the LA+PJ group in comparison to the LA group (Figure 1 DIV).

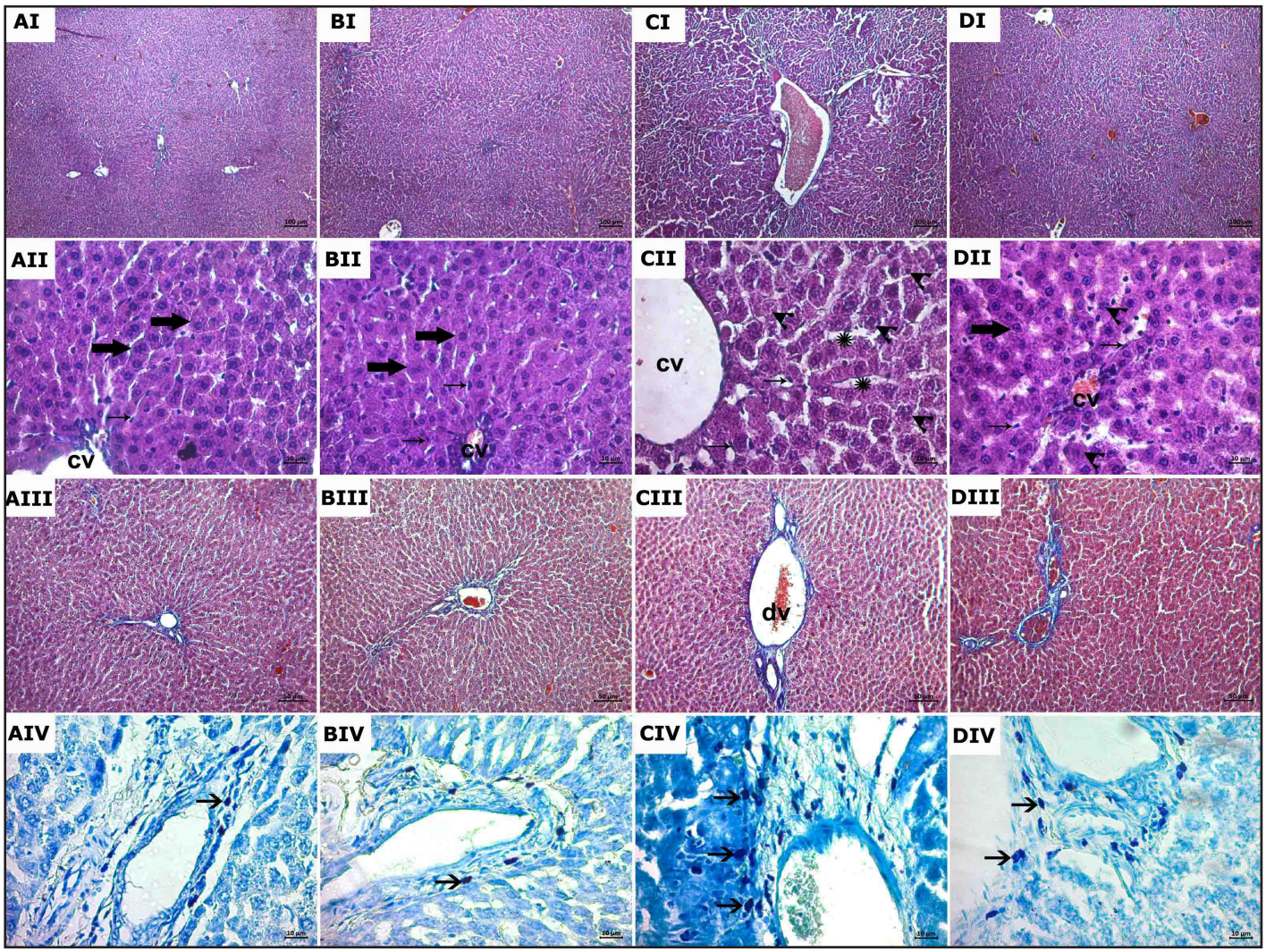


Figure 1. Histological examination of the effects of LA and PJ on the rat liver tissues

AI-AIV C group, **BI-BIV** PJ group, **CI-CIV** LA group, **DI-DIV** LA and PJ group.

AI, BI, CI and DI: General image of the groups at x4 magnification;

AII, BII, CII and DII: Images of groups at x40 magnification-Hematoxylin and Eosin Staining;

AIII, BIII, CIII and DIII: Images of the groups at x10 magnification-Masson Trichrome Staining;

AIV, BIV, CIV and DIV: Images of the groups at x40 magnification-Toluidin Blue Staining; **cv**, v. centralis; **dv,** dilated vein; **thick arrow**, healthy hepatocyte**; thin arrow**, kuppfer cell; **arrowhead**, degenerated hepatocyte cells; **star**, dilated sinusoid; **middle thick arrow**, mast cell.

Histopathological Scoring

In this study, a semi-quantitative evaluation was made using the histopathological scoring system adapted from Bekheet [21]. The evaluation was graded as 0 (absent), 1 (slight), 2 (moderate) and 3 (severe). Inflammation, hemorrhage, fibrosis, cell damage, and sinusoidal dilatation findings were examined. Each parameter was evaluated independently and blindly by an expert histologist.

In the evaluation, a statistically significant difference was found between the LA group with the control group and the PJ in terms of cell damage and sinusoidal dilatation ($p<0.005$). No statistically significant difference was detected between the groups in terms of fibrosis, inflammation and hemorrhage($p>0.05$). Statistical data regarding the scoring obtained because of the evaluation are shown in Table 3.

Table 3. Histopathological Scoring

Parameters	Control	LA	PJ	LA+PJ
Cell damage	0.57 ± 0.535[a]	2.14 ± 1.069	0.43 ± 0.535[b]	1.00 ± 0.816
Sinusoidal Dilatation	0.71 ± 0.488[c]	2.29 ± 0.756	0.86 ± 0.378[d]	1.14 ± 0.690
Fibrosis	0.29 ± 0.488	0.43 ± 0.535	0.14 ± 0.378	0.71 ± 0.488
Inflammation	0.43 ± 0.535	0.57 ± 0.535	0.29 ± 0.488	0.71 ± 0.488
Hemorrhage	0.29 ± 0.488	0.57 ± 0.535	0.29 ± 0.488	0.57 ± 0.535

Statistical significancy compared to the LA group: a: $p < 0.05$; b: $p < 0.05$, c: $p = 0.005$, d: $p = 0.01$.
Scoring data obtained because of semi-quantitative evaluation (Mean ± SD)

DISCUSSION

Lead causes oxidative stress, and consequently, free radical levels increase which induces lipid peroxidation [22]. As a result, the MDA, a lipid peroxidation product, increases [1]. Liver tissue shows elevated levels of MDA and oxidative stress as a result of lead exposure, as indicated by previous studies [1, 23]. The results of these studies are similar to those of our research. Our investigation determined that the MDA level was reduced in the LA+PJ group compared to the LA group.

Flavonoids and phenolic compounds in PJ have been reported to have high antioxidant activity [24]. GSH and GST are essential antioxidants [25]. In our study, a statistically significant decrease was observed in the GST and GSH levels of rats treated with LA compared to the control group. Numerous studies have demonstrated that exposure to lead in laboratory animals results in a reduction of GSH levels in liver tissues [1, 2, 26]. In line with our findings, there have been studies indicating a decrease in GST levels as a result of exposure to lead [1, 27]. The GST enzyme has many functions in the cell. Compounds such as hydroxyalkanels, acroneils, and hydro peroxides formed in the cell are destroyed by the antioxidant effect of the GST enzyme. The presence of the GSH molecule is essential for optimal GST enzyme activity [27]. Our research has revealed a notable decrease in both GSH molecules and GST enzymes in liver tissues of rats exposed to lead. This decline in GST enzyme levels may be attributed to the increased activation and excessive utilization of GSH molecules required for this activity.

Changing enzyme activities in tissues is clinically critical [10, 28]. In a study conducted by Ozkaya et al. [1] on rats, the application of Pb resulted in a decrease in the activity level of the Ces enzyme in the rats' livers. These findings parallel the results of our research. In our study, while Ces enzyme activity levels in the LA group decreased compared to the control group; it increased in the PJ and LA+PJ groups compared to the LA group. Based on our analysis, it appears that the detoxifying properties of the Pb molecules may be responsible for a decrease in enzyme activity. This suggests that Ces may be impacted by these effects.

Lead is one of the toxic elements that can accumulate in the liver. Therefore, as we expected in our study, the Pb level in the liver tissue increased in the LA group compared to the control group. It has been reported in previous studies that PJ reduces lead accumulation in tissues [12, 16]. Similarly, in our research, the Pb level decreased in the LA+PJ group compared to the LA group. Aksu et al. [12] reported in their study that LA increases the amount of Fe in the liver and does not change the Zn level. However, in our study, no significant difference was found between the groups in the Fe level. Also, the amount of Zn in the liver was decreased in the LA group. Fe and Pb tend to accumulate in similar environments within the body, leading to a competition between the two elements. In our study, it's possible that the absorption of Pb may have restricted the accumulation of Fe. Furthermore, it should be noted that the liver plays a significant role in Zn metabolism [29]. Therefore, it is possible that Pb-induced liver damage may affect the amount of Zn in the liver tissue.

PJ contains a significant amount of Fe, Ca, and Zn minerals [12, 30]. In this study, although Zn increased in the LA+PJ group compared to the LA group, no significant difference was found in the Fe level. Although the Ca level increased in the PJ group compared to LA, this increase was not significant in the LA+PJ group. It is known that the amount of Zn in the tissues decreases

in liver damage [31]. It is possible that the antioxidant properties of Zn, a component found in PJ, may have counteracted the decrease of Zn in the liver caused by Pb. Unlike our study, Aksu et al. [12] found that PJ decreased Fe and Zn levels in the liver even lower than the control group. Different concentration of PJ in our study compared to theirs may explain the difference between our results.

In this study, histopathological changes such as cellular degeneration and irregular hepatic cords were observed in the light microscopic examination of the liver tissue of rats exposed to Pb. Previous studies have reported that Pb causes cellular degeneration and irregular hepatic cords in liver tissue [1, 26, 32]. The histopathological findings we found in the liver regarding lead exposure are coherent with the results of the above studies. In addition, in our research, it was seen that the toxic effects of LA decreased with the application of PJ.

Limitations

Our study focused on the impact of PJ solely on male rats, and it's worth noting that the effects could vary in female rats due to hormonal differences. Further research on larger sample sizes across different age ranges would provide more comprehensive results. Expanding the scope of biochemical and histological parameters could also lead to more effective outcomes. It's worth mentioning that we did not include an analysis of the total weight of liver tissues in our study, which could be a pertinent factor in evaluating other parameters.

CONCLUSIONS

Our research findings indicate that the administration of LA resulted in a decline in the liver function of the rats. It was found that these toxic effects of LA can be prevented by the PJ. Toxic substances cause oxidative stress and cause cell and tissue damage. Antioxidants are an effective treatment method for preventing tissue damage caused by oxidative stress. Discovering natural products and new substances has gained significant importance in treating the adverse effects of diseases and toxic substances that threaten human health. Our research has indicated that consumption of PJ may offer potential benefits in mitigating the negative effects of LA-induced oxidative stress.

Acknowledgments: We express our gratitude to the staff of Fırat University Experimental Animal Center.

Conflict of Interest: The authors declare no conflict of interest, financial or otherwise.

Informed Consent: We declare that we participated in the study and the development of the manuscript titled ''Protective effect of pomegranate juice on lead acetate-induced liver toxicity in male rats''. We have read the final version and consent to publish the article.

Funding: This study has no financial resources and no sponsors.

Ethical Approval: The research was carried out in the Animal Experiment Center of Fırat University. Ethics committee approval was obtained by Fırat University Animal Experiments Local Ethics Committee with the 2018/04 protocol number and 09 decision number.

Author Contributions: Study concept and design: HP, EA; Acquisition of subjects and data, analysis and interpretation of data: HP, EA, ÖB, AA; Preparation of manuscript: HP, BZ, MA.

REFERENCES

[1] Ozkaya A, Sahin Z, Kuzu M, Saglam YS, Ozkaraca M, Uckun M, Yologlu E, Comakli V, Demirdag R, Yologlu S (2018) Role of geraniol against lead acetate-mediated hepatic damage and their interaction with liver carboxylesterase activity in rats. Arch Physiol Biochem. 124:80-87. https://doi.org/10.1080/13813455.2017.1364772

[2] Abdelhamid FM, Mahgoub HA, Ateya AI (2020) Ameliorative effect of curcumin against lead acetate–induced hemato-biochemical alterations, hepatotoxicity, and testicular oxidative damage in rats. Environ Sci Pollut Res. 27:10950-10965. https://doi.org/10.1007/s11356-020-07718-3

[3] Zhou L, Wang S, Cao L, Ren X, Li Y, Shao J, Xu L (2021) Lead acetate induces apoptosis in Leydig cells by activating PPARγ/caspase-3/PARP pathway. Int J Environ Health Res. 31:34-44. https://doi.org/10.1080/09603123.2019.1625034

[4] El-Boshy ME, Refaat B, Qasem AH, Khan A, Ghaith M, Almasmoum H, Mahbub A, Almaimani RA (2019) The remedial effect of Thymus vulgaris extract against lead toxicity-induced oxidative stress, hepatorenal damage,

immunosuppression, and hematological disorders in rats. Environ Sci Pollut Res. 26:22736-22746 https://doi.org/10.1007/s11356-019-05562-8

[5] Malik A, Ashraf MAB, Khan MW, Zahid A, Shafique H, Waquar S, Gan SH, Ashraf M (2020) Implication of physiological and biochemical variables of prognostic importance in lead exposed subjects. Arch Environ Contam Toxicol. 78:329-336. https://doi.org/10.1007/s00244-019-00673-2

[6] Sahin Z, Ozkaya A, Uckun M, Yologlu E, Kuzu M, Comakli V, Demirdag R, Tel AZ, Aymelek F, Yologlu S (2019) Evaluation of the effects of Cyclotrichium niveum on brain acetylcholinesterase activity and oxidative stress in male rats orally exposed to lead acetate. Cell Mol Biol. 65:3-8. https://doi.org/10.14715/cmb/2019.65.5.2

[7] Manthou E, Georgakouli K, Deli CK, Sotiropoulos A, Fatouros IG, Kouretas D, Haroutounian S, Matthaiou C, Koutedakis Y, Jamurtas AZ (2017) Effect of pomegranate juice consumption on biochemical parameters and complete blood count. Exp Ther Med. 14:1756-1762. https://doi.org/10.3892/etm.2017.4690

[8] Saeed M, Naveed M, BiBi J, Kamboh AA, Arain MA, Shah QA, Alagawany M, El-Hack ME, Abdel-Latif MA, Yatoo M (2018) The promising pharmacological effects and therapeutic/medicinal applications of Punica granatum L. (Pomegranate) as a functional food in humans and animals. Recent Pat Inflamm Allergy Drug Discov. 12:24-38. https://doi.org/10.2174/1872213X12666180221154713

[9] Alkadi H (2020) A review on free radicals and antioxidants. Infect Disord Drug Targets. 20:16-26. https://doi.org/10.2174/1871526518666180628124323

[10] Soares GR, de Moura CFG, Silva MJD, Vilegas W, Santamarina AB, Pisani LP, Estadella D, Ribeiro DA (2018) Protective effects of purple carrot extract (Daucus carota) against rat tongue carcinogenesis induced by 4-nitroquinoline 1-oxide. Med Oncol. 35:1-14. https://doi.org/10.1007/s12032-018-1114-7

[11] Kujawska M, Jourdes M, Kurpik M, Szulc M, Szaefer H, Chmielarz P, Kreiner G, Krajka-Kuźniak V, Mikołajczak PŁ, Teissedre P-L (2019) Neuroprotective effects of pomegranate juice against Parkinson's disease and presence of ellagitannins-derived metabolite—Urolithin a—In the brain. Int J Mol Sci. 21:202. https://doi.org/10.3390/ijms21010202

[12] Aksu DS, Saglam YS, Yildirim S, Aksu T (2017) Effect of pomegranate (Punica granatum L.) juice on kidney, liver, heart and testis histopathological changes, and the tissues lipid peroxidation and antioxidant status in lead acetate-treated rats. Cell Mol Biol. (Noisy-le-grand) 63:33-42. https://doi.org/10.14715/cmb/2017.63.10.5

[13] Jafarirad S, Goodarzi R, Mohammadtaghvaei N, Dastoorpoor M, Alavinejad P (2023) Effectiveness of the pomegranate extract in improving hepatokines and serum biomarkers of non-alcoholic fatty liver disease: A randomized double blind clinical trial. Diabetes Metab Syndr. 17(1):102693. https://doi.org/10.1016/j.dsx.2022.102693

[14] Nemati S, Tadibi V, Hoseini R (2022) Pomegranate juice intake enhances the effects of aerobic training on insulin resistance and liver enzymes in type 2 diabetic men: a single-blind controlled trial. BMC Nutr. 8:48. https://doi.org/10.1186/s40795-022-00538-3

[15] Hassan NF, Soliman GM, Okasha EF, Shalaby AM (2018) Histological, immunohistochemical, and biochemical study of experimentally induced fatty liver in adult male albino rat and the possible protective role of pomegranate. J Microsc Ultrastruct. 6:44. https://doi.org/10.4103/JMAU.JMAU_5_18

[16] Annaç E, Uçkun M, Özkaya A, Yoloğlu E, Pekmez H, Bulmuş Ö, Aydın A (2021) The protective effects of pomegranate juice on lead acetate-induced neurotoxicity in the male rat: A histomorphometric and biochemical study. J Food Biochem. e13881. https://doi.org/10.1111/jfbc.13881

[17] Placer ZA, Cushman LL, Johnson BC (1966) Estimation of product of lipid peroxidation (malonyl dialdehyde) in biochemical systems. Anal Biochem. 16:359-364. https://doi.org/10.1016/0003-2697(66)90167-9

[18] Sedlak J, Lindsay RH (1968) Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem. 25:192-205. https://doi.org/10.1016/0003-2697(68)90092-4.

[19] Habig WH, Pabst MJ, Jakoby WB (1974) Glutathione S-transferases: the first enzymatic step in mercapturic

acid formation. J Biol Chem. 249:7130-7139. https://doi.org/10.1016/S0021-9258(19)42083-8

[20] Bradford MM (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem. 72:248-254. https://doi.org/10.1006/abio.1976.

[21] Bekheet SH (2010) Morphine sulphate induced histopathological and histochemical changes in the rat liver. Tissue Cell. 42:266-272. https://doi.org/10.1016/j.tice.2010.06.001.

[22] Erişir M, Benzer F, Özkaya A, Dağ Ü (2018) The effect of naringenin on oxidative stress in some tissues (heart, lung, brain, spleen, muscle) of lead-treated rats. Atatürk Üniversitesi Vet Bilim Derg. 13:34-41. https://doi.org/10.17094/ataunivbd.417125

[23] Ozkaya A, Sahin Z, Dag U, Ozkaraca M (2016) Effects of naringenin on oxidative stress and histopathological changes in the liver of lead acetate administered rats. J Biochem Mol Toxicol. 30:243-248. https://doi.org/10.1002/jbt.21785

[24] Delgado NT, Rouver WN, Dos Santos RL (2020) Protective effects of pomegranate in endothelial dysfunction. Curr Pharm Des. 26:3684-3699. https://doi.org/10.2174/1381612826666200406152147

[25] Kisaoglu A, Borekci B, Yapca OE, Bilen H, Suleyman H (2013) Tissue damage and oxidant/antioxidant balance. Eurasian J Med. 45:47. https://doi.org/10.5152/eajm.2013.08

[26] Abubakar K, Mailafiya MM, Chiroma SM, Danmaigoro A, Zyoud TY, Abdul Rahim E, Abu Bakar Zakaria MZ (2020) Ameliorative effect of curcumin on lead-induced hematological and hepatorenal toxicity in a rat model. J Biochem Mol Toxicol. 34:e22483. https://doi.org/10.1002/jbt.22483

[27] Khandare V, Walia S, Singh M, Kaur C (2011) Black carrot (Daucus carota ssp. sativus) juice: processing effects on antioxidant composition and color. Food Bioprod Process. 89:482-486. https://doi.org/10.1016/j.fbp.2010.07.007

[28] Müslüm K, Özkaya A, Şahin Z, Üzeyir D, Comakli V, Demirdağ R (2017) In vivo effects of naringenin and lead on rat erythrocyte carbonic anhydrase enzyme. Turk J Pharm Sci. 14:9. https://doi.org/10.4274/tjps.13008

[29] Grüngreiff K, Reinhold D, Wedemeyer H (2016) The role of zinc in liver cirrhosis. Ann Hepatol. 15:7-16. https://doi.org/10.5604/16652681.1184191

[30] Çiftçi H, Çalışkan ÇE, Kar F, Özkaya A, Güçlü K (2022) Evaluation of The Effects of Pomegranate Juice on Hepato-Nephrotoxicity in Male Rats Exposed to Aluminum. J Agric Nat. https://doi.org/10.18016/ksutarimdoga.vi.896611

[31] McClain C, Vatsalya V, Cave M (2017) Role of zinc in the development/progression of alcoholic liver disease. Curr Treatm Opt Gastroenterol. 15:285-295. https://doi.org/10.1007/s11938-017-0132-4

[32] Liu B, Jiang H, Lu J, et al. (2018) Grape seed procyanidin extract ameliorates lead-induced liver injury via miRNA153 and AKT/GSK-3β/Fyn-mediated Nrf2 activation. J Nutr Biochem. 52:115-123. https://doi.org/10.1016/j.jnutbio.2017.09.025

How to Cite;

Pekmez H, Annaç E, Bulmuş Ö, Zencirci B, Aydın M, Aydın A (2024) Protective Effect of Pomegranate Juice on Lead Acetate-Induced Liver Toxicity in Male Rats. 30(2):160-169. Eur J Ther. https://doi.org/10.58600/eurjther1927

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):170-174.
https://doi.org/10.58600/eurjther1913

Original Research

Is the Text of Ibn Lūqā "A New Evidence" on Pulmonary Circulation Discovery?

Ahmet Acıduman [1], Abdullah Yıldız [1], Kemal Tuzcu [2], Hicabi Kırlangıç [3]

[1] Department of History of Medicine and Ethics, Faculty of Medicine, Ankara University, Ankara, Türkiye
[2] Sub-Department of Arabic Language and Literature, Department of Eastern Languages and Literature, Faculty of Languages and History-Geography, Ankara University, Ankara, Türkiye
[3] Sub-Department of Persian Language and Literature, Department of Eastern Languages and Literature, Faculty of Languages and History-Geography, Ankara University, Ankara, Türkiye

Received: 2023-11-02 **Accepted:** 2023-12/20 **Published Online:** 2023-12-20

Corresponding Author
Ahmet Aciduman, MD, PhD
Address: Department of History of Medicine and Ethics, Faculty of Medicine, Ankara University, Ankara, Türkiye.
E-mail(s): aciduman@medicine.ankara.edu.tr; ahmetaciduman@yahoo.com

ABSTRACT

Objective: The discovery of the pulmonary circulation is one of the most important issues in the history of medicine. Recently, an article appeared comprising an assertion that this discovery may have been made before Ibn al-Nafīs by Qusṭā b. Lūqā. The purpose of our study is to examine the text of Qusṭā b. Lūqā to ascertain whether it offers "new evidence" on the discovery of pulmonary circulation.

Methods: A comprehensive analysis of the text Qusṭā b. Lūqā and its different copies referenced for the discovery made by Qusṭā b. Lūqā has been made regarding the history of medicine.

Results: While Qusṭā b. Lūqā's text contains detailed descriptions of cardiovascular anatomy, the terminologies and concepts employed were consistent with the prevailing medical knowledge of his time. From the perspective of the history of medicine, it can be said that Qusṭā b. Lūqā's text does not sufficiently differentiate from those of his predecessors' regarding the issue of pulmonary circulation. In addition, Qusṭā b. Lūqā mentions the sources he used in his text and does not explicitly claim that he made a discovery different from them.

Conclusion: With the available findings, it is difficult for now to say that Qusṭā b. Lūqā discovered the pulmonary circulation in the referenced text.

Keywords: Pulmonary circulation, lesser circulation, history of medicine, history of cardiovascular system

INTRODUCTION

The history and discovery of pulmonary circulation has been a very important topic in the history of medicine and science and continues to be a topic of interest today [1]. Galen (129–200) has been an authority on cardiovascular anatomy and physiology for a long time, as with many other subjects. However, over time, the flaws of the system that Galen theorised have been observed, and today's anatomical and physiological information has been obtained with the contributions of important physicians and scientists. It is known that one of the most important developments in the history of the circulatory system, which contradicts Galen's system, is the work of Ibn al-Nafīs (1213–1288) [2]. Ibn al-Nafīs was a physician who challenged the long-held belief of the Galen School that blood could pass through the cardiac interventricular septum and proposed that all blood that reached the left ventricle passed through the lung [3,4]. He also predicted the existence of small communications or pores between the pulmonary artery and vein, which was later

confirmed by the discovery of pulmonary capillaries by Marcello Malpighi (1628–1694) 400 years later [4]. However, recently, some authors in an article have expressed quite interestingly that the discovery of pulmonary circulation may have occurred before Ibn al-Nafīs by referring to the work of Qusṭā b. Lūqā (860-912) [5]. In this study, we evaluate and discuss such a groundbreaking discourse by considering the sources cited by the authors of the article, which contains important claims about the pulmonary circulation history and is also very interestingly constructed.

MATERIALS AND METHODS

Depending on the importance of the assertions, as a result of our detailed research on this article's sources, we have reached a text of Qusṭā b. Lūqā's *Kitāb al-farq bayn al-rūḥ wa l-nafs* edited by Hilmi Ziya Ülken [6] using a facsimile, which is in İstanbul, Topkapı Palace Library, III. Ahmed Collection, nr. 3483 [6], and a different Arabic print of the same work in the literature [7], and an Italian translation [8] published together with the Arabic version [8], as well as two Turkish translations [9,10]. We also had the opportunity to examine a Latin translation of Qusṭā b. Lūqā's aforementioned work by John of Seville [11] and a thesis on the work written by Judith Wilcox [12]. After examination of the aforementioned sources, we saw that in the authors' articles, the English translations, which quoted from the mentioned work, were different from our English translations of the different copies of the Arabic texts of the work in the literature.

RESULTS AND DISCUSSION

In the Arabic texts [6-8], also in the Italian [8] and Turkish translations [9,10], Qusṭā b. Lūqā [6-10] does not mention the pulmonary artery and vena cava emerging from the heart's right cavity, as the authors of the article claim, but on the contrary, two vessels emerge from the heart's left cavity, one goes to the lung, which is called the *al-shiryānī al-warīdī,* and the other vessel is called the *al-abhar* (the aorta), which is divided into two branches at the place of origin. Also, the vessel that Qusṭā b. Lūqā calls *al-shiryānī al-warīdī* is not the today's pulmonary artery, as claimed by the article's authors, but the pulmonary vein, because, as Qusṭā b. Lūqā also reported, this vessel is vein-like, but its function is the artery's function. According to the Galenic understanding of that period, this vessel brings something from the air to the heart, in other words, it carries the spirit:

> "Statement about the spirit – The spirit is a subtle matter, which emanates from the heart (al-qalb) into the arteries (al-shiryānāt), that activates the vitality (al-hayāt), breathing (al-tanaffus) and pulse (al-nabḍ), and that emanates from the brain (al-dimāgh) into the nerves (al-aʿṣāb) and activates movement (al-ḥaraka) and sense (al-ḥiss) in the body. Physicians and philosophers, who are praised for vivisection practice, claimed that there are two cavities (tajwīfān) in the heart, one of them on the right side (jānib al-ayman) and the other on the left side (jānib al-aysar). In these two cavities, there are blood (dam) and spirit (rūḥ), and in the right cavity, the blood is more than spirit, and in the left cavity, the spirit is more than blood. **Two vessels emerge from the cavity, which is on the left side, one of these two vessels ends in the lung (al-riʾa)**, and the heart breathes through it, because the heart contracts and dilates, and with its dilatation and contraction, the pulse (al-nabḍ) occurs in the rest of the body. Therefore, the pulse is indicative of natural conditions of the heart, which are regular, uniform, and different, which differs for a reason that affects the heart in itself or from some of its neighbouring organs. So, when the heart dilates, by that vessel, it draws something of the air, which arrives at the lungs by breathing, in order to fan the innate heat (al-ḥarara al-gharīziyya), which is in the heart, and it becomes a substance for the spirit, which is in its cavities, and when the heart contracts, it pushes the smoky vapours, which are generated in the heart from the heat of fire that is in it, to the lungs through this [vessel], and the lungs drive them out of the body, and **this vessel is known as the venous artery (al-shiryānī al-warīdī) and is called by this name because its shape is a vein and its action is an artery. The other vessel is called the aortic vessel (al-ʿirq al-abhar)**, and it is divided into two parts at its origin from the heart, one of them rises to the top of the body, and branches come out of it from the chest to the ends of the head, and through these branches, life arises in the human body. And the other one descends to the bottom of the body to the ends of the feet, and branches come out it, through these branches, life arises in the lower

Main Points;

- Is the text of Qusṭā b. Lūqā "a new evidence" on pulmonary circulation discovery?
- Qusṭā b. Lūqā's view is not different from his predecessors' views regarding the vascular relation between the heart and lungs.
- With the available findings, it is difficult for now to say that Qusṭā b. Lūqā discovered the pulmonary circulation in the referenced text.

part of the human body. And the divisional branches of these vessels, which are scattered throughout the rest of the body, are called arteries (al-shiryānāt), and they are the proximate cause of the life in the human body **when it conveys to each member of the body from the spirit that is in the cavity of the heart, which is on its left side** [6]."

In the light of the obtained information, we thought that the reason for this difference between the claims of the article's authors and the information in the Arabic texts we reached may be the author's translation error or a Persian translation error used by the authors. For this reason, we have reached the book used as a source by the authors, which was published by Bahrām Zāhdī [13] after being analysed and translated. There is a Persian translation of Qusṭā b. Lūqā's work along with its Arabic in the aforementioned book. Although the information in the book's Arabic text is the same as in the other Arabic texts, we noticed that the Persian text translation was different from the Arabic text, and it was an incorrect translation:

"A Word About the Spirit – The spirit is a subtle body, and spreads from the heart to the arteries (shiryānāt) in the human body, and life, breathing and pulse are affected by it. The part of the spirit that spreads from the brain to the nerves provides movement and sensation. Physicians and philosophers who are competent in the dissection of living things have said (claimed): There are two cavities (khufra) in the heart. One of them is on the right side and the other is on the left side, and blood (dam) and spirit (rūḥ) are in these two cavities. In the right cavity, there is more blood than the spirit, and in the left ventricle, the spirit is more than blood, **and from the right ventricle, two vessels emerge (originate). One of them goes to the lungs**, through which the heart breathes, and so heart contracts and expands, and as it expands and contracts, the pulse (nabż) occurs in other parts of the body, and therefore, in its best natural state, the heart is usually in a stationary state (sobriety, uniformity) and differentiation occurs due to damage to the heart and its adjacent organs. So when the heart expands, it absorbs something from the air through that vessel connected to the lungs [and] by breathing, [the air] returns to the lungs to cool (fanning) the innate heat (ḥararat-i gharīzī). For the spirit that is [in the heart]... (The text is disconnected-Persian translator's note). When the heart contracts, [because of this contraction], the heart rises a little towards the lungs, thus the lungs remove the smoky vapours caused by the intense heat in the heart from the body. This vessel [which is a tool for the lung to perform this process] is known as the venous artery (shiryān-i warīdī) and is called by this name, because its shape is the shape of the vein, its action is the action of the artery. **The other vessel is called the aortic vessel (shāh-rag/ʿırq al-abhar)** and is divided into two parts from the very beginning in the heart. One of them moves to the upper parts of the body, and from it, some branches depart from the chest to the upper part of the head, so that life occurs in that part of the human body. The other part descends towards the lower part of the body, and this vessel is divided into branches and provides life to the lower part of the human body. The various branches of these kinds of vessels, which are scattered in various parts of the body, are also called arteries (shiryānāt). This is the proximate cause of the vitality of the human body. **In this way, it provides the spirit, which is in the left cavity of the heart, for all organs of the body (….)** [13]"

In the Latin translation of John of Seville, a similar mistranslation is found, among the works we studied. Judith Wilcox, who prepared a thesis on the work based on the aforementioned Latin text, also states that this translation is incorrect and makes her explanation of the English translation in her thesis in the 7th footnote:

"Spiritus is a certain subtle body which in the human body arises from the heart and is borne in assuirenet, that is, in the pulsing veins, for the vivification of the body, and it effects life, the breath and the pulse; and similarly it arises from the brain into the nerves and effects sense and motion. And some praiseworthy physicians and natural philosophers who were experienced in performing surgery on living bodies thought regarding this that there are two ventricles or cavities in the heart, one in its right part and the other in the left; and in these two ventricles are contained blood and spiritus, but in the right ventricle there is more blood than spirit, and in the left there is more spirit than blood. **And two veins grow out from the right[7] ventricle, one of which leads to the lung**, and the breath of the heart is made by it. For the heart is contracted and extended, and by its extension and contraction the pulse is created throughout the whole body and therefore the pulse shows the state of the heart, that is, its own passions, regular as well as irregular, and foreign which occur on account of various difficulties of the heart which happens to it in itself or through some member near it. So when the heart extends, it draws in from the lung through the aforementioned vein part of the air which has been taken into the lung by breathing to cool the natural heat which is in it,

to be the nutriment or sustenance of that same spiritus which is contained in its ventricles. When the heart is contracted, it drives through that vein to the lung whatever is produced in it of smoky vapors and it expels them from the fiery heat which is in it, and the lung sends them out of the body, and this vein is called the "pulsing" one. **The other vein is called by the Arabs alabhar**, and this vein, at the very place from which it arises from the heart, is divided into two parts, one of which ascends upwards in the body; out of it from the chest to the top of the head proceed branches from which this part of the body is vivified; and the other part, leading downwards in the body, descends to the farthest extremities of the body to the feet, and from it proceed branches by which the lower part of the human body is vivified. And branches from each part of the aforesaid veins which are distributed throughout the rest of the body are called surienet, that is "pulsing", and this is the immediate cause of life in the human body, **because through this it carries to each member some of the spirit which is in the left ventricle of the heart** [12]."

"[7]This is an error. The Arabic has "left" ventricle, as the context further on clearly verifies [12]."

On the other hand, in the introduction to the treatise, Qusṭā b. Lūqā clearly states the sources he used for this treatise, which he wrote to explain the difference between spirit and soul. When we consider the writers from whom Qusṭā b. Lūqā has benefited, for on the soul, he cites Plato's *Phaedo [Bādan]* and *Timaeus [Ṭīmāūs]*, and Aristotle's and Theophrastus's *On the Soul [Fī al-nafs]*, and on the spirit, he cites Galen's *On the Doctrines of Hippocrates and Plato [Fī ittifāq ārāʾ Buqrāṭ wa Falāṭūn], On Anatomical Procedures [ʿAmal al-tashrīḥ],* and *On the Usefulness of the Parts of the Body [Fī manafiʿ al-aʿḍāʾ]* [6,13]:

"You inquired, may God honor you, about the difference between the spirit and the soul, and what the ancients said about it. I have drawn for you sentences on this that I extracted from Plato's book called *Phaedo [Bādan]*, from his book called *Timaeus [Ṭīmāūs]*, from Aristotle's and Theophrastus's book *On the Soul [Fī al-nafs]*, from Galen's book *On the Doctrines of Hippocrates and Plato [Fī ittifāq ārāʾ Buqrāṭ wa Falāṭūn]*, and from his book *On Anatomical Procedures [ʿAmal al-tashrīḥ]* and *On the Usefulness of the Parts of the Body [Fī manafiʿ al-aʿḍāʾ]* [6]."

Indeed, explanations about the issues reported by Qusṭā b. Lūqā are found in detail in the mentioned works of Galenus [14-16]. Regarding the pulmonary artery and pulmonary vein, an example of these is given below:

"I follow what I take to be the better view of those who call the vessel springing from the left ventricle of the heart 'venous artery' [pulmonary vein] and that springing from the right ventricle 'arterial vein' [pulmonary artery]. I think it preferable (since we cannot distinguish them clearly by the pulse) to call the vessel containing pneuma an 'artery' but, since it has the covering of a vein, to add 'venous.' So to the other I give the name of 'vein' from its function, but since its substance is that of an artery, I add 'arterial' [14]."

CONCLUSION

In his work, Qusṭā b. Lūqā did not give any information about pulmonary circulation, as claimed by the authors. Also, taking into consideration the sources he used, it seems difficult to say that Qusṭā b. Lūqā might have benefited from Persian sources. It is seen that while Qusṭā b. Lūqā was writing his article, he carried into his work the accepted Galenic views of that period and shared them openly. In this respect, based on the sources we have used, it is possible to consider the interpretations made by article's authors regarding the pulmonary circulation, without mentioning the sources used by Qusṭā b. Lūqā, as extreme interpretations.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study was not funded.

Ethics Committee Approval: Not applicable.

Author Contributions: Concept – A.A, A.Y; Design – A.A, A.Y; Supervision – A.A, A.Y, K.T, H.K.; Materials – A.A, A.Y, K.T, H.K.; Data Collection and/ or Processing – A.A, A.Y, K.T, H.K.; Analysis and/or Interpretation – A.A, A.Y, K.T, H.K.; Literature Review – A.A, A.Y, K.T, H.K.; Writing – A.A, A.Y, K.T, H.K.; Critical Review – A.A, A.Y, K.T, H.K.

REFERENCES

[1] West JB (2011). The Human Pulmonary Circulation: Historical Introduction. In: Yuan JXJ, Garcia JGN, West JB, Hales CA, Rich S, Archer SL (eds). Textbook of Pulmonary Vascular Disease. Springer US, pp 3-12. https://doi.org/10.1007/978-0-387-87429-6_1

[2] Loukas M, Lam R, Tubbs RS, Shoja MM, Apaydin N

(2008) Ibn al-Nafis (1210–1288): The First Description of the Pulmonary Circulation. Am Surg. 74(5):440-442. https://doi.org/10.1177/000313480807400517

[3] Meyerhof M (1935). Ibn An-Nafîs (XIIIth Cent.) and His Theory of the Lesser Circulation. Isis. 23(1):100-120. https://doi.org/10.1086/346938

[4] West JB (2008) Ibn al-Nafis, the Pulmonary Circulation, and the Islamic Golden Age. J Appl Physiol. 2008;105.

[5] Mahlooji K, Abdoli M, Tekiner H, Zargaran A (2021) A new evidence on pulmonary circulation discovery: A text of Ibn Luqa (860–912 AD). Eur Heart J. 42(26):2522-2523. https://doi.org/10.1093/eurheartj/ehab039

[6] Qosta b. Luqa (1953) The Book of the Difference Between the Spirit and the Soul [Le Livre De La Différence Entre L'esprit et L'âme]. In: Ülken HZ (ed), İbn Sina Risaleleri 2 Les Opuscules D'Ibn Sina et Le Livre De La Différence Entre L'esprit et L'âme. İstanbul Üniversitesi Edebiyat Fakültesi Yayınları, İstanbul, pp 81-108 ([In Arabic])

[7] Cheikho L (ed) (1996) Booklet on the Difference Between the Spirit and the Soul [Risāla fī l-farq baina r-rūḥ wa n-nafs]. In: Sezgin F (ed). Islamic Medicine. Volume 34. Qusṭā ibn Lūqā (3rd/9th cent.) Text and Studies, Collected and Reprinted. Institute for the History of Arabic-Islamic Science at the Johann Wolfgang Goethe University, Frankfurt am Main, pp 151-166 ([In Arabic])

[8] Gabrieli G (1996) The Risālah of Qusṭā b. Lūqā "On the Difference Between the Spirit and the Soul" [La Risālah di Qusṭā b. Lūqā "Sulla Differenza Tra Lo Spirito E L'anima"]. In: Sezgin F (ed). Islamic Medicine. Volume 34. Qusṭā ibn Lūqā (3rd/9th cent.) Text and Studies, Collected and Reprinted. Institute for the History of Arabic-Islamic Science at the Johann Wolfgang Goethe University, Frankfurt am Main, pp 168-201 ([In Italian and Arabic])

[9] Aydın H (1999) Kusta b. Luka and His Book the Distinction between the Spirit and the Soul [Kusta b. Luka ve Ruh ile Nefs Arasındaki Ayırım Adlı Kitabı]. Ankara Üniversitesi İlahiyat Fakültesi Dergisi. 40:387-402 ([In Turkish])

[10] Kusta b. Luka el-Yunânî (2009) About the Difference Between the Spirit and the Soul [Ruh ve Nefs Arasındaki Fark Hakkında], Üçer İH (trans). M.Ü. İlahiyat Fakültesi Dergisi. 36:195-208 ([In Turkish])

[11] Barach CS (ed) (1878). Bibliotheca Philoaophorum Mediae Aetatis. II. Excerpta E Libro Alfredi Anglici De Motu Cordis Item Costa-Ben-Lucae De Differentia Anima Et Spiritus Liber Translatus A Johanne Hispalensi. Als Beitraege zur Geschichte der Anthropologie und Psyclogie des Mittelalters. Verlag Der Wagner'schen Universitaets-Buchhandlung, Innsbruck. ([In Latin])

[12] Wilcox J (1985) The Transmission and Influence of Qusta Ibn Luqa's "On the Difference Between Spirit and the Soul". A dissertation submitted to the Graduate Faculty in History in partial fulfillment of the requirements for the degree of Doctor of Philosophy The City University of New York.

[13] Qusṭā b. Lūqā (2017). The Difference between Spirit and Soul [Farq Bayna Rūḥ wa Nafs]. Zāhedī B (ed, trans). Mūlā, Tehran. ([In Persian and Arabic])

[14] Galen (1956) On Anatomical Procedures. Translation of the Surviving Books with Introduction and Notes by Singer C. Published for The Wellcome Historical Medical Museum by Geoffrey Cumberlege Oxford University Press, London, New York, Toronto.

[15] Galen (1968) On the Usefulness of the Parts of the Body: Peri Chreias Moriōn [romanized Form] De Usu Partium. Vol. I-II. Translated from the Greek with an Introduction and Commentary by May MT. Cornell University Press, Ithaca, New York.

[16] Galeni De placitis Hippocratis et Platonis, edidit, in linguam Anglicam vertit, commentatus est Ph. De Lacy, CMG V 4,1,2, 3 vol., Berlin 1978-1984; vol. I: editio tertia lucis ope expressa, vol. II: editio altera lucis ope expressa, vol. III: editio altera lucis ope expressa addendis et corrigendis aucta, Berlin 2005. https://cmg.bbaw.de/epubl/online/cmg_05_04_01_02.php?p=65=609 Accessed 15 Oct 2023

How to Cite;

Acıduman A, Yıldız A, Tuzcu K, Kırlangıç H (2024) Is the Text of Ibn Lūqā "A New Evidence" on Pulmonary Circulation Discovery?. 30(2):170-174. Eur J Ther. https://doi.org/10.58600/eurjther1913

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):175-185.
https://doi.org/10.58600/eurjther1898

Original Research

Cross-cultural Adaptation of the Activity Questionnaire for Adults and Adolescents into Turkish and Investigation of its Validity and Reliability

Akın Süzer [1,*], Özlem Çinar Özdemir [2]

[1] Department of Therapy and Rehabilitation, Burdur Vocational School of Health Services, Burdur Mehmet Akif Ersoy University, Burdur, Türkiye
[2] Department of Physical Therapy and Rehabilitation, Faculty of Health Sciences, Izmir Democracy University, İzmir, Türkiye

Received: 2023-10-17 **Accepted**: 2023-12-15 **Published Online**: 2023-12-18

Corresponding Author
Özlem Çinar Özdemir, Assoc. Prof.
Address: Department of Physical Therapy and Rehabilitation, Faculty of Health Sciences, Izmir Democracy University, İzmir, Türkiye
E-mail: ozlemcinar314@hotmail.com

This study was presented as an oral presentation at the International Medical Congress of Izmir Democracy University held in Izmir on 6-8 December 2019.

ABSTRACT

Objective: The Activity Questionnaire for Adults and Adolescents (AQuAA) is used to evaluate physical activity (PA) levels in different age groups. Its validity and reliability in the Turkish language have not been studied yet. This study aims to adapt the AQuAA into Turkish and to investigate its validity and reliability.

Methods: A total of 124 volunteers were included in the study. After the Turkish adaptation of AQuAA, the AQuAA-Tr version was administered to the volunteers for test-retest reliability twice, with an interval of two weeks, and the International Physical Activity Questionnaire Short Form (IPAQ-SF) for criterion validity. For construct validity, the step counts of the volunteers were followed for two weeks with the Samsung Health® smartphone pedometer application. The reliability of the AQuAA-Tr was evaluated with intra-class correlation coefficients (ICC). Spearman correlation coefficients (r) were used to analyze the relationships between continuous variables.

Results: A total of 72 adolescents (51 females and 21 males, mean age 14.5 ± 0.1 years) and 52 young adults (32 females and 20 males, mean age 25.8 ± 1.3 years) participated in the test-retest reliability and criterion validity study. Thirty-four adolescents (26 female, 8 male, mean age 14.7 ± 0.2 years) and 39 young adults (27 female, 12 male, mean age 25.6 ± 1.5 years) were included in the construct validity study. The test-retest reliability of the questionnaire was in the range of strong to very strong (ICC = 0.704 to 0.982) in adolescents and moderate to strong (ICC = 0.606 to 0.851) in adults for different levels of PA. In the context of the criterion validity, although there were moderate to strong correlations (r = 0.413 to 0.768) between some PA levels of the IPAQ-SF and AQuAA-Tr in adolescents and moderate correlations (r = 0.422 to 0.525) in adults, the correlations were mostly weak or negligible. In relation to construct validity, although there were moderate correlations (r = 0.435 to 0.504) between the Samsung Health® data and some PA levels of the AQuAA-Tr in adults, the correlations were mostly weak or negligible. There were no correlations between the Samsung Health® data and AQuAA-Tr in adolescents.

Conclusion: The reliability of the AQuAA-Tr was confirmed in both adolescents and adults. However, the criterion and construct validity of the AQuAA-Tr were not confirmed for either adolescents or adults. Introducing a PA questionnaire, which can provide detailed information about sedentary, light, moderate, and vigorous PA scores separately and total PA scores and allows the evaluation of PA in different categories, into our language is considered beneficial. Yet, the results of AQuAA-Tr should be interpreted carefully in the clinic.

Keywords: Physical Activity, Surveys and Questionnaires, Adult, Adolescent, Turkish People.

INTRODUCTION

Evidence regarding the risks of a sedentary lifestyle and the gains of regular physical activity (PA) on health outcomes is now well known [1]. With the increase in people's PA levels, there is a significant decrease in the risk of diabetes mellitus (DM), stroke, cancer (especially breast and colon), and heart disease [2]. PA assessment is important in terms of understanding the relationships between PA and health, as well as assessing the effectiveness of PA interventions [3]. PA questionnaires are the most frequently used assessment tools for epidemiological, cross-sectional, surveillance, and behaviour change studies on PA [4]. They are used to define the types and components of PA behaviours and are conducted as self-report tools or interviews [5].

Current evidence supports the findings that a sedentary lifestyle is associated with all-cause death, metabolic syndrome, cardiovascular disease, and type 2 DM [6, 7]. For this reason, the assessment of the time spent on certain sedentary lifestyle behaviours is also important within the scope of PA evaluation. However, very few PA questionnaires focus on sedentary lifestyle behaviour [8]. In addition, PA questionnaires are often designed for specific age groups, and therefore the main shortcoming of these questionnaires is that they do not allow comparison of PA levels across age groups [9]. Accordingly, there is a need for a PA questionnaire that can predict sedentary behaviours in a standard way as well as PA that can be used in dissimilar age groups.

The AQuAA is a PA questionnaire that provides data about the same PA variables in both adolescent and adult age groups. The aim of the AQuAA is to evaluate total and light, moderate, and vigorous PA as well as sedentary behaviours in both adolescents and adults [9]. This questionnaire is now widely used in the Netherlands to observe national trends in PA among young people or to evaluate PA interventions [10]. In Türkiye, the International Physical Activity Questionnaire (IPAQ) and its versions are widely used to evaluate PA in adults. However, as far as we know, there is no valid and reliable questionnaire used to evaluate PA, especially in adolescents. The validity and responsiveness of the AQuAA in overweight and obese pregnant women [11] and its psychometric properties in cancer patients [12] have already been studied. However, its validity and reliability in Turkish-speaking people have not yet been studied.

Main Points;

- The Turkish version of the Activity Questionnaire for Adults and Adolescents is a reliable physical activity questionnaire in both adolescents and adults.
- This is the first cross-cultural adaptation study of the Activity Questionnaire for Adults and Adolescents.
- This is the first study to evaluate the criterion validity of the Activity Questionnaire for Adults and Adolescents.

The aim of our study is to adapt the AQuAA, which was developed to evaluate the PA levels and effectiveness of interventions to increase PA in different age groups, into Turkish and to investigate its validity and reliability.

MATERIALS AND METHODS

Procedures

Before the study was initiated, necessary permission was obtained from the researchers who developed the AQuAA to adapt the questionnaire into Turkish and to investigate its validity and reliability, via e-mail. The study was carried out in Burdur/Türkiye between December 2017 and June 2019. The approval of the Burdur Mehmet Akif Ersoy University Non-Interventional Clinical Research Ethics Committee was obtained for the study (date: 07.02.2018, decision number: GO 2017/28). Informed consent of all individuals [parents of adolescents (because adolescents are under 18 years of age)] included in the study was obtained. In this study, first, the AQuAA was adapted into Turkish, and then its Turkish version (AQuAA-Tr) was applied to adolescents and adults and its validity and reliability were investigated.

Translation

The adaptation of the AQuAA into Turkish was performed according to a protocol recommended by the American Academy of Orthopaedic Surgeons (AAOS) for cross-cultural adaptation studies [13]. The questionnaire was first translated from the source language (English) into the target language (Turkish) by independent translators, whose mother tongue was the target language, who were bilingual, and who were unaware of the concepts examined in the assessment tool being adapted. A common translation was produced by analyzing the expressions that were difficult to understand and uncertainties of the questionnaire by a board of translators and an observer recording the process. In the next step, the Turkish version of the questionnaire was translated back into English by a translator who was completely blind to the original version of the questionnaire, was unaware of the concepts examined in the measurement tool,

did not have expertise in medicine, and was fluent in Turkish and a native speaker of English. No discrepancies or differences were found between the translations. Along with the original questionnaire, the materials produced during the translation phase were reviewed by a committee of experts involving academics, health professionals, and translators. The pre-final version of the questionnaire was administered to 10 volunteers as a pre-test. The final version of the questionnaire was created by interviewing the individuals who took the pre-test and replacing the difficult-to-understand expressions in the target language with more culturally appropriate ones.

Participants

As a general rule, a sample size of at least 50 subjects is acceptable for studies on the evaluation of the validity and reliability of measurement tools [14]. In sample selection, a weighted stratified sampling method was used, considering the gender and age distribution of the people in the institutions included in the study. We aimed to include 50 adolescents (volunteers among the students of Burdur/Merkez Mehmet Uzal Social Sciences High School and Suna Uzal Middle School) and 50 adults (volunteers among the staff and students of Burdur Mehmet Akif Ersoy University Burdur Health Services Vocational School and Faculty of Education) in this study. The voluntary individuals who did not have a physical disability or disease that limited their daily activities were included. Individuals with musculoskeletal problems that could change their PA habits, cardiorespiratory problems, and diabetes mellitus were excluded from the study. The test-retest reliability and criterion validity study was completed with 124 (72 adolescents, 52 adults) individuals, and the construct validity study was completed with 73 (34 adolescents, 39 adults) individuals. As a result of the study, a power value of 60% (r=0.219) was obtained for the correlation coefficient between total scores in adolescents and a power value of 72% (r=0.299) in adults.

Measurements

Sociodemographic information of all the individuals included in the study was recorded. For the test-retest reliability study, the AQuAA-Tr was administered to 72 adolescent and 52 adult individuals twice, with a two-week interval (the two-week time interval between the administrations was deemed long enough to prevent recall and short enough to avoid changes in the measured property). For the criterion validity study of the AQuAA-Tr, the IPAQ-SF was administered to 72 adolescent and 52 adult individuals. The relationships between sedentary, light, moderate, vigorous, and total activity scores obtained from the AQuAA-Tr and walking, moderate, vigorous, and total activity scores obtained from the IPAQ-SF were examined. For the construct validity study of the AQuAA-Tr, the step count data of 34 adolescent and 39 adult individuals was followed for two weeks on the smartphone pedometer application (Samsung Health®). The relationships between step counts obtained from Samsung Health® and sedentary, light, moderate, vigorous, and total activity scores obtained from the AQuAA-Tr were examined. Adolescents completed the questionnaires with their classmates under the supervision of a teacher and a physiotherapist in the classroom, while adults completed the questionnaires under the supervision of a physiotherapist. After the questionnaires were filled out, they were checked by a physiotherapist.

The Activity Questionnaire for Adults and Adolescents (AQuAA): The AQuAA is a PA questionnaire that measures both PA and sedentary behaviour, can be self-reported by adolescents and young adults, and is adequate for evaluating changes over short periods of time. It includes questions about different intensities of physical activities (light intensity, moderate intensity, and vigorous intensity) and examples of sedentary lifestyle behaviours and age-specific activities. Table 1 shows the cut-off values for activities of different intensities. Physical activities in the AQuAA are divided into five categories: commuting, work or school, household, leisure time, and active sports activities. For each activity, the duration, frequency, and perceived intensity are questioned. The AQuAA was developed by Chinapaw et al. [9].

The International Physical Activity Questionnaire Short Form (IPAQ-SF): The IPAQ was developed by a group of experts in 1998 to facilitate PA surveillance [15]. It has become the most widely used PA questionnaire today [16, 17] and has a long form (IPAQ-LF) and a short form (IPAQ-SF). The IPAQ-SF consists of seven questions about varying degrees of PA and sedentary behaviour within the past week. It allows the classification of a person's PA level in terms of MET*minute/week as walking, moderate, vigorous, and total. The Turkish validity and reliability study of this questionnaire was conducted by Sağlam et al. [18].

Step Count Tracking on the Smartphone Pedometer Application: Nolan et al. [19] reported that an iPhone®/iPod Touch® can assess movements with similar accuracy to other accelerometer-based tools. In addition, Manohar et al. [20] reported that a smartphone with an accelerometer is an accurate and reliable tool for assessing PA in a laboratory setting. In this context, Johnson

et al. [21] reported that the smartphone pedometer application (Samsung Health®) accurately measures steps in young adults during walking, regardless of where the smartphone is placed in the body. For this reason, we used the Samsung Health® smartphone pedometer application to evaluate the construct validity of the AQuAA-Tr. For step count tracking on the smartphone pedometer application, the participants were assisted to download and install a free pedometer application, Samsung Health®, on their smartphones. For two weeks in a row, the participants were instructed to carry the same smartphone in their pocket from soon after waking up until they fell asleep at the end of the day (except when taking a shower). In addition, the participants were taught how to see the total number of steps at the end of each day on the application, how to reset the counter, and how to record the data on the registration form. The application recorded the number of steps taken a day by the study participants for two weeks. Table 1 shows the cut-off values for activities of different intensities.

Table 1. Cut-off values for activities of different intensities [9].

Activity Intensity	Adolescents (< 18 year)		Adults (≥ 18 year)	
	MET Range	**Step Count**	**MET Range**	**Step Count**
Sedentary Activity	< 2	< 699	< 2	< 699
Light Activity	2 - 5	700 - 4478	2 - 4	700 - 3220
Moderate Activity	5 - 8	4479 - 8252	4 - 6.5	3221 - 6365
Vigorous Activity	≥ 8	≥ 8253	≥ 6.5	≥ 6366

MET: metabolic equivalent

Statistical Analysis

The statistical significance level was set at $p \leq 0.05$, and the Statistical Package of Social Sciences, version 24 for Windows (SPSS Inc, Chicago, Illinois, USA) program was used for data analysis. Continuous variables were expressed as mean ± standard deviation and categorical variables were presented using frequencies (n) and percentages (%). The reliability of the questionnaire was evaluated with intra-class correlation coefficients (ICC). The assumption of normal distribution was examined with the Shapiro Wilk test when the number of data was below 50 and with the Kolmogorov Smirnov test when the number of data was 50 and above. Spearman correlation coefficients (r) were used to analyze the relationships between continuous variables. The coefficients were interpreted as follows: 0.00-0.09, negligible; 0.10-0.39, weak; 0.40-0.69, moderate; 0.70-0.89, strong; 0.90-1.00, very strong [22].

RESULTS

Test-Retest Reliability Study

The AQuAA-Tr was administered to 72 adolescents [51 women (%70.8) and 21 men (%29.2) with a mean age of 14.5 ± 0.1 years] and 52 young adults [32 women (%61.5) and 20 men (%38.5) with a mean age of 25.8 ± 1.3 years] twice, two weeks apart, for the test-retest reliability. In adolescents, ICC was 0.982 for vigorous activity scores and ranged from 0.704 to 0.826 for sedentary, light, moderate, and total activity scores. In addition, it was found that the highest agreement was in vigorous activity scores, whereas the lowest agreement was in light activity scores in adolescents. In adults, ICC ranged from 0.709 to 0.851 for sedentary, light, vigorous, and total activity scores, and was 0.606 for moderate activity scores. In addition, it was found that the highest agreement was in vigorous activity scores, while the lowest agreement was in moderate activity scores in adults. Table 2 shows the AQuAA-Tr scores on the first and second tests (MET*min/week for activities of different intensities) and ICCs.

Criterion Validity Study

For the criterion validity study of the AQuAA-Tr, the IPAQ-SF was administered to 72 adolescents (51 women and 21 men with a mean age of 14.5 ± 0.1 years) and 52 young adults (32 women and 20 men with a mean age of 25.8 ± 1.3 years). A moderate correlation (Spearman Correlation coefficients (r)=0.413, 0.471, 0.500 and 0.660, respectively) was found between the sedentary, light, moderate, and vigorous activity scores of the AQuAA-Tr and vigorous activity scores of the IPAQ-SF in adolescents. However, a strong (r=0.768) correlation was found between the total PA scores of the AQuAA-Tr and the vigorous activity scores of the IPAQ-SF. Other correlations were weak or negligible. A moderate correlation (r=0.525, 0.423, respectively) was found between the light and total activity scores of the AQuAA-Tr and walking activity scores of the IPAQ-SF in adults. However, a moderate (r=0.42) correlation was found between the vigorous activity scores of the AQuAA-Tr and the vigorous activity scores of the IPAQ-SF. Other correlations were weak or negligible. Table 3 shows the correlations between the AQuAA-Tr and the IPAQ-SF.

Table 2. Test-retest correlations (ICCs) of the AQuAA-Tr scores for adolescents and adults

Adolescent (n=72)						
	Test 1 (test)		**Test 2 (re-test)**		**ICC**	**%95 C.I. for ICC**
	Mean ± SD	**Med (Min - Max)**	**Mean ± SD**	**Med (Min - Max)**		
Sedentary Activities (MET*min/week)	5274.05 ± 3321.41	5094 (0 - 15261)	5612.45 ± 3849.61	4917 (0 - 18257.2)	0.772	0.635 – 0.857
Light Activities (MET*min/week)	5874.58 ± 6370.37	3872 (315 - 28762.5)	5531.94 ± 6205.85	3351.75 (350 - 31692)	0.704	0.526 – 0.815
Moderate Activities (MET*min/week)	2655.54 ± 4589.28	810 (0 - 21420)	2649.43 ± 3876.34	967.5 (0 - 18361)	0.731	0.57 – 0.832
Vigorous Activities (MET*min/week)	2668.39 ± 3750.38	1160 (0 - 23200)	2716.39 ± 3831.2	1200 (0 - 23912)	0.982	0.972 – 0.989
Total AQuAA-T Score (MET*min/week)	16472.56 ± 12622.51	13587 (2440 - 58954.5)	16510.21 ± 13505.36	11962.25 (2257.5 - 72451.9)	0.826	0.721 – 0.891
Adult (n=52)						
	Test 1 (test)		**Test 2 (re-test)**		**ICC**	**%95 C.I. for ICC**
	Mean ± SD	**Med (Min - Max)**	**Mean ± SD**	**Med (Min - Max)**		
Sedentary Activities (MET*min/week)	5738.08 ± 3495.78	4920 (990 - 15990)	5510.73 ± 3120.93	5385.75 (660 - 12990)	0.709	0.493 – 0.833
Light Activities (MET*min/week)	5234.52 ± 4512.53	4168.5 (105 - 22312.5)	5517.06 ± 3843.69	4960.5 (306.5 - 18135)	0.752	0.569 – 0.858
Moderate Activities (MET*min/week)	1262.88 ± 3216.62	0 (0 - 20280)	774.62 ± 1294.93	150 (0 - 5040)	0.606	0.314 – 0.774
Vigorous Activities (MET*min/week)	937.4 ± 1212.35	480 (0 - 4800)	927.65 ± 1068.06	705 (0 - 3840)	0.851	0.741 – 0.915
Total AQuAA-T Score (MET*min/week)	13172.88 ± 9008.99	10706.25 (2715 - 53002.5)	12730.06 ± 6770.2	11922.75 (966.5 - 31989)	0.75	0.565 – 0.857

SD: standart deviation, Med (Min - Max): median (minimum - maximum), MET*min: metabolic equivalent*minute, ICC: intraclass correlation coefficient; C.I: Confidence Interval

Table 3. Spearman's rank-correlation coefficients between the AQuAA-Tr and the IPAQ-SF for adolescents and adults

Adolescent (n=72)					
		IPAQ-SF Walking Activities	**IPAQ-SF Moderate Activities**	**IPAQ-SF Vigorous Activities**	**IPAQ-SF Total Score**
AQuAA-Tr Sedentary Activities	r	0.172	0.250	0.413*	0.304*
	p	0.151	0.182	0.045	0.009
AQuAA-Tr Light Activities	r	0.150	0.024	0.471*	0.172
	p	0.211	0.900	0.020	0.149
AQuAA-Tr Moderate Activities	r	0.060	0.117	0.500*	0.223
	p	0.617	0.537	0.013	0.059
AQuAA-Tr Vigorous Activities	r	-0.036	-0.018	0.660*	0.115
	p	0.763	0.926	0.000	0.337
AQuAA-Tr Total Score	r	0.103	0.036	0.768*	0.219
	p	0.391	0.851	0.000	0.064
Adult (n=52)					

		IPAQ-SF Walking Activities	IPAQ-SF Moderate Activities	IPAQ-SF Vigorous Activities	IPAQ-SF Total Score
AQuAA-Tr Sedentary Activities	r	0.248	-0.084	0.070	0.148
	p	0.082	0.719	0.763	0.294
AQuAA-Tr Light Activities	r	0.525*	-0.306	-0.362	0.315*
	p	0.000	0.178	0.107	0.023
AQuAA-Tr Moderate Activities	r	0.043	0.057	0.019	0.069
	p	0.766	0.807	0.934	0.629
AQuAA-Tr Vigorous Activities	r	0.151	-0.262	0.422*	0.290*
	p	0.297	0.252	0.05	0.037
AQuAA-Tr Total Score	r	0.423*	-0.294	-0.143	0.299*
	p	0.002	0.196	0.536	0.031

r: Spearman's rank correlation coefficient, * significant correlation

Construct Validity Study

For the construct validity study of the AQuAA-Tr, step counts were followed for two weeks in 34 adolescents (26 women and 8 men, with a mean age of 14.7 ± 0.2 years) and 39 young adults (27 women and 12 men, with a mean age of 25.6 ± 1.5 years) with Samsung Health® mobile application. In adolescents, correlations between activity scores of the AQuAA-Tr and step counts measured on Samsung Health® applications were weak or negligible. A moderate (r=0.504) correlation was found between the light activity scores of the AQuAA-Tr and step counts measured on Samsung Health® applications in adults. Other correlations were weak or negligible. Table 4 shows the correlations between the AQuAA-Tr and data from the Samsung Health® application.

Table 4. Spearman's rank-correlation coefficients between the AQuAA-Tr and the Samsung Health® for adolescents and adults

		Adolescent (n=34)	Adult (n=39)
AQuAA-Tr Sedentary Activities	r	-0.002	0.348*
	p	0.990	0.030
AQuAA-Tr Light Activities	r	0.093	0.504*
	p	0.600	0.001
AQuAA-Tr Moderate Activities	r	-0.149	-0.009
	p	0.400	0.955
AQuAA-Tr Vigorous Activities	r	-0.144	0.011
	p	0.417	0.948
AQuAA-Tr Total Score	r	-0.061	0.435*
	p	0.730	0.006

r: Spearman's rank correlation coefficient,
* significant correlation

DISCUSSION

In this study, the test-retest reliability, criterion validity, and construct validity of the AQuAA-Tr, which was created by applying the protocol recommended by AAOS for cross-cultural adaptation studies, were investigated.

As a result of our study, the Turkish version of the AQuAA (AQuAA-Tr), which is a PA questionnaire that allows collecting information about PA from both adolescent and adult age groups, was introduced into our language. However, while the reliability of the AQuAA-Tr was confirmed in both adolescents and adults, its criterion and construct validity was not confirmed in either adolescents or adults. We think that introducing a PA questionnaire, which can provide detailed information about sedentary, light, moderate and vigorous PA separately and total PA and allows the evaluation of PA in different categories, into our language will be useful for clinical and research environments related to PA.

Test-Retest Reliability

In the current study, the test-retest reliability of the AQuAA-Tr ranged from very strong to strong in adolescents and moderate to strong in adults. Chinapaw et al. [9] reported fair to moderate test-retest reliability in their study, in which they administered the AQuAA to healthy adolescent and adult individuals twice, with an interval of two weeks. Liu et al. [12] reported good to excellent test-retest reliability in their study, in which they administered the same questionnaire to cancer patients twice, with an interval of five days. The test-retest reliability findings of the AQuAA-Tr in the current study seem to be consistent with those of previous

studies but slightly higher. The highest reliability findings of the AQuAA-Tr were observed for the scores of vigorous activities in both adolescents and adults. One reason for this may be that people can remember the vigorous activities they did during the last week more easily than sedentary, light, and moderate activities. Another reason may be that people with vigorous activity levels have more regular PA habits than those with sedentary, light, and moderate activity levels, and accordingly, their awareness of PA behaviours is higher.

Criterion Validity

During the development stage of the AQuAA, no criterion validity study was conducted on the grounds that there was no gold standard method for assessing the criterion validity of PA questionnaires [9]. However, no studies on the evaluation of the criterion validity of the AQuAA were found. Therefore, our study is thought to be the first to evaluate the criterion validity of the AQuAA. In the current study, the criterion validity of the AQuAA-Tr was generally weak and negligible in both adolescents and adults although some moderate and strong correlations were found. Therefore, the criterion validity of the AQuAA-Tr could not be verified. There is no consensus in the literature on defining PA intensity and classifying PA levels. While there are researchers [23] who divide PA levels into four categories (sedentary, light, moderate, and vigorous), there are also those [24] who divide them into five categories (very light, light, moderate, vigorous, and very vigorous). While the AQuAA is used to examine PA levels in four categories [9], IPAQ-SF, which we used to evaluate the criterion validity of the AQuAA-Tr in our study, is utilized to examine PA levels in three categories [15]. This situation makes it difficult to compare instruments used to assess PA with each other and may be the reason for the weak and negligible criterion validity between the AQuAA-Tr and the IPAQ-SF. On the other hand, moderate correlations were found between the vigorous activity scores of the AQuAA-Tr and the IPAQ-SF in both adolescents and adults. Therefore, it can be said that there is a correlation between the AQuAA-Tr and the IPAQ-SF in terms of the assessment of vigorous activities in both adolescents and adults. This may be due to the configured and usual nature of vigorous physical activities, which often consist of organized sports. Besides, in the current study, the highest correlations between the AQuAA-Tr and the IPAQ-SF were observed in the vigorous PA scores of IPAQ-SF in adolescents and in walking PA scores of the IPAQ-SF in adults. This suggests that the general tendency of individuals toward weekly physical activities is in favour of vigorous physical activities in adolescents and in favour of walking or light physical activities in adults. Therefore, when preparing PA programs, it will be useful to consider that the intensity preferences for weekly physical activities may differ between age groups (adolescent-adult).

Construct Validity

The construct validity of the AQuAA-Tr in the current study was generally weak and negligible in both adolescents and adults, although some moderate correlations were found in adults. Therefore, the construct validity of the questionnaire could not be verified. Chinapaw et al. [9] reported insignificant construct validity in their study, in which they evaluated the construct validity of the AQuAA in adolescents and adults by using step counts obtained from the ActiGraph accelerometer. Liu et al. [12] reported poor construct validity in their study, in which they evaluated the construct validity of the AQuAA in cancer patients by using the step counts obtained from the ActiGraph accelerometer. Oostdam et al. [11] reported poor construct validity in their study, in which they evaluated the construct validity of the AQuAA in overweight and obese pregnant women by using the step counts obtained from the ActiGraph® accelerometer. In their review, Sallis and Saelens [25] reported that the validity correlations of self-report PA questionnaires ranged from .07 to .88 in children and adolescents and from .14 to .36 in adults. For these reasons, it can be said that the construct validity findings of the AQuAA-Tr in our current study are similar to previous studies in which the construct validity of many PA questionnaires were examined along with the AQuAA. It was considered that the reason for the low correlation between the AQuAA-Tr and the data from the Samsung Health® application was that both age groups participating in the study might have had difficulty remembering the duration and perceived intensity of the physical activities they completed in the last seven days and that the perceived PA levels of the participants and their actual PA levels might have differed. Another reason for these results may be that the AQuAA-Tr and the Samsung Health® application do not focus on exactly the same parameters in terms of PA assessment. Therefore, in our study, while only information about the number of steps was obtained from the Samsung Health® application, the AQuAA-Tr was utilized to obtain information about different areas of PA and different PA intensities.

For future research, we recommend that studies with samples including a wider age range in both adolescents and adults should be conducted to have more insights into the validity of the AQuAA-Tr.

Limitations

This study has several limitations. In the evaluation of the construct validity of the AQuAA-Tr, the number of steps was obtained from the Samsung Health® application not from the ActiGraph® accelerometer, as in the previous studies. Another limitation of our study is that the adults who participated in our study were mostly young adults, and adults from a wider age range could not be included in our study.

CONCLUSIONS

The AQuAA, which is used in many clinical settings and studies related to PA, was adapted to Turkish and its validity and reliability were examined. Introducing a PA questionnaire, which can provide detailed information about sedentary, light, moderate, and vigorous PA scores separately and total PA scores and allows the assessment of PA in different categories, into our language will be useful. In addition, considering that PA questionnaires that can be used to evaluate the PA levels of adolescents and young adults in our language are more limited than those used to assess other age groups, the AQuAA-Tr will contribute to studies conducted to increase the PA levels in children, adolescents, and young adults. However, the results of the AQuAA-Tr should be interpreted carefully in the clinic.

Acknowledgments: The authors would like to thank all the volunteers who took part in this study. In addition, the authors would like to present their thanks to Asst. Prof. Hande Senol, an expert in biostatistics (with a PhD in biostatistics), for her contribution to the statistical analysis of this study.

Informed Consent: All participants gave informed consent to participate in the research.

Conflict of interest: The authors report that they have no conflicts of interest to declare.

Funding: This research was not funded.

Ethical Approval: The ethical approval for this research was obtained from Burdur Mehmet Akif Ersoy University Non-Interventional Clinical Research Ethics Committee (date: 07.02.2018, decision no: GO 2017/28).

Author Contributions: Conception: Ö, ÇÖ - Design: Ö, ÇÖ; A, S - Supervision: Ö, ÇÖ - Materials: Ö, ÇÖ; A, S - Data Collection and/or Processing: Ö, ÇÖ; A, S - Analysis and/or Interpretation: Ö, ÇÖ; A, S - Literature: A, S - Review: Ö, ÇÖ; A, S - Writing: Ö, ÇÖ; A, S - Critical Review: Ö, ÇÖ

REFERENCES

[1] Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD (2018) The physical activity guidelines for Americans. JAMA - J Am Med Assoc 320:2020-2028. https://doi.org/10.1001/jama.2018.14854

[2] Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, Veerman JL, Delwiche K, Iannarone ML, Moyer ML, Cercy K, Vos T, Murray CJL, Forouzanfar MH (2016) Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 354:i3857. https://doi.org/10.1136/bmj.i3857

[3] Westerterp KR (2009) Assessment of physical activity: A critical appraisal. Eur J Appl Physiol 105:823-828. https://doi.org/10.1007/s00421-009-1000-2

[4] Ainsworth B, Cahalin L, Buman M, Ross R (2015) The current state of physical activity assessment tools. Prog Cardiovasc Dis 57:387-395. https://doi.org/10.1016/j.pcad.2014.10.005

[5] Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, Richardson CR, Smith DT, Swartz AM (2013) Guide to the assessment of physical activity: Clinical and research applications: A scientific statement from the American Heart association. Circulation 128:2259-2279. https://doi.org/10.1161/01.cir.0000435708.67487.da

[6] Young DR, Hivert M-F, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, Yong CM (2016) Sedentary Behavior and Cardiovascular Morbidity and Mortality: A Science Advisory From the American Heart Association. Circulation 134:e262-79. https://doi.org/10.1161/CIR.0000000000000440

[7] Atencio-Osorio MA, Carrillo-Arango HA, Correa-Rodríguez M, Rivera D, Castro-Piñero J, Ramírez-Vélez R (2021) Youth leisure-time sedentary behavior questionnaire (Ylsbq): Reliability and validity in colombian university students. Int J Environ Res Public Health 18:1-10. https://doi.org/10.3390/ijerph18157895

[8] Helmerhorst HJF, Brage S, Warren J, Besson H, Ekelund U (2012) A systematic review of reliability and objective criterion-related validity of physical activity

questionnaires. Int J Behav Nutr Phys Act 9:103. https://doi.org/10.1186/1479-5868-9-103

[9] Chinapaw MJM, Slootmaker SM, Schuit AJ, Van Zuidam M, Van Mechelen W (2009) Reliability and validity of the activity questionnaire for adults and adolescents (AQuAA). BMC Med Res Methodol 9:1-8. https://doi.org/10.1186/1471-2288-9-58

[10] Slootmaker SM, Chin A Paw MJM, Schuit AJ, Seidell JC, Van Mechelen W (2005) Promoting physical activity using an activity monitor and a tailored web-based advice: Design of a randomized controlled trial [ISRCTN93896459]. BMC Public Health 5:. https://doi.org/10.1186/1471-2458-5-134

[11] Oostdam N, van Mechelen W, van Poppel M (2013) Validation and responsiveness of the AQuAA for measuring physical activity in overweight and obese pregnant women. J Sci Med Sport 16:412-416. https://doi.org/10.1016/j.jsams.2012.09.001

[12] Liu RDK, Buffart LM, Kersten MJ, Spiering M, Brug J, van Mechelen W, Chinapaw MJM (2011) Psychometric properties of two physical activity questionnaires, the AQuAA and the PASE, in cancer patients. BMC Med Res Methodol 11:30. https://doi.org/10.1186/1471-2288-11-30

[13] Beaton DE, Bombardier C, Guillemin F, Ferraz MB (2000) Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976) 25:3186-3191. https://doi.org/10.1097/00007632-200012150-00014

[14] Altman DG (1990) Practical statistics for medical research. CRC press.

[15] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 35:1381-1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB

[16] van Poppel MNM, Chinapaw MJM, Mokkink LB, van Mechelen W, Terwee CB (2010) Physical activity questionnaires for adults: a systematic review of measurement properties. Sports Med 40:565-600. https://doi.org/10.2165/11531930-000000000-00000

[17] Lee PH, Macfarlane DJ, Lam TH, Stewart SM (2011) Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. Int J Behav Nutr Phys Act 8:115. https://doi.org/10.1186/1479-5868-8-115

[18] Saglam M, Arikan H, Savci S, Inal-Ince D, Bosnak-Guclu M, Karabulut E, Tokgozoglu L (2010) International physical activity questionnaire: reliability and validity of the Turkish version. Percept Mot Skills 111:278-284. https://doi.org/10.2466/06.08.PMS.111.4.278-284

[19] Nolan M, Mitchell JR, Doyle-Baker PK (2014) Validity of the Apple iPhone® /iPod Touch® as an accelerometer-based physical activity monitor: a proof-of-concept study. J Phys Act Health 11:759–769. https://doi.org/10.1123/jpah.2011-0336

[20] Manohar CU, McCrady SK, Fujiki Y, Pavlidis IT, Levine JA (2011) Evaluation of the Accuracy of a Triaxial Accelerometer Embedded into a Cell Phone Platform for Measuring Physical Activity. J Obes Weight Loss Ther 1:. https://doi.org/10.4172/2165-7904.1000106

[21] Johnson M, Turek J, Dornfeld C, Drews J, Hansen N (2016) DIGITAL Validity of the Samsung Phone S Health application for assessing steps and energy expenditure during walking and running : Does phone placement matter ? 2:1-8. https://doi.org/10.1177/2055207616652747

[22] Schober P, Boer C, Schwarte LA (2018) Correlation Coefficients: Appropriate Use and Interpretation. Anesth Analg 126:1763-1768. https://doi.org/10.1213/ANE.0000000000002864

[23] Kemper H, Ooijendijk WTM, Stiggelbout M (2000) Consensus on the Dutch Healthy Physical Activity Guidelines. TSG 78:180-183

[24] Crespo CJ, Smit E, Troiano RP, Bartlett SJ, Macera CA, Andersen RE (2001) Television watching, energy intake, and obesity in US children: results from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med 155:360-365. https://doi.org/10.1001/archpedi.155.3.360

[25] Sallis JF, Saelens BE (2000) Assessment of physical activity by self-report: status, limitations, and future directions. Res Q Exerc Sport 71 Suppl 2:1-14. https://doi.org/10.1080/02701367.2000.11082780

How to Cite;

Süzer A, Özdemir ÖÇ (2024) Cross-cultural Adaptation of the Activity Questionnaire for Adults and Adolescents into Turkish and Investigation of its Validity and Reliability. Eur J Ther. 30(2):175-185. https://doi.org/10.58600/eurjther1898

APPENDIX

Turkish Version of Activity Questionnaire for Adults and Adolescents (AQuAA-Tr)
Yetişkinler ve Adölesanlar için Aktivite Anketi (YAAA)

Geçen hafta hakkında düşünün (yedi gün). Lütfen aşağıdaki aktiviteleri bu hafta kaç gün boyunca gerçekleştirdiğinizi, günde ortalama kaç saat yaptığınızı ve (uygulanabilirse) bu aktivitenin sizin için ne kadar yorucu olduğunu belirtiniz.

1. İŞE GİDİŞ-GELİŞ AKTİVİTELERİ			
	Haftalık gün sayısı	**Günde ortalama süre**	**Efor**
1.1. İşe ve okula gidip gelirken yürüme	…gün	…saat, …dakika	yavaş/orta/hızlı
1.2. İşe ve okula gidip gelirken bisiklet kullanma	…gün	…saat, …dakika	yavaş/orta/hızlı
1.3. İşe ve okula gidip gelirken toplu taşıma, araba veya motosiklet kullanma	…gün	…saat, …dakika	
Uygulanamaz	…..		
2. İŞTEKİ VE OKULDAKİ AKTİVİTELER **Öğle tatili sırasında yürüyüş yapmak, bölüm 4: boş zaman aktivitelerine doldurulmalıdır**			
		Haftalık gün sayısı	**Günde ortalama süre**
2.1. Hafif iş Örneğin oturmak/biraz yürüme ile ayakta durmak, örneğin masa başı bir iş, dersleri takip etmek[b], kahve yapmak[a].		…gün	…saat, …dakika
2.2. Orta iş Örneğin düzenli yürüme ile çalışmak (merdivenler), hafif nesneleri taşıyarak yürümek, temizlik, beden eğitimi, gazeteleri dağıtmak[b].		…gün	…saat, …dakika
2.3. Yoğun iş Örneğin ağır bir çanta/okul çantası gibi ağır nesneleri taşıyarak yürüme (merdivenler)[b].		…gün	…saat, …dakika
Uygulanamaz		…..	
3. EV AKTİVİTELERİ (evin içinde ve çevresinde)			
		Haftalık gün sayısı	**Günde ortalama süre**
3.1. Hafif ev işleri Örneğin yemek pişirme, bulaşık yıkama, yatak yapma, evde çocuk bakımı[a]		…gün	…saat, …dakika
3.2. Orta ev işleri Örneğin süpürme, hafif objeler ile yürüme/taşıma, süpürme.		…gün	…saat, …dakika
3.3. Yoğun ev işleri Örneğin ağır alışveriş çantaları ile yürüme		…gün	…saat, …dakika
Uygulanamaz		…..	

4. BOŞ ZAMAN AKTİVİTELERİ **İşe veya okula gidiş-geliş aktiviteleri hariçtir. Aktif sporlar, 6. bölümde doldurulmalıdır.**			
	Haftalık gün sayısı	**Günde ortalama süre**	**Efor**
4.1. Yürüyüş Örneğin süpermarket-e/den, öğle tatilinde yürüyüş, köpek gezdirmek.	…gün	…saat, …dakika	yavaş/orta/hızlı
4.2. Bisiklete binme Örneğin süpermarket-e/den, spor kulübü, sinema.	…gün	…saat, …dakika	yavaş/orta/hızlı
4.3. Bahçe işleri/Ufak tefek işler Örneğin çim biçme (elektrikli olmayan), duvar boyama, marangozluk	…gün	…saat, …dakika	yavaş/orta/hızlı
Uygulanamaz		…..	
5. SEDANTER BOŞ ZAMAN AKTİVİTELERİ			
		Haftalık gün sayısı	**Günde ortalama süre**
5.1. Televizyon izleme		…gün	…saat, …dakika
5.2. Bilgisayar kullanma Örnegin evde internette sörf yapmak, bilgisayar oyunları oynamak		…gün	…saat, …dakika
5.3. Okuma		…gün	…saat, …dakika
5.4. Diğer sedanter aktiviteler Örnegin arkadaşlarla konuşmak, masa oyunları, arabada oturmak		…gün	…saat, …dakika
Uygulanamaz		…..	
6. AKTİF SPOR **Geçen hafta yaptığınız sporları aşağıya yazınız (en fazla 3 spor).** **En aktif spor ile başlayın.** Örneğin tenis, fitness, paten kayma, yüzme ve dans.			
	Haftalık gün sayısı	**Günde ortalama süre**	**Efor**
1.	…gün	…saat, …dakika	yavaş/orta/hızlı
2.	…gün	…saat, …dakika	yavaş/orta/hızlı
3.	…gün	…saat, …dakika	yavaş/orta/hızlı
Uygulanamaz	…..		

[a] yalnızca yetişkinler için örnek
[b] yalnızca adölesanlar için örnek

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):186-197.
https://doi.org/10.58600/eurjther1934

Original Research

Evaluation of Sacrum Measurements in Healthy Individuals and Patients with L5-S1 Spondylolisthesis

Esin Erbek [1,*], Nadire Unver Dogan [1], Mehmet Ozturk [1], Neriman Akdam [2], Zeliha Fazliogullari [1], Ahmet Kagan Karabulut [1]

[1] Department of Anatomy, Faculty of Medicine, Selcuk University, Konya, Türkiye
[1] Department of Radiology, Faculty of Medicine, Selcuk University, Konya, Türkiye
[2] Department of Biostatistics, Faculty of Medicine, Selcuk University, Konya, Türkiye

Received: 2023-11-17 **Accepted:** 2024-02-06 **Published Online:** 2024-02-08

Corresponding Author
Esin Erbek, PhD
Address: Department of Anatomy, Faculty of Medicine, Selcuk University, Konya, Türkiye
E-mail: esinerbek89@gmail.com

This study was presented as an oral presentation at the 1. International Congress on Sports, Anthropology, Nutrition, Anatomy and Radiology Nevşehir Hacı Bektaş Veli University congress held in Nevşehir on May 3-5, 2018.

ABSTRACT

Objective: In recent studies, the relationship between sacrum morphology and orientation and spondylolisthesis has gained importance. The present study aimed to compare the morphometry of the sacrum between patients with L5-S1 spondylolisthesis and healthy subjects on multidetector computed tomography (MDCT) images.

Methods: In this study, abdominopelvic MDCT images of 191 individuals (age range 20-92 years; 101 males and 90 females; 56 patients diagnosed with L5-S1 spondylolisthesis and 135 healthy individuals) were retrospectively evaluated. In this study, the sacrum parameters (Intercornual distance (ICD), sacral hiatus length (LHS), anteroposterior diameter of hiatus at the apex of sacral hiatus(APCWHSA), sacral height (SH), sacral table angle (STA), sacral table index (STI), S1 superior angle (S1A), sacral slope(SS)) evaluated morphometric and morphological in healthy individuals and patients with L5-S1 spondylolisthesis. Kolmogorov–Smirnov test was used to test the normality, which is one of the parametric test assumptions, of the data.

Results: Age parameter was found statistically significant higher in the patient group ($p<0.001$). STA, S1A, SH, LHS and APCWHSA measurements were found to be significantly higher in the healthy group. ($p<0.001$, $p<0.001$, $p=.008$, $p=.005$, and $p=.002$, respectively). STI and ICD were found to be significantly higher in women in the healthy group ($p=.031$, $p=.010$), while SH parameter was found statistically significant higher in men in the healthy group ($p=.007$). SS was found statistically significant lower in the healthy group ($p<0.001$). S1A, L5-S1 spondylolisthesis was found statistically significant higher than Grade 1, Grade 2 according to the degree of slippage ($p=.045$).

Conclusion: The results of this study showed that sacral morphology is important in the development or at least progression of spondylolisthesis.

Keywords: Morphology, multidetector computed tomography, L5-S1 spondylolisthesis, sacrum, spinopelvic

INTRODUCTION

The lumbar vertebrae in the sagittal plane should continue the row aligned with each vertebral body lower and upper vertebral body. In other words, the anterior-inferior endplate of the upper vertebral body should be aligned with the anterior-superior endplate of the lower vertebral body. Spondylolisthesis occurs when the upper vertebral body slips over the lower vertebral body, or there is an anterior subluxation. Many cases and symptoms are associated with chronic spondylolisthesis [1]. Spondylolisthesis begins to be seen over the age of 50 and many factors such as joint degeneration, spinal sagittal imbalance, excess weight, sedentary lifestyle and subsequent muscle weakness have been reported to affect the progression of Spondylolisthesis [2]. The sagittal spinal alignment is affected by various factors, including age, posture, spinal diseases, the pelvis, and the entire lower extremity.

Previous studies have shown that sagittal spinal alignment is of great importance in treating degenerative spinal diseases and examining pathomechanisms [2,3]. In studies on the sacro-pelvic morphology of L5-S1 spondylolisthesis, abnormal sacro-pelvic morphology has been shown to cause deterioration of the global sagittal balance and sacro-pelvic orientation of the spinal cord. Studies have reported that findings related to sacro-pelvic morphology significantly influence the evaluation and treatment of patients with spondylolisthesis showing a high degree of slippage [4-6].

Main Points:

- In people with L5-S1 spondylolisthesis, the morphology of the sacrum is disrupted and thus the sagittal balance of the spine is impaired.
- In this study, STA and S1A values were lower in people with spondylolisthesis and SS values were higher in people with spondylolisthesis.
- We think that STA, SS and S1A values are important in the development of spondylolisthesis and S1A value is effective in the progression of the disease.We think that low SH is an important factor for the development of spondylolisthesis, but it is not associated with the progression of the disease.
- The SH value was found to be lower in people with spondylisthesis.

In our study, it was aimed to evaluate the relationship between multiple detector computed tomography (MDCT) images and the sacrum morphology of the patient group with L5-S1 spondylolisthesis and to compare the sacro-pelvic anatomical parameters with the group of healthy individuals.

MATERIALS AND METHODS

The study was started with the decision taken by Selcuk University Ethics Committee with the date 23.08.2017 and number 2017/255. Informed Consent Form was obtained from the participants. MDCT images of a total of 191 cases (101 males and 90 females), consisting of 56 patients diagnosed with L5-S1 spondylolisthesis and 135 healthy individuals by radiologists at the Department of Radiology, Selçuk University Faculty of Medicine, were included in the study. The data of the cases were obtained from retrospective abdominopelvic images obtained by MDCT with 128 slices of 1 mm slice thickness from the sacral region between 2010 and 2017. According to the cross-sectional study design, people who met the inclusion and exclusion criteria between 2010 and 2017 were included in our study. Abdominopelvic images of a total of 201 patients were evaluated.

A total of 10 patients under 19 years of age (3 cases) and patients with outliers between observations (7 cases) were excluded. Patients diagnosed with spondylolisthesis at the lumbosacral level by radiologists in the MDCT reports were named as the patient group with L5-S1 spondylolisthesis, and the patients aged between 20 and 92 without sacral pathology were named as the healthy group. Patients with previous spinal surgery, trauma findings, lumbar scoliosis, osteoporosis, spinal metastatic or primary tumor, and severe congenital anomalies were not included in either group.The sacropelvic parameters used in the morphometric evaluation are the measurement parameters made in the literature and were made in the computer environment. These measurements were evaluated according to gender and age in healthy subjects and patients with spondylolisthesis.

Our study aimed to compare the age range (between 20-92 years) with the parameters examined while the cases were screened. Care was taken to ensure that the distribution of both genders was close to each other in the groups. In the group of healthy individuals, the gender distribution was close to each other, while in the group of patient individuals, the number of women was higher than the number of men.

Measurements

Grading of spondylolisthesis: In the group of patients with L5-S1 spondylolisthesis, evaluation was made using the method that Meyerding staged according to the amount of vertebral slippage in patients with spondylolisthesis. Meyerding spondylolisthesis was divided into stages according to the percentage of slippage. According to the degree of Meyerding slip, grade 1 (0-25%) and grade 2 (26-50%) slip were detected in the spondylolisthesis group [7] (Figure 1).

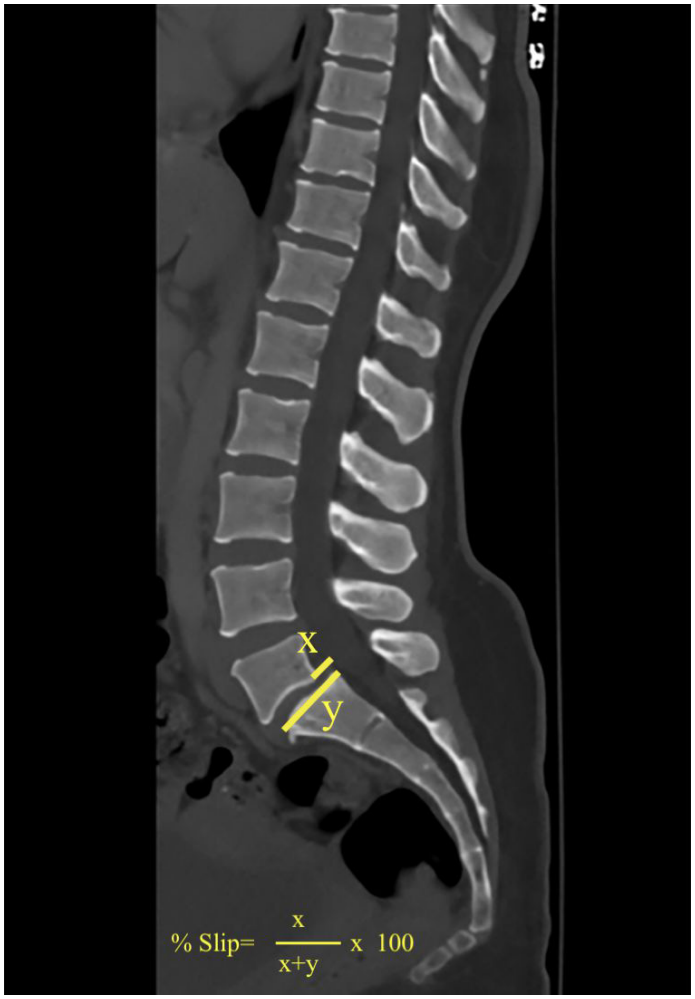


Figure 1. Spondylolisthesis slip value measurement on sagittal CT

Measurements of the Sacrum

Sacral table angle (STA): It is the angle between the line drawn along the sacral endplate and the line drawn along the posterior wall of the S1 vertebral corpus. Sacral table index (STI): It is the percentage of the anterior-posterior diameter of the superior endplate of the L5 vertebra to the maximum anterior-posterior diameter of the sacral endplate. S1 superior angle (S1A): It is the angle between the line drawn in the middle of the S1 vertebra and the perpendicular line drawn in the middle of the superior endplate of the S1 vertebra [8]. Sacral slope angle (sacral slope (SS)): It is the angle formed between the sacral endplate and the horizontal plane [9] (Figure 2).

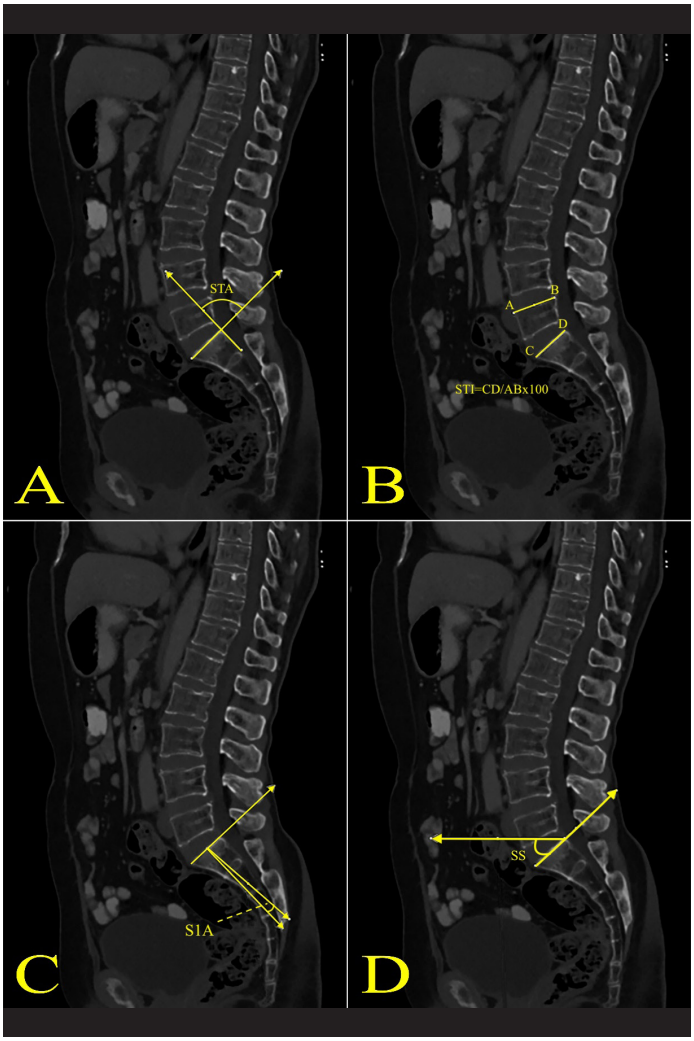


Figure 2. A. STA measurement on sagittal CT, **B.** STI measurement on sagittal CT, **C.** S1A angle on sagittal CT, **D.** SS angle measurement on sagittal CT

Sacrum height (SH): It is the distance measurement between the promontorium and apex ossis sacri notes of the anterior os sacrum [10]. Anterior posterior canal width of hiatus sacralis apex (APCWHSA): It is the distance between the anterior wall and posterior wall of the hiatus apex [11]. Intercornual distance (ICD): It is the distance between the bilateral cornu sacrales at their apex [12] (Figure 3).

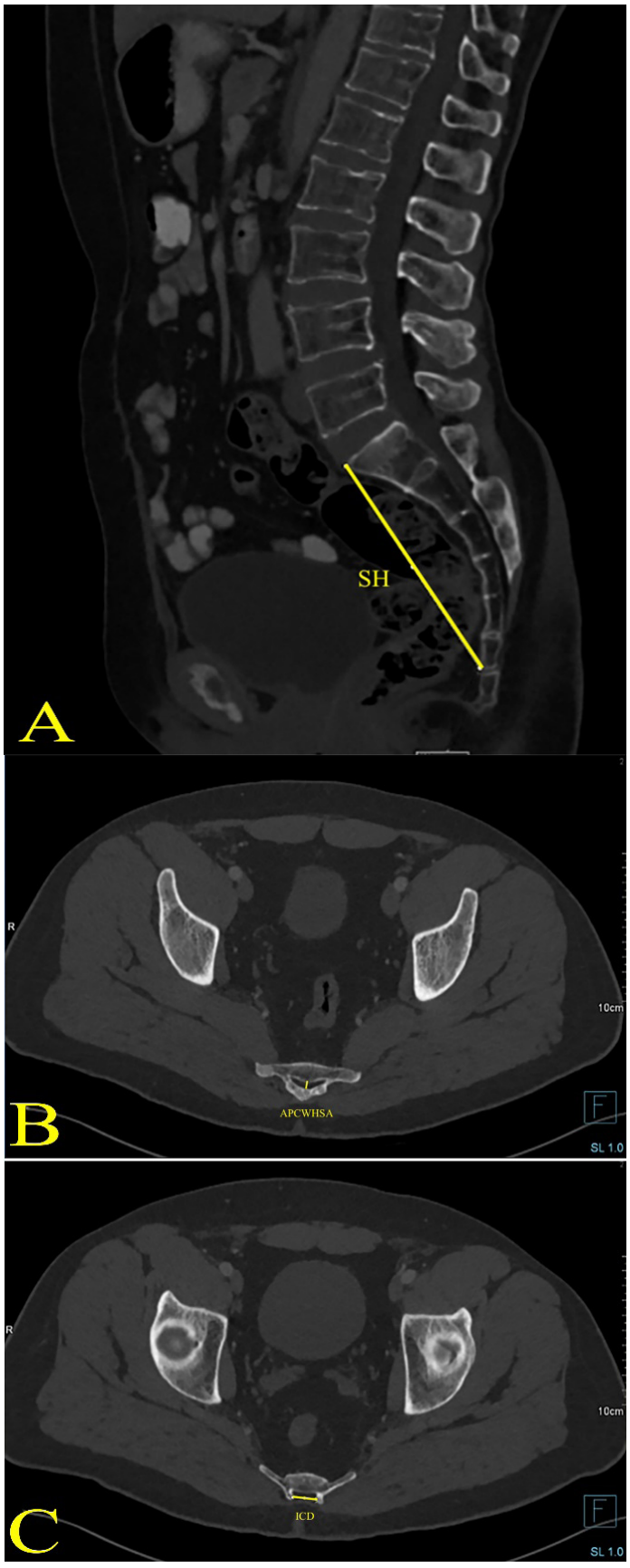


Figure 3. A. SH measurement on sagittal CT, **B.** APCWHSA measurement on axial CT, **C.** ICD measurement on axial CT

The length of the hiatus sacralis (LHS): It is the distance between the midpoint of the lower opening of the canalis sacralis and the midpoint of the part of the os sacrum that articulates with the os coccygis [13]. It was calculated by multiplying the number of sections between the first section where the hiatus sacralis begins (A) and the section at the level it ends (B) on the axial CT (Figure 4).

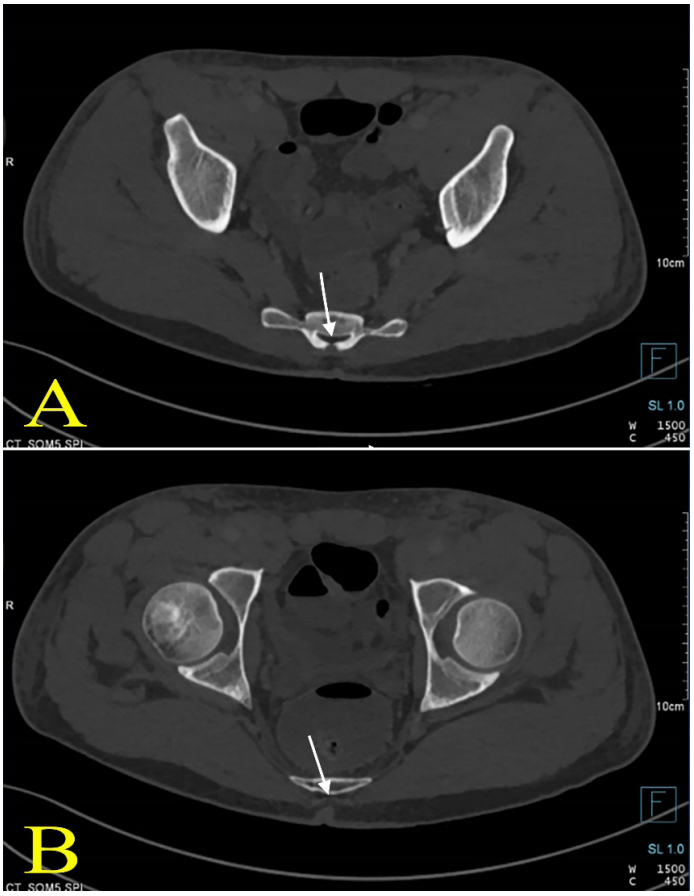


Figure 4. LHS measurement on axial CT. **A.** Hiatus sacralis starting place, **B.** Hiatus sacralis ending point.

Statistical Analysis

Statistical analysis was performed using the software IBM SPSS Statistics 21. Descriptive statistics were presented as minimum-maximum, mean±standart deviation, median, 1. Quartile and 3. Quartile. Kolmogorov–Smirnov test was used to test the normality, which is one of the parametric test assumptions, of the data. It was statistically accepted that the distribution of the data of age, STA, STI, SS, SH, APCWHSA, ICD distance variables for each group was in accordance with the normal distribution ($p>0,05$). In additioan, the distribution of S1A, LHS variables was not suitable with normal distribution ($p<0.05$). Independent

Samples T test was used to compare means of groups with normality and Mann-Whitney U test was used to compare groups with non-normality for all parameters. All analyses were evaluated at α=0.05 significance level (95% confidence level). p<0.05 is statistically significant.

RESULTS

Findings Related to Age Variable

The age value was found to be significantly higher in patient individuals (p<0.001) (Table 2). The age value was not statistically significant between the genders in the patient and healthy groups (p=.162, p=.625, respectively) (Table 1). When the age variable was analyzed according to the L5-S1 spondylolisthesis slippage grade, it was found to be higher in grade 2 than in grade 1, which was not statistically significant (p=.748) (Table 3).

Morphometric Findings of Os Sacrum

The mean values of STA and S1A of healthy individuals were determined as 94.8±7.24˚ and 12.39±4.75˚, respectively. The mean values of LHS, APCWHSA and SS in the healthy group were 29.32±9.06 mm and 5.5±0.20 mm and 41.26±8.90˚, respectively. While STA, S1A, LHS, SH and APCWHSA parameters were found to be significantly higher in the healthy group (p<0.001, p<0.001, p=.005, p=.008 and p=.002, respevtively), SS value was found statistically significant lower in the healthy group (p=.000). While STI and ICD values were found to be significantly higher in the healthy group of women (p=.031, p=.010), SH value was found statistically significant higher in the healthy group of men (p=.007). Comparison of parameters between healthy and patient groups and between genders are presented in Table 2 and Table 3.

The mean values of grade 1 and grade 2 of S1A were 6.41±4.45%, 4.12±4.15%, respectively. When S1A, L5-S1 spondylolisthesis was examined according to the degree of slippage, grade 1 was found statistically significant higher than grade 2 (p=.045). No significant difference was detected between grade 1 and grade 2 in all other measurements. Comparison of parameters according to grade 1 and grade 2 is presented in Table 3.

Table 1. Comparison of age and sacrum parameters according to gender and healthy- spondylolisthesis group

	Group	Gender	Min.-Max.	Mean±SD	Median	p
AGE	Healthy	Female(n=65)	22-92	50,54±16,15	49,0	0,162
		Male(n=70)	20-82	46,90±16,40	43,0	
	L5-S1 Spondylolisthesis	Female(n=36)	24-84	58,28±15,30	60,0	0,625
		Male(n=20)	39-82	57,3±15,12	50,5	
STA (°)	Healthy	Female(n=65)	79-109	94,38±7,05	95,0	0,523
		Male(n=70)	80-120	95,19±7,44	95,0	
	L5-S1 Spondylolisthesis	Female(n=36)	76-104	88,69±7,24	88,0	0,588
		Male(n=20)	73-101	87,60±7,11	86,0	
STI (%)	Healthy	Female(n=65)	84-11,5	98±0,65	0,98	**0,031***
		Male(n=70)	81-10,8	96±0,59	0,96	
	L5-S1 Spondylolisthesis	Female(n=36)	85-12,1	99±0,92	0,99	0,246
		Male(n=20)	88-10,9	97±0,63	0,97	
S1A (°)	Healthy	Female(n=65)	2-24	12,92±4,50	13,0	0,152
		Male(n=70)	1-24	11,89±4,95	11,0	
	L5-S1 Spondylolisthesis	Female(n=36)	0-16	5,78±4,86	4,5	0,712
		Male(n=20)	0-14	5,6±3,72	5,0	
SS (°)	Healthy	Female(n=65)	26-64	41,98±9,44	42,0	0,364
		Male(n=70)	18-64	40,59±8,40	40,5	
	L5-S1 Spondylolisthesis	Female(n=36)	30-76	49,64±10,55	49,0	0,307
		Male(n=20)	29-62	46,65±10,08	49,0	

SH (cm)	Healthy	Female(n=65)	7,84-12,85	10,80±1,12	10,78	**0,007***
		Male(n=70)	8,83-13,83	11,30±1,02	11,31	
	L5-S1 Spondylolisthesis	Female(n=36)	7,68-12,46	10,44±1,26	10,64	0,156
		Male(n=20)	8,34-13,49	10,95±1,30	10,97	
APCWHSA (cm)	Healthy	Female(n=65)	0,12-1,01	0,54±0,21	0,53	0,476
		Male(n=70)	0,17-1,30	0,57±0,20	0,56	
	L5-S1 Spondylolisthesis	Female(n=36)	0,0-0,96	0,46±0,21	0,44	0,786
		Male(n=20)	0,15-0,72	0,45±0,16	0,45	
LHS (mm)	Healthy	Female(n=65)	14,2-48,5	27,60±7,44	27,0	0,078
		Male(n=70)	11,0-52,0	30,93±10,14	30,6	
	L5-S1 Spondylolisthesis	Female(n=36)	9,0-50,0	25,66±8,50	24,0	0,832
		Male(n=20)	12,0-45,0	25,15±8,44	22,5	
ICD (cm)	Healthy	Female(n=65)	0,79-2,00	1,36±0,25	1,37	**0,010***
		Male(n=70)	0,66-2,06	1,48±0,30	0,56	
	L5-S1 Spondylolisthesis	Female(n=36)	0,70-1,90	1,35±0,28	1,35	0,750
		Male(n=20)	0,71-1,93	1,38±0,34	1,34	

STA sacrum table angle, *STI* sacrum table index, *S1A* S1superior angle, *SS* sacral slope, *SH* sacrum height, *APCWHSA* anterior posterior canal width of hiatus sacralis apex, *LHS* length of the hiatus sacralis, *ICD* intercornual distance, min. minimum, max. maximum, show statistical signifcance (*) p<0.05, SD—standard deviation.

Table 2. Comparison of age and sacrum parameters according to healthy-spondylolisthesis group

	Group	**Min.-Max.**	**Mean±SD**	**Median**	**p**
AGE	Healthy(n=135)	20-92	48,65±16,32	47,0	**<0,0001***
	Spondylolisthesis(n=56)	24-84	57,93±15,10	59,0	
STA (°)	Healthy(n=135)	79-120	94,8±7,24	95,0	**<0,0001***
	Spondylolisthesis(n=56)	73-104	88,3±7,15	87,5	
STI (%)	Healthy(n=135)	81-11,5	97±0,63	0,97	0,083
	Spondylolisthesis(n=56)	85-12,1	99±0,84	0,99	
S1A (°)	Healthy(n=135)	1-24	12,39±4,75	12,0	**<0,0001***
	Spondylolisthesis(n=56)	0-16	5,71±4,45	5,0	
SS (°)	Healthy(n=135)	18-64	41,26±8,90	41,0	**<0,0001***
	Spondylolisthesis(n=56)	29-76	48,57±10,39	49,0	
SH (cm)	Healthy(n=135)	7,84-13,83	11,06±1,09	11,11	**0,018***
	Spondylolisthesis(n=56)	7,68-13,49	10,62±1,29	10,76	
APCWHSA (cm)	Healthy(n=135)	0,12-1,30	0,55±0,20	0,53	**0,002***
	Spondylolisthesis(n=56)	0-0,96	0,46±0,19	0,45	
LHS (mm)	Healthy(n=135)	11-52	29,32±9,06	29,0	**0,005***
	Spondylolisthesis(n=56)	9-50	25,48±8,41	23,5	
ICD (cm)	Healthy(n=135)	0,66-2,06	1,42±0,28	1,43	0,168
	Spondylolisthesis(n=56)	0,70-1,93	1,36±0,30	1,35	

STA sacrum table angle, *STI* sacrum table index, *S1A* S1superior angle, *SS* sacral slope, *SH* sacrum height, *APCWHSA* anterior posterior canal width of hiatus sacralis apex, *LHS* length of the hiatus sacralis, *ICD* intercornual distance, min. minimum, max. maximum, show statistical signifcance (*) p<0,05, SD-standard deviation.

Table 3. Comparison of age and sacrum parameters according to grade 1 and grade 2.

	Group (%)	Min.-Max.	Mean±SD	Median	p
AGE	Grade1 (n=39)	24-84	57,74±15,78	59,0	0,748
	Grade2 (n=17)	26-78	58,35±13,87	59,0	
STA	Grade1 (n=39)	73-104	88,79±7,67	88,0	0,441
	Grade2 (n=17)	76-100	87,18±5,83	87,0	
STI	Grade1 (n=39)	0,85-1,21	0,99±0,082	0,98	0,482
	Grade2 (n=17)	0,85-1,16	0,98±0,088	0,97	
S1A	Grade1 (n=39)	0-16	6,41±4,45	5,0	**0,045***
	Grade2 (n=17)	0-13	4,12±4,15	4,0	
SS	Grade1 (n=39)	29-69	48,44±9,58	49,0	0,884
	Grade2 (n=17)	29-76	48,88±12,38	49,0	
SH	Grade1 (n=39)	8,84-13,07	10,75±1,24	10,86	0,262
	Grade2 (n=17)	8,84-13,07	10,75±1,24	10,86	
APCWHSA	Grade1 (n=39)	0,15-0,96	0,48±0,19	0,45	0,216
	Grade2 (n=17)	0-0,82	0,41±0,19	0,39	
LHS	Grade1 (n=39)	12-50	25,61±8,73	22,0	0,721
	Grade2 (n=17)	9-42	25,18±7,86	24,0	
ICD	Grade1 (n=39)	0,70-1,93	1,33±0,30	1,30	0,235
	Grade2 (n=17)	0,73-1,90	1,43±0,30	1,44	

STA sacrum table angle, *STI* sacrum table index, *S1A* S1superior angle, *SS* sacral slope, *SH* sacrum height, *APCWHSA* anterior posterior canal width of hiatus sacralis apex, *LHS* length of the hiatus sacralis, *ICD* intercornual distance, min. minimum, max. maximum, show statistical signifcance (*) p<0.05, SD—standard deviation.

DISCUSSION

Among the studies to understand the anatomy and relationships of the os sacrum, methods such as dry bone, radiography, and MDCT are used. Because MDCT provides high-resolution images, it is very effective in revealing the anthropometric features of the sacrum [14]. There is a lot of data in the literature on the relationship between other anatomical parameters and the prevalence of spondylolisthesis. This applies in particular to the parameters defining the morphology of the appendages and joint surfaces. This feature is crucial in maintaining the stability of the spine and the appropriate distribution of loads acting on its elements because facet joints are responsible for the transmission of 35% of the static load and 33% of the dynamic load affecting the spinal column [15].

Degenerative spondylolisthesis is seen after the age of 40 and mostly in women. It is considered one of the major causes of low back pain among the elderly and is a major cause of spinal canal stenosis associated with low back and leg pain [16]. Kong et al. [17] reported that the mean value of age was significantly higher in individuals with spondylolisthesis and that there was a positive correlation between age and spondylolisthesis. In our study, individuals between the ages of 20-92 were examined. Similar to this study, the mean age in the patient group (57.93±15.10) was found to be significanty higher than in the healthy group (48.65±16.32) (p<0.001). However, no significant difference was detected between genders. The STA parameter is among the descriptors of sacral morphology, and the difference in sacral morphology in patients with L5-S1 spondylolisthesis in the literature has increased the importance of STA. In the literature, it has been observed that the STA value decreases as the degree of spondylolisthesis slippage increases between spondylolisthesis and the control group, and it has been reported that lower STA value is an influential factor for disease progression and development [18].

Ergun et al. [19] study reported that STA was low in the degenerative spondylolisthesis group and reported that having a low STA parameter could be used to identify individuals with a tendency to develop degenerative spondylolisthesis. Sugawara et al. [20] STA of end-stage L5 spondylolysis (95.4 ± 1.5) was statistically significant lower than that of patients with low back pain (100.4 ± 0.8). We reported that STA was observed at a significantly higher angle in the healthy group (94.8±7.24˚)

than in the patient group (88.3±7.15˚). In our study, unlike the studies in the literature, no statistically significant difference was found in grade 2 compared to grade 1. This makes us think that STA is important in the development of spondylolisthesis but is not associated with its progression. Literature studies observed a strong correlation between pelvic incidence (PI) and STA. A high PI is seen in people with spondylolisthesis, and it has also been positively correlated with the percentage of slippage. It has been observed that STA is more closely related than PI in the development of spondylolysis and increased a decreased STA accompanies PI. In a cohort study, high PI was observed in people with spondylolisthesis, while a decrease in STA was observed [21,22].

Few studies are available in the literature for the STI parameter, one of the sacrum morphological evaluation parameters. The STI value is one of the parameters that help us understand the sagittal structure of the sacrum. Inoue et al. reported that STI was higher in people with spondylolisthesis (>102.5%) than in normal people (≤102%) [23]. However, another study reported that STI was higher in normal people (106±4%) than in people with spondylolisthesis (99±3%) [19]. In our study, the STI parameter was compared with the healthy and patient groups, and no significant difference was detected between them. However, the mean STI parameter was significantly higher in women (98±6.5%) than in men (96±5.9%) in the healthy group. We think this difference is due to the normal anatomical difference between the male and female pelvises. In addition, we think that STI may be important in gender determination. S1A, among the other important parameters we use to evaluate sacrum morphology, help define the sacrum sagittal structure. Marty et al. [9] showed that S1 and S2 vertebrae differ significantly in the adult population with spondylolisthesis. When Wang et al. [8] compared the spondylolisthesis group with the normal group on lateral radiographic images, it was found that the S1A value was lower in the spondylolisthesis group. In our study, similar to the literature, the mean of S1A in healthy individuals (12.39±4.75˚) was found statistically significant (p<0.001) higher than the mean of individuals with spondylolisthesis (5.71±4.45˚).

It was statistically significant lower in grade 2 than in grade 1 (p=.045). We think that the S1A value is important in the development and progression of spondylolisthesis. In people with spondylolisthesis, changes are observed in the SS, PI and PT angles as the pelvic positions change. It is thought that the increase in SS, PI and PT angles leads to the progression of spondylolisthesis and many spinal problems [24]. People with L5-S1 spondylolisthesis have an increased SS angle, which affects the progression of spondylolisthesis. In active young people, SS is an important cause of the development of isthmic spondylolysis. In a study of 37 people with spondylolysis and 37 people in a control group, radiographs were analyzed. This study, which consisted of active young people in both groups, found that the SS angle was statistically 5° larger in the group with spondylolysis [25]. In our study, the SS value was found statistically significant higher in people with spondylolisthesis, which is consistent with the literature study (p<0.001). In the literature, the relationship of PI, PT, and SS spinopelvic parameters between age and gender was examined, but no relationship was found between men and women. In the literature, no statistically significant difference has been found between age and gender in PI, PT and SS parameters in normal adult individuals [26,27].

Our study showed no significant difference between the genders in the SS value in the healthy and patient groups. We reported that the mean SS was found to be significantly higher in the spondylolisthesis patient group. (p=.000). Labella et al. [28] grouped the degree of spondylolisthesis according to Newman's grades I and IV and found that PI, PT and SS mean values increased as the grade increased. Unlike Labella et al. [28] no statistically significant difference was found between grade 1 and grade 2 of spondylolisthesis in our study. In some studies in the literature, no statistically significant difference was found between grades in the SS mean value measured according to Meyerding in spondylolisthesis grading [29-31].

In our study, the grade was classified according to Meyerding, and the mean SS value was not statistically significant between grade 1 and grade 2 (p=.884). However, the S1A parameter was found statistically significant higher than Grade 1 (p=.045). It was concluded that as the spondylolisthesis grade increased, the SS value was not affected, but the S1A value decreased. In addition, previous studies on normal subjects have reported a strong correlation between PI and SS [32,33]. In the MDCT studies conducted in the literature, the mean SH of men and women were higher than in the dry bone studies. In all studies, men's mean SH value was higher than women's [34,35].

In our study, SH value of healthy individuals was found statistically significant higher in males (11.30±1.02cm) than in females (10.80±1.12cm) (p=.007). The SH mean value of healthy individuals was statistically significant higher than those

with spondylolisthesis (p=.018). This study was determined that SH was lower in patients with spondylolisthesis and women (within the healthy group). We think that low SH is an important factor for the development of spondylolisthesis, but it is not associated with the progression of the disease. Caudal epidural block is widely used in diagnosing and treating lumbar spinal disorders in the orthopedic field [36]. It may become complicated by weight gain, advancing age, and congenital and shape variations in the sacrum. Therefore, reaching the epidural space for a safe caudal epidural block is possible by knowing well the anatomical structure of the SH. In this application, the depth of the sacral canal at the apex and the intercornual distance are the most frequently used anatomical landmarks and require good anatomical knowledge of this region [13].

In the literature, LHS, APCWHSA, and ICD measurements were made on MDCT, (Ultrasonography) USG, and dry bone [37,38]. The literature found that the mean values of LHS and APCWHSA decreased with age while the mean value of ICD increased. In MDCT and dry bone studies, the mean value of LHS in men was higher than in women. In MDCT studies, the mean value of APCWHSA was similar in men and women, and it was higher in men in studies conducted with USG. In studies conducted in MDCT, the mean value of male and female ICD was found to be lower than in studies performed with USG [39-41]. We think that the differences seen in USG-guided interventions should be taken into consideration. This study observed that LHS was similar to studies in the literature. LHS in the healthy group (29.32±9.06 mm) was found statistically significant higher than the mean value of the patient group (25.48±8.41mm) (p=.005). In healthy individuals, LHS was statistically significantly higher in men (p=.078). We think that the differences in LHS may be related to the similarity to the differences in SH (lower in women and the group with spondylolisthesis). It is reported in the literature that the average anterior-posterior diameter of APCWHSA varies between 4.6 ± 2 mm and 6.1 ± 2.1 mm, and the diameter decreases with age. It has been reported that this diameter is less than 3.7 mm at the apex in the procedure of needle insertion into the caudal epidural space, and less than 1.6 mm in the case of USG. It has been said that this attempt cannot be made in the variant where the hiatus sacralis is completely closed. The incidence of this variation has been reported as 2-3% in dry sacral bone studies [42].

In our study, APCWHSA in the healthy group (5.5±2 mm) was found to be significantly higher than the mean value of the patient group (4.6±1.9mm) (p=.002). The mean APCWHSA value was statistically insignificant higher in healthy male subjects than in female subjects (p=.476). In our study, ICD in healthy women was statistically significant higher than in men (p=.010). In the patient group with spondylolisthesis, there was no statistically significant difference in the mean value of ICD in men and women. No significant difference was detected between the spondylolisthesis and healthy groups (p=.168).

Limitations

In our study, we could not find the opportunity to measure and evaluate PI and PT angles, which are important for sagittal spinopelvic balance, due to the technique we chose. In addition, since our study was a retrospective study, we could not evaluate important information such as body mass indexes, occupations, and sports activities of individuals in our groups. For these reasons, we aim to conduct prospective studies that will include PI and PT parameters in our future studies.

CONCLUSIONS

In conclusion, the mean age value was statistically significantly higher in the patient group. This result shows that the likelihood of spondyloisthesis increases with increasing age. The results obtained in this study demonstrated that sacrum morphology is important in the development of spondylolisthesis and spinal sagittal balance of the spine. As seen in previous studies, decreased STA, one of the important morphologic parameters of the sacrum, is effective in the development of spondylolisthesis and the likelihood of this disease is high. We think that a prospective and longitudinal study should be done to demonstrate this recommendation. A good knowledge of the changes in the normal anatomy of the sacrum is very important in terms of preventing complications in interventions to be performed in patients with spondylolisthesis. For this reason, we think that studies on patient groups with altered sacrum anatomy such as spondylolisthesis should be increased and the changes in the anatomical structure should be fully revealed.

Acknowledgments: NA

Conflict of interest: The authors declare that they have no conflicts of interest.

Funding: This article was not supported by any grant.

Informed Consent: NA

Ethical Approval: Approval from the Selcuk University Faculty of Medicine noninvasive clinical research ethics committee (Date: 23.08.2017, Decision No: 2017/255) was obtained.

Author Contributions: Conception: EE, NUD; MO; NA; ZF, AKK - Design: EE, NUD - Supervision: NUD - Fundings: Selcuk University Faculty of Medicine -Materials: EE, MO- Data Collection and/or Processing: EE, NUD, MO- Analysis and/or Interpretation: NA- Literature - Review: EE, NUD, ZF, AKK - Writing: EE - Critical Review: EE

REFERENCES

[1] Burton MR, Mesfin FB (2017) Isthmic spondylolisthesis. Available from https://pubmed.ncbi.nlm.nih.gov/28722876/ Accessed 17 Jan 2022.

[2] Leng Y, Tang C, Liao Y, Tang Q, Ma F, Pu X, He B, Wang Q, Zhong D (2022) Correlation between sacral slope and pedicle morphology of the fourth lumbar vertebra in degenerative lumbar spondylolisthesis. Global Spine J 0(0):1-10. https://doi.org/10.1177/21925682221117151

[3] Funao H, Tsuji T, Hosogane N, Watanabe K, Ishii K, Nakamura M, Chiba K, Toyama Y (2012) Comparative study of spinopelvic sagittal alignment between patients with and without degenerative spondylolisthesis. Eur Spine J. 21(11):2181-2187. https://doi.org/10.1007/s00586-012-2374-0

[4] Shao X, Liu H, Wu J, Qian Z, Qu R, Liu T (2022) A retrospective comparative study of postoperative sagittal balance in isthmic L5-S1 spondylolisthesis using single segment or two-segment pedicle screw fixation. BMC Musculoskelet Disord. 23(1):145. https://doi.org/10.1186/s12891-022-05098-y

[5] Roussouly P, Gollogly S, Berthonnaud E, Dimnet J (2005) Classification of the normal variation in the sagittal alignment of the human lumbar spine and pelvis in the standing position. Spine (Phila Pa 1976) 30(3):346-353. https://doi.org/10.1097/01.brs.0000152379.54463.65

[6] Labelle H, Mac-Thiong JM, Roussouly P (2011) Spino-pelvic sagittal balance of spondylolisthesis:a review and classification. Eur Spine J 20(5):641-646. https://doi.org/10.1007/s00586-011-1932-1

[7] Niggemann P, Kuchta J, Grosskurth D, Beyer HK, Hoeffer J, Delank KS (2012) Spondylolysis and isthmic spondylolisthesis: impact of vertebral hypoplasia on the use of the Meyerding classification. Br J Radiol. 85(1012):358-362. https://doi.org/10.1259/bjr/60355971

[8] Wang Z, Parent S, Mac-Thiong J-M, Petit Y, Labelle H (2008) Influence of sacral morphology in developmental spondylolisthesis. Spine (Phila Pa 1976) 33(20):2185-2191. https://doi.org/10.1097/BRS.0b013e3181857f70

[9] Marty C, Boisaubert B, Descamps H, Montigny J, Hecquet J, Legaye J, Duval-Beaupere G (2002) The sagittal anatomy of the sacrum among young adults, infants, and spondylolisthesis patients. Eur Spine J. 11(2):119-125. https://doi.org/10.1007/s00586-001-0349-7

[10] Basaloglu H, Turgut M, Taser F, Ceylan T, Basaloglu H, Ceylan A (2005) Morphometry of the sacrum for clinical use. Surg Radiol Anat. 27(6):467-471. https://doi.org/10.1007/s00276-005-0036-1

[11] Seema, Singh M, Mahajan A (2013) An anatomical study of variations of sacral hiatus in sacra of North Indian origin and its clinical significance. Int J Morphol. 31(1):110-114. https://doi.org/10.4067/S0717-95022013000100017

[12] Singh A, Gupta R, Singh A (2018) Morphological and morphometrical study of sacral hiatus of human sacrum. Nat J Integr Res Med. 9(4):65-73.

[13] Bagheri H, Govsa F (2017) Anatomy of the sacral hiatus and its clinical relevance in caudal epidural block. Surg Radiol Anat. 39(9):943-951. https://doi.org/10.1007/s00276-017-1823-1

[14] Karakas H, Celbis O, Harma A, Alicioglu B (2011) Total body height estimation using sacrum height in anatolian caucasians: multidetector computed tomography-based virtual anthropometry. Skeletal Radiol. 40(5):623-630. https://doi.org/10.1007/s00256-010-0937-x

[15] Mazurek M, Kulesza B, Gołębiowska N, Tyzo B, Kura K, Szczepanek D (2023) Factors predisposing to the formation of degenerative spondylolisthesis-a narrative review. Medicina (Kaunas) 59(8):1430. https://doi.org/10.3390/medicina59081430

[16] Kalichman L, Hunter DJ (2008) Diagnosis and conservative management of degenerative lumbar spondylolisthesis. Eur

Spine J. 17(3):327-335. https://doi.org/10.1007/s00586-007-0543-3

[17] Kong Q, Wei B, Niu S, Liao J, Zu Y, Shan T (2023) Age, pelvic incidence, facet joint angle and pedicle-facet angle as correlative factors for isthmic spondylolisthesis: a retrospective case control study. BMC Musculoskelet Disord. 24(1):497. https://doi.org/10.1186/s12891-023-06569-6

[18] Wang Z, Parent S, de Guise JA, Labelle H (2010) A variability study of computerized sagittal sacral radiologic measures. Spine (Phila Pa 1976) 35(1):71-75. https://doi.org/10.1097/BRS.0b013e3181bc9436

[19] Ergun T, Sahin MS, Lakadamyali H (2010) Two and three dimensional reformatted computed tomography imaging analysis of the lumbosacropelvic structure in degenerative anterolisthesis. Clin Radiol. 65(11):908-915. https://doi.org/10.1016/j.crad.2010.06.012

[20] Sugawara K, Lesato N, Katayose M (2020) Comparison of the sacral table angles by progression stage of lumbar spondylolysis. Spine Deform. 8(1):123-127. https://doi.org/10.1007/s43390-020-00043-2

[21] Baker JF (2022) Sacropelvic parameters and L5 spondylolysis: computed tomography analysis. Asian Spine J. 16(1):66-74. https://doi.org/10.31616%2Fasj.2020.0442

[22] Ru N, Li J, Li Y, Sun J, Wang G, Cui X (2021) Sacral anatomical parameters varies in different sagittal shapes as well as their relations to lumbopelvic parameters. JOR Spine 4(4):e1180. https://doi.org/10.1002/jsp2.1180

[23] Inoue H, Ohmori K, Miyasaka K (2002) Radiographic classification of L5 isthmic spondylolisthesis as adolescent or adult vertebral slip. Spine (Phila Pa 1976) 27(8):831-838. https://doi.org/10.1097/00007632-200204150-00010

[24] Cosgun Z, Dagistan E, Dagistan Y (2019) Effects of sagittal balance differences on spondylolisthesis. Acta Ortop Bras. 27(2):120-123. https://doi.org/10.1590/1413-785220192702205665

[25] Hanke LF, Tuakli-Wosornu YA, Harrison JR, Moley PJ (2018) The relationship between sacral slope and symptomatic isthmic spondylolysis in a cohort of high school athletes: a retrospective analysis. PM&R 10(5):501-506. https://doi.org/10.1016/j.pmrj.2017.09.012

[26] Sudhir G, Acharya S, Kalra KL, Chahal R (2016) Radiographic analysis of the sacropelvic parameters of the spine and their correlation in normal asymptomatic subjects. Glob Spine J. 6(2):169-175. https://doi.org/10.1055/s-0035-1558652

[27] Triwidodo A, Rahyussalim A J, Yulisa ND, Pandelaki J, Huraiby LS, Hadi IAN, Liosha FY (2021) Sacrum morphometry and spinopelvic parameters among the Indonesian population using computed tomography scans. Medicine (Baltimore) 100(47):e27955. https://doi.org/10.1097%2FMD.0000000000027955

[28] Labelle H, Roussouly P, Berthonnaud É, Transfeldt E, O'brien M, Chopin D, Hresko T, Dimnet J (2004) Spondylolisthesis, pelvic incidence, and spinopelvic balance: a correlation study. Spine (Phila Pa 1976) 29(18):2049-2054. https://doi.org/10.1097/01.brs.0000138279.53439.cc

[29] Harroud A, Labelle H, Joncas J, Mac-Thiong J-M (2013) Global sagittal alignment and health-related quality of life in lumbosacral spondylolisthesis. Eur Spine J. 22(4):849-856. https://doi.org/10.1007/s00586-012-2591-6

[30] Min W-K, Lee C-H (2014) Comparison and correlation of pelvic parameters between low-grade and high-grade spondylolisthesis. J Spinal Disord Tech. 27(3):162-165. https://doi.org/10.1097/BSD.0b013e31829c07a4

[31] Lai Q, Gao T, Lv X, Liu X, Wan Z, Dai M, Zhang B, Nie T (2018) Correlation between the sagittal spinopelvic alignment and degenerative lumbar spondylolisthesis: a retrospective study. BMC Musculoskelet Disord. 19(1):151. https://doi.org/10.1186/s12891-018-2073-z

[32] Nakamae T, Nakanishi K, Kamei N, Adachi N (2019) The correlation between sagittal spinopelvic alignment and degree of lumbar degenerative spondylolisthesis. J Orthop Sci 24(6):969-973. https://doi.org/10.1016/j.jos.2019.08.021

[33] Suzuki H, Imai N, Nozaki A, Hirano Y, Endo N (2019) Anatomical sacral slope, a new pelvic parameter, is associated with lumbar lordosis and pelvic incidence in healthy Japanese women: a retrospective cross-sectional study. J Orthop Surg. 28(1):1-5. https://doi.org/10.1177/2309499019888809

[34] Mishra S, Singh P, Agrawal A, Gupta R (2003) Identification of sex of sacrum of agra region. J Anat Soc India 52(2):132-

136.

[35] Bakici R S, Oner Z, Oner S (2021) The Analysis of sacrum and coccyx length measured with computerized tomography ımages depending on sex. Egypt J Forensic Sci. 11(1):1-13. https://doi.org/10.1186/s41935-021-00227-5

[36] Sekiguchi M, Yabuki S, Satoh K, Kikuchi S (2004) An anatomic study of the sacral hiatus: a basis for successful caudal epidural block. Clin J Pain. 20(1):51-54. https://doi.org/10.1097/00002508-200401000-00010

[37] Mrudula C, Naveena S (2013) Morphometry of sacral hiatus and its clinical relevance. Int J Adv Res. 1(7):12-18.

[38] Saikia R, Sarma M (2016) Variations of sacral hiatus in dry human sacra: an anatomical study. J Evid Based Med Health 3(60):3238-3242.

[39] Kamal AM, Ara S, Ashrafuzzaman M, Khatun K, Islam MS (2014) Morphometry of sacral hiatus and its clinical relevance in caudal epidural block. J Dhaka Medical College 23(1):31-36. https://doi.org/10.3329/jdmc.v23i1.22690

[40] Kilicaslan A, Keskin F, Babaoglu O, Gok F, Erdi MF, Kaya B, Ozbıner H, Ozbek O, Koc O, Karıca BK (2015) Morphometric analysis of the sacral canal and hiatus using multidetector computed tomography for interventional procedures. Turk Neurosurg. 25(4):566-573. https://doi.org/10.5137/1019-5149.JTN.10942-14.0

[41] Park GY, Kwon DR, Cho HK (2015) Anatomic differences in the sacral hiatus during caudal epidural injection using ultrasound guidance. J Ultrasound Med. 34(12):2143-2148. https://doi.org/10.7863/ultra.14.12032

[42] Kao SC, Lin CS (2017) Caudal epidural block: an updated review of anatomy and techniques. Biomed Res Int. 2017:9217145. https://doi.org/10.1155/2017/9217145

How to Cite;

Erbek E, Unver Dogan N, Ozturk M, Akdam N, Fazliogullari Z, Karabulut AK (2024) Evaluation of Sacrum Measurements in Healthy Individuals and Patients with L5-S1 Spondylolisthesis. 30(2):186-197. Eur J Ther. https://doi.org/10.58600/eurjther1934

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):198-199.
https://doi.org/10.58600/eurjther1880

Letter to Editor

Should We Wait for Major Frauds to Unveil to Plan an AI Use License?

Istemihan Coban [1]

[1] Department of Anatomy, İzmir Democracy University Faculty of Medicine, Konak, İzmir, Türkiye

Received: 2023-12-10 **Accepted**: 2023-12-21 **Published Online**: 2023-12-22

Corresponding Author
Istemihan Coban, MD
Address: Izmir Democracy University Faculty of Medicine, Department of Anatomy, Konak, Izmir, Türkiye.
E-mail: istemihancoban@gmail.com.

Dear Editor,

I have followed with great interest your editorial content [1] which encourages academics to create a common mind, and the writings of our contributing colleagues, and I wanted to share my views and suggestions in order to offer a perspective on the subject. While the focal point of the debate is the question of whether AI can be included in an article as a co-author, it is evident that there are various debates on the periphery. When we discuss the peripheral questions, the answer to the focal question will emerge automatically. Thanks to the computer and internet revolution, we now have the simplest, fastest, and cheapest way to access any data that we have ever known, and this development does not seem to stop. For example, it is argued that the 6G communication network will enter the market in 2030–2040 and that extended reality and augmented reality tools will be integrated into our lives together with the internet of things with smart intelligence [2]. While the easy storage and accessibility of information uploaded to the Internet environment facilitates the production of new data, the production of false information can be uploaded to information repositories and circulated easily, which creates other major problems in itself, such as the use of reliable scientific data [3].

Artificial intelligence (AI) tools, especially large language models (LLMs), such as ChatGPT, which is on the agenda, have entered our lives like “aliens born on Earth” with their ability to access information in millions of different data sets from almost every language and culture. It is obvious that if this super-powered extraterrestrial from this world uses his powers on issues that humans demand in common, it will be described as “Superman”, and vice versa, it will be described as the mythological “Erlik”, and the current debate is exactly in the middle of these two superheroes. It is true that AI tools can be very useful when we use them to extract vast oceans of data or for various other academic tasks (e.g. automated draft generation, article summarizing, and language translation) [4]. However, at this point, it should be taken into account that the artificial AI tools available today may not be limited to performing the given tasks and may present a world reality that is adorned with “artificial hallucinations” [5]. We may end up fighting an unrelenting force in the production and distribution of misinformation that we lose control over.

We should discuss the responsibility for the control of products that will be obtained using artificial intelligence and prepare appropriate guidelines. Responsibility for control means that any digital result (whether it is an analysis of data or an analysis of a situation or an interpretation) must be reliable, i.e., it must be testable, rationally reproducible, and ethically attainable. Three different

interlocutors—the producer, the distributor, and the consumer—have different but critical responsibilities in controlling liability. When using AI tools, the scientific research group (producer party) working on any subject unconditionally bears the responsibility for each and every sentence of each and every piece of data obtained through these digital machines, and it should be declared that any negative consequences that may arise otherwise are accepted in advance. The acceptance of these digital machines as a kind of co-author in scientific products (translation text, statistical analysis, research title determination, or any text that will bring the research result to the academic literature) obtained with AI tools that cannot legally bear responsibility is similar to the acceptance of the computer, operating system, or code groups that enable any digital operation as the author. It is also a fact that this topic will come up for discussion again in the future when the issue of the individualization of AI (in terms of legal responsibility and rights) begins to be discussed. Scientific journals and publishing houses consisting of competent referees at the point of control of the academic products produced are the gatekeepers in protecting the naivety of the literature. There are many examples of how these indomitable guardians can be easily circumvented due to bad intentions and a failure to internalize ethical principles. In this respect, it can be predicted that the use of AI tools will help publishers in their work and that the quality and quantity of this help will gradually increase [6]. On the other hand, another major problem of the near future is that it will become increasingly easy to circumvent the gatekeepers with the malicious intent and misdirection of the people who take responsibility for AIs, and the content of the broadcasts may become corrupt. At the last point, the responsibilities of us, the readers who will consume the product, are also increasing. While reading articles that are declared to be written with the help of AI, we should question and check each sentence we read in more detail and increase our positive or negative feedback. To sum up, the use of AI tools as a technique in research should be explained in detail, trainings where the effective and ethical use of the tools are taught and licensed should be given to researchers urgently, and people who do not have an AI Usage License should not take part in scientific articles in the near future. It might be safe to say that the planning of a special education accompanied by leading scientists from every society is behind us and that the frauds of today could cripple the science of the future.

Yours sincerely,

Keywords: Artificial intelligence, ChatGPT, Research Ethics

Conflict of Interest: The author declared that there is no conflict of interest in this paper.

REFERENCES

[1] Balat A, Bahsi I (2023) May Artificial Intelligence Be a Co-Author on an Academic Paper?. Eur J Ther. 29(3):e12-e13. https://doi.org/10.58600/eurjther1688

[2] Ahammed TB, Patgiri R, Nayak S (2023). A vision on the artificial intelligence for 6G communication. ICT Express. 9(2):197-210.3. https://doi.org/10.1016/j.icte.2022.05.005

[3] Lee JY (2023). Can an artificial intelligence chatbot be the author of a scholarly article?. J Educ Eval Health Prof. 20. https://doi.org/10.3352/jeehp.2023.20.6

[4] Salvagno M, Taccone FS, Gerli AG (2023). Can artificial intelligence help for scientific writing?. Crit care. 27(1):1-5. https://doi.org/10.1186/s13054-023-04380-2

[5] Alkaissi H, McFarlane SI (2023). Artificial hallucinations in ChatGPT: implications in scientific writing. Cureus.15(2). https://doi.org/10.7759/cureus.35179

[6] Dadkhah M, Oermann MH, Hegedüs M, Raman R, Dávid LD (2023). Detection of fake papers in the era of artificial intelligence. Diagnosis. https://doi.org/10.1515/dx-2023-0090

How to Cite;

Coban I (2024) Should We Wait for Major Frauds to Unveil to Plan an AI Use License?. 30(2):198-199. Eur J Ther. https://doi.org/10.58600/eurjther1880

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):200-202.
https://doi.org/10.58600/eurjther1842

Letter to Editor

ChatGPT's Capabilities for Use in Anatomy Education and Anatomy Research

Yunus Emre Kundakcı [1]

[1] Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye

Received: 2023-09-06 **Accepted**: 2023-09-14 **Published Online**: 2023-09-14

Corresponding Author
Yunus Emre Kundakcı, PhD
Address: Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye
E-mail(s): emre.kundakci@afsu.edu.tr, y.emre.kndkc@gmail.com

Dear Editors,

Recently, the discussion of an artificial intelligence (AI) - fueled platform in several articles in your journal has attracted the attention of many researchers [1, 2]. I believe that including such current discussions in your journal will guide my future work plans on similar topics. I wanted to present my views on academic cooperation and co-authorship with ChatGPT (Chat Generative Pre-Trained Transformer) to your journal.

Innovations brought by technology undoubtedly arouse curiosity in almost every branch of science. Researchers are among the professional groups that follow new technological developments most closely because the basic nature of research consists of concepts such as curiosity, innovation, and information sharing. Technology-based materials may be needed for anatomy education to be permanent and to be used pragmatically during clinical practices. Especially in recent years, tools such as augmented reality, virtual reality and 3D printing, which offer 3D images of anatomical structures, as well as social media platforms have started to be used in anatomy education [3]. Similarly, anatomy is a window of opportunity for the first trials of many innovative researches. Indeed, it did not take long for meet with AI-based chatbot platforms such as ChatGPT and Artificial Intelligence Support System (AISS) [4-8]. AISS was reported by several researchers about a year before ChatGPT. AISS is a chatbot equipped with only anatomy knowledge based on a machine learning platform and neural network module [8]. According to the developers of the AISS, students feel comfortable making mistakes with this chatbot, and therefore students' interaction with anatomy is at a high level. Recent studies with ChatGPT are also contributing to the critical role of these AI-based chatbots in anatomy education. Some studies questioned the current capabilities and potential of AI in anatomy education and anatomy research through interviews [5, 7]. In another study, students and ChatGPT were quizzed on anatomy and their knowledge was compared [6]. The results obtained from the studies are that ChatGPT is more successful than the students and has the potential to increase student participation. However, this AI software model will increase the likelihood of making errors in basic knowledge in anatomy as we move to complex topics. Sometimes the same anatomical knowledge will be presented differently depending on how widely the internet-based data is scanned [4]. This situation is likely to be overcome in the future with the

learning potential of AI. In this context, I think that the use of AI can help physicians and physiotherapists by increasing the dynamic connections between anatomy knowledge and clinical practices. Furthermore, advances in educational technologies cannot provide equal opportunities to students in every country and university. ChatGPT partially eliminates this limitation. At this point, educators who want to increase student participation can design an anatomy education supported by ChatGPT and create research opportunities for students. It is stated that AI chatbots can be more useful in anatomy education and can provide students with access to educational resources regardless of location or time [5].

Apart from chatbots, the use of AI in anatomy can be seen in anatomy teaching approaches where student-centered and active learning is supported. Artificial Neural Networks or Convolutional Neural Networks are modelled similar to neural networks in the human brain. Bayesian U-Net is used to diagnose pathological anatomical deviations based on supervised deep learning by learning the normal anatomical structure and utilizing various biomarkers [9]. AI-based tools other than ChatGPT can also be used to display, classify or scale differences in anatomical structures. Thus, it may have pragmatic benefits for clinicians in the management of disease processes. In some studies indicate that the interpretation of anatomical regions in ultrasound, magnetic resonance and computed tomography images integrated with AI is facilitated [10]. Similarly, in specialties (such as dermatology) that require visual-oriented clinical skills in the processes required for diagnosis and treatment, AI's functions in recognition on images, computer-aided diagnosis and decision-making algorithms can be useful. I think that the use of ChatGPT in research in these fields can produce innovative and practical solutions if they provide information from an accurate and reliable database. In addition, its contributions to the research cause its collaborative position in the research to be questioned.

In my opinion, the explanations under the heading "Promoting collaborative partnerships" in the third answer of this editorial, which includes an interview with ChatGPT, are satisfactory [2]. This supports traditional norms of authorship. Besides, concerns about co-authorship are already strictly protected by international organizations. The Committee on Publication Ethics (COPE) clearly rejects the contribution of AI tools such as ChatGPT or Large Language Models in co-authorship and explains several reasons for this in the COPE position statement. Responsibility for the study should be shared among the authors. However, it is unclear to what extent an AI can fulfil this criterion, which is one of the most basic requirements of authorship. What is known today about anatomy has been obtained by sharing the knowledge of many famous anatomists who lived in ancient history. ChatGPT is already collecting this information and making it available to the researcher. Can we talk about a real contribution at this point? Partly yes. AI can document this information quickly, but it can only make a general contribution when formulating a research question. For example, I asked it for an example of a research question that I use to examine the role of the pelvis in gait function. I received a response like "What is the effect of the anatomical and biomechanical properties of the pelvis on a person's balance, stride length, stride speed and gait efficiency during walking?". It is seen that the answers consist of general concepts. However, a researcher who has worked on the subject can broaden your horizons more during an in-depth conversation over a coffee. AI's contribution will not require its to be a co-author. Currently, ChatGPT or other AI tools are not yet capable of performing a literature search suitable for academic writing. However, if ChatGPT is developed in this field, it may be suitable for use by researchers. If ChatGPT has been used in research, I think it is necessary and sufficient to indicate in one sentence in the acknowledgments or method section how and in what way it contributed to the article. The data processing, collection and synthesis potential of ChatGPT is used for different purposes in every field [9]. For example, good agricultural practices or research on existing jurisprudence in law. No matter how it is used in areas whose subject is qualified professions, there is a fact that does not change. It alone is not an educator; it does not have the conscientious conviction of a judge and it does not have the skill of a doctor in caring for the sick. It should only be used as a complementary tool in the fields where it is used. It should be used by all health educators and researchers, including the field of anatomy, with awareness of its risks.

In conclusion, the expectations of this new AI technology in anatomy are on students. The 3D model feature and its potential contribution to case-based learning practice during clinical applications can be further developed in the future. On the other hand, it is clear that ChatGPT cannot be a co-author of a publication. If ChatGPT is a co-author of a publication, who and how will prepare the response letters to the referee comments on this issue? While contributing to this editorial discussion, I thought that the reviewer assigned to review an academic

publication could prepare a reviewer comment with the help of ChatGPT. I hope this will never happen. Otherwise, we may soon encounter a journal publisher consisting of AI authors and reviewers.

Yours sincerely,

Keywords: Anatomy, Artificial Intelligence.

REFERENCES

[1] Balat A, Bahşi İ (2023) May Artificial Intelligence Be a Co-Author on an Academic Paper? Eur J Ther. 29(3):e12-e13. https://doi.org/10.58600/eurjther1688

[2] Balat A, Bahşi İ (2023) We Asked ChatGPT About the Co-Authorship of Artificial Intelligence in Scientific Papers. Eur J Ther. 29(3):e16-e19. https://doi.org/10.58600/eurjther1719

[3] Kundakcı YE, Atay E (2023) Bibliometric and Visualized Analysis of Global Research on Technology in Anatomy Education from 1987 to 2021. Eur J Anat. 27:517-528. https://doi.org/10.52083/HNNY3374

[4] Choudhary OP, Saini J, Challana A (2023) ChatGPT for Veterinary Anatomy Education: An Overview of the Prospects and Drawbacks. Int J Morphol. 41:1198-1202. https://doi.org/10.4067/S0717-95022023000401198

[5] Mogali SR (2023) Initial Impressions of ChatGPT for Anatomy Education. Anat Sci Educ. https://doi.org/10.1002/ase.2261

[6] Talan T, Kalinkara Y (2023) The Role of Artificial Intelligence in Higher Education: ChatGPT Assessment for Anatomy Course. International Journal of Management Information Systems and Computer Science. 7:33–40. https://doi.org/10.33461/uybisbbd.1244777

[7] Totlis T, Natsis K, Filos D, Ediaroglou V, Mantzou N, Duparc F, Piagkou M (2023) The Potential Role of ChatGPT and Artificial Intelligence in Anatomy Education: a conversation with ChatGPT. Surg Radiol Anat. https://doi.org/10.1007/s00276-023-03229-1

[8] Li YS, Lam CSN, See C (2021) Using a Machine Learning Architecture to Create an AI-Powered Chatbot for Anatomy Education. Med Sci Educ. 31:1729-1730. https://doi.org/10.1007/s40670-021-01405-9

[9] Abdellatif H, Al Mushaiqri M, Albalushi H, Al-Zaabi AA, Roychoudhury S, Das S (2022) Teaching, Learning and Assessing Anatomy with Artificial Intelligence: The Road to a Better Future. Int J Environ Res Public Health. 19(21): 14209. https://doi.org/10.3390/ijerph192114209

[10] Zhang Z, Sejdić E (2019) Radiological Images and Machine Learning: Trends, Perspectives, and Prospects. Comput Biol Med 108:354-370. https://doi.org/10.1016/j.compbiomed.2019.02.017

How to Cite;

Kundakçı YE (2024) ChatGPT's Capabilities for Use in Anatomy Education and Anatomy Research. 30(2):200-202. Eur J Ther. https://doi.org/10.58600/eurjther1842

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2)203-206.
https://doi.org/10.58600/eurjther2001

Letter to Editor

Innovative Reconstruction Techniques for Extensive Head and Neck Tumors

Ullyanov Bezerra Toscano Mendonça [1,2], Bernardo Correia Lima [3,4], Ricardo Grillo [5,6], Leonardo Augustus Peral Ferreira Pinto [7,8]

[1] Division of Head and Neck Surgery, Department of Otorhinolaryngology, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[2] Private Practice, Rio de Janeiro, Brazil
[3] Department of Oral Diagnosis, Dental Radiology and Imaginology, Dental School of University of São Paulo, São Paulo, Brazil
[4] Department of Oral Surgery and Oral Diagnosis, Hospital da Boca, Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, Brazil
[5] Department of Oral and Maxillofacial Surgery, Traumatology and Prosthesis, Dental School of University of São Paulo, São Paulo, Brazil.
[6] Department of Oral and Maxillofacial Surgery, Faculdade Patos de Minas, Brasília, Brazil.
[7] Department of Oral Surgery, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[8] Private Practice, Rio de Janeiro, Brazil

Received: 2024-01-09 **Accepted**: 2024-02-26 **Published Online:** 2024-02-29

Corresponding Author
Bernardo Correia Lima
Address: Dental School of University of São Paulo Av. Prof. Lineu Prestes, 2227. Cidade Universitária, São Paulo-SP-Brazil.
E-mail: bernardoclima@usp.br

Abstract

In the challenging landscape of malignant head and neck tumors, surgeons grapple with intricate obstacles to achieve effective reconstruction. When facing extensive involvement of soft and bone tissue, reestablishing acceptable aesthetics and function to patients should always be focused on restoring both form and function, we encountered a compelling case—a significant squamous cell carcinoma deeply rooted in the anterior mandibular region, necessitating substantial soft tissue and bone resection. Our innovative approach involved a carefully tailored extended prosthesis designed for the mandible and its temporomandibular joint, accompanied by a skillfully deployed deltopectoral myocutaneous flap. This surgical intervention successfully brought about the triumphant resurgence of reconstruction of mandibular function, marking a state of disease-free well-being for the patient. This narrative unfolds at the forefront of transformative reconstruction, where the synergy of innovation and expertise redefines the narrative, showcasing victory over adversity in the intricate realm of head and neck tumor surgery.

Keywords: deltopectoral flap; extended temporomandibular joint prosthesis; total joint replacement; head and neck cancer; reconstruction surgery.

Dear Editor,

The Deltopectoral Myocutaneous Flap (DP) with a medial base was historically regarded as the primary flap for reconstructing oropharyngeal and pharyngoesophageal defects. This flap derives its primary irrigation from the perforating branches of the internal mammary artery, coursing through the second, third, and fourth intercostal spaces. An irrigation terminal emanates from a local subdermal plexus [1]. In 1965, Bakamjian employed a medial deltopectoral flap for pharyngoesophageal reconstruction, bearing a striking resemblance to Aymard's flap published in The Lancet half a century earlier; however, Bakamjian did not reference Aymard in any of his articles [2].

The flap's positioning relative to the head and neck renders it an excellent choice for reconstructing defects in this region. DP boasts advantages in both the quality and quantity of harvestable tissue. Its robust nature facilitates not only the closure of various defects in the head and neck but also covers reconstruction plates used in mandibular surgery, consequently reducing the likelihood of exposure of the reconstruction plate through the skin or mucosa [3,4].

In scenarios necessitating mandibular resection without the option of preserving the temporomandibular joint (TMJ), the consideration of customized implants catering to both the mandible and TMJ becomes imperative. Elledge et al. validated a system and classification for these defects [5]. In cases involving substantial losses of associated soft tissue during ablative head and neck cancer (HNC) surgeries with mandibular involvement, pedicle flaps can be deployed to shield mandibular reconstruction plates [6,7].

This study elucidates the application of DP for coating a customized implant employed in mandibular and TMJ reconstruction, along with soft tissue reconstruction following ablative surgery for oral cavity cancer.

In this case, a woman of 78 years presented with an extensive oral squamous cell carcinoma that had infiltrated the mandibular body, extending into the right parasinfisary region, and exhibiting exophytic characteristics in the adjacent labiogenious region (Figure 1). An incisional biopsy confirmed the presence of squamous cell carcinoma.

Subsequent diagnostic procedures included a CT scan to assess the extent of the lesion's intraosseous component and a PET SCAN to evaluate tumor invasion in adjacent tissues. Upon evaluation, it was determined that the lesion exhibited significant local infiltration in the skin, adjacent tissues, and mandible. However, there were no metastases observed in nearby lymph nodes, and there was no invasion into the tongue region. Consequently, a plan for ablative surgery involving the total resection of the lesion in the affected soft tissue and mandible was devised.

Given the extensive bone defect resulting from the safety margin, which extended from the right temporomandibular joint (TMJ) to the contralateral parasinfisary region, the chosen approach involved the utilization of an extended customized prosthesis for the TMJ, ramus, body, and symphysis. This prosthesis featured perforations to facilitate the fixation of the microvascularized free graft of the fibula, intended for the reconstruction of intra and extraoral soft tissue (Osteomed®, Rio Claro, Brazil) (Figure 2). Simultaneously, the severely destroyed contralateral TMJ, afflicted by osteoarthritis, was replaced by a stock prosthesis (Osteomed®, Rio Claro, Brazil).

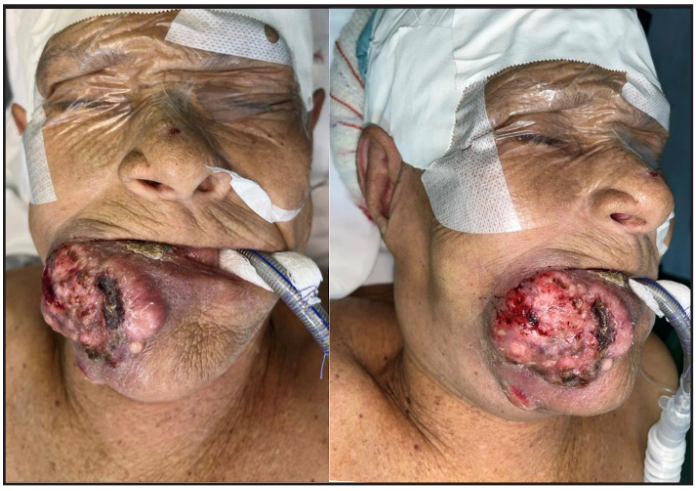


Figure 1. Extra oral view of the extensive oral squamous cell carcinoma in the right mandible. The exophytic pattern along with the bad medical status influenced in the decision of a pedicle flap to reconstruct the soft tissue defect created with the resection.

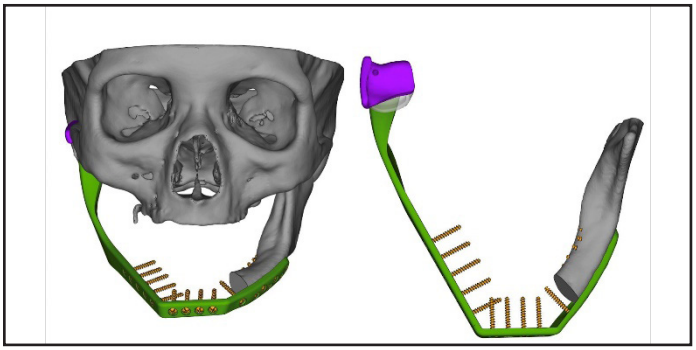


Figure 2. 3D virtual planning of the extended TMJ and mandibular reconstruction with a customized prosthesis designed by Osteomed® (Rio Claro, Brazil). Note the virtual simulation of the bicortical screws designed for fixation of the fibula graft. Only after the prosthesis manufacture, the patient's primary physician contraindicated the fibula graft due to her medical status that would make a more extensive surgery more dangerous to the patient. The virtual planning also showed the condylotomy of contralateral TMJ due to aggressive osteoarthritis for the TJR with a stock prosthesis (Osteomed® Rio Claro, Brazil).

In executing a strategy for intra and extraoral soft tissue reconstruction, an ipsilateral deltopectoral flap was implemented. The initial choice of a microvascularized free fibula graft for reconstruction was, however, discarded at the last minute by the patient's physicians due to her severe coronary disease. This decision was influenced by the need to avoid subjecting her to an extended period of general anesthesia typically associated with the use of this technique. The entire procedure unfolded smoothly over a span of 5 hours, in contrast to the potential 8 hours that might have been required for the use of free grafts (Figure 3).

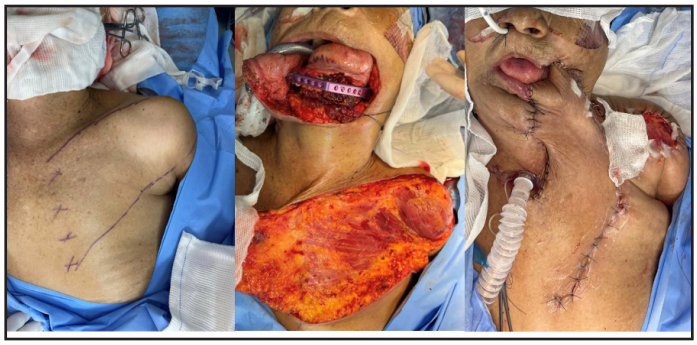


Figure 3. Design of the deltopectoral lap elevated after dissection and after lesion resection and TMJ and mandibular prosthesis placement. Then, the flap was rotated and sutured in place for both intra and extra oral soft tissue reconstruction. Patient underwent tracheostomy for mechanical ventilation and NG tube for parenteral feeding.

Although osseocutaneous free flaps are considered a superior option for reconstructing mandibular defects after ablative head and neck cancer (HNC) surgeries, their application is constrained in elderly patients with significant comorbidities, anticipating a low rate of graft absorption. Due to the advanced age and extensive comorbidities of our patient, we opted for the Deltopectoral Myocutaneous Flap (DP). This choice was motivated by its thickness, which effectively covers the mandibular implant and reconstructs all lost soft tissue following lesion resection, whether intra or extraoral—a capability commonly achieved by this flap. A retrospective study by Sekhar et al. [8], encompassing 127 patients, demonstrated that DP is widely employed for post-ablation reconstruction in HNC, particularly in cases involving extensive intra and extraoral defects without bone reconstruction. The flap exhibits commendable success rates, minimal recovery time, and favorable aesthetic outcomes, positioning it as a viable option for HNC treatment.

Lee et al. [6] detailed the successful use of myocutaneous pedicle flaps for the customized coating of titanium mesh after HNC ablation. Customized implants tailored to individual patients are extensively discussed in the literature, particularly for TMJ reconstructions and extensive mandibular defects. Huang et al. [9] emphasized the diverse anatomical considerations, complex mandibular movements, saliva contamination, and dental rehabilitation as key factors leading to the utilization of customized implants in maxillofacial reconstructions. The authors reported that, when used in conjunction with flaps for complex mandibular defects, patient-specific cutting and perforation guides corresponding to the specific reconstruction plate enable precise 3D orientation of bone segments. Elledge et al. [5] validated a protocol for the classification of extended alloplastic reconstructions of the temporomandibular joint (TMJ). According to the size of the mandibular bone defect and the extent of the prosthetic component involved, the prosthesis used corresponds to an M2, with a fossa component equivalent to F0.

Voss et al. [10] also described the use of customized implants for post-ablation reconstruction involving the mandible and TMJ, albeit using vascularized flaps from the scapula and latissimus dorsi. Notably, there was no mention of the reconstruction of the mandibular fossa, only the condylar component. To date, there are no reported cases employing our approach.

The removal of the TMJ was not directly related to cancer involvement but rather due to the scant bone remnant needed to fix a reconstruction plate. In most oncological or infectious processes of the head and neck, TMJ engagement is uncommon. This rarity can be attributed to the protective distance of most intraoral tumors, which initially infiltrate the mandibular body before extending late to the TMJ. Similarly uncommon is the involvement of cutaneous and subcutaneous tumors on the right wing, although infiltration due to parotid tumors is observed. The occurrence of metastatic oncological disease in the TMJ is infrequent and rarely warrants ablative surgery [10].

Oncological or infectious indications for TMJ reconstruction introduce several complex factors, including scarring and tissue loss from previous surgery or destruction, as well as potential poor vascularization. These factors contribute to increased complications, limited function, and decreased quality of life. The management of TMJ involvement in cancer patients varies significantly, ranging from non-reconstruction and free

autologous grafts to vascularized grafts and partial or total replacement with prostheses. Despite numerous case reports and comparative series, there is a scarcity of guidelines regarding the management of resected TMJ components in cancer patients.

Yours Sincerely,

Conflict of Interest: Authors declare there are no conflicts of interest, and the research was self-funded.

Funding: This article was not supported by any grant.

Authors Contribution: All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

During the preparation of this work the authors used ChatGPT in order to translate parts of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

REFERENCES

[1] Shah JP, Patel SG, Singh B. Chap. 15: Reconstructive Surgery. In: Head and Neck Surgery. 4th Ed., Mosby, 2012.

[2] Hwang K. The Origins of Deltopectoral Flaps and the Pectoralis Major Myocutaneous Flap. J Craniofac Surg. 2016. 27(7):1845-1848. https://doi.org/10.1097/SCS.0000000000003057

[3] Aldelaimi TN, Khalil AA. Reconstruction of Facial Defect Using Deltopectoral Flap. J Craniofac Surg. 2015.26(8):e786-8 https://doi.org/10.1097/SCS.0000000000002056

[4] Abrar Y, Muntaha ST, Khan K, Hameed U. Successful Use of Deltopectoral Flap in Reconstruction of Defect Caused by Squamous Cell Carcinoma. J Coll Physicians Surg Pak. 2018. 28(6): S125-S127. https://doi.org/10.29271/jcpsp.2018.06.S125

[5] Elledge ROC, Higginson J, Mercuri LG, Speculand B. Validation of an extended total joint replacement (eTJR) classification system for the temporomandibular joint (TMJ). Br J Oral Maxillofac Surg. 2021. 59(7):788-791 https://doi.org/10.1016/j.bjoms.2020.10.020

[6] Lee WB, Choi WH, Lee HG, Choi NR, Hwang DS, Kim UK. Mandibular reconstruction with a ready-made type and a custom-made type titanium mesh after mandibular resection in patients with oral cancer. Maxillofac Plast Reconstr Surg. 2018. 25;40(1):35. https://doi.org/10.1186/s40902-018-0175-z

[7] Sekhar MR, Patil BR, Krishnamurthy B, Rao CB, Gopalkrishna K. Soft tissue reconstruction after hemimandibulectomy in oral malignancies: a retrospective study. J Maxillofac Oral Surg. 2012. 11(1):72-7. https://doi.org/10.1007/s12663-011-0272-3

[8] Huang MF, Alfi D, Alfi J, Huang AT. The Use of Patient-Specific Implants in Oral and Maxillofacial Surgery. Oral Maxillofac Surg Clin North Am. 2019. 31(4):593-600. https://doi.org/10.1016/j.coms.2019.07.010

[9] Voss PJ, Steybe D, Fuessinger MA, Semper-Hogg W, Metzger M, Schmelzeisen R, Poxleitner P. Vascularized scapula and latissimus dorsi flap for CAD/CAM assisted reconstruction of mandibular defects including the mandibular condyle: technical report and clinical results. BMC Surg. 2019. 26;19(1):67. https://doi.org/10.1186/s12893-019-0535-3

[10] Bredell M, Grätz K, Obwegeser J, Gujer AK. Management of the temporomandibular joint after ablative surgery. Craniomaxillofac Trauma Reconstr. 2014. 7(4):271-9. https://doi.org/10.1055/s-0034-1378181

How to Cite;

Bezerra Toscano Mendonça U, Correia Lima B, Grillo R, Peral Ferreira Pinto LA. (2024) Innovative Reconstruction Techniques for Extensive Head and Neck Tumors: A Technical Note. 30(2):203-206. Eur J Ther. https://doi.org/10.58600/eurjther2001

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):207-210.
https://doi.org/10.58600/eurjther2020

Letter to Editor

Ghost Passenger in the Heart: The Story of an Intracardiac Cyst Dancing with Coronary and Peripheral Embolisms

Nergiz Aydın [1], Ahmet Lütfü Sertdemir [1], Yakup Alsancak [1]

[1] Department of Cardiology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye

Received: 2024-01-22 **Accepted**: 2024-02-28 **Published Online**: 2024-03-04

Corresponding Author
Nergiz Aydın, MD
Address: Necmettin Erbakan University, Department of Cardiology, Konya, 42000, Türkiye
E-mail: nrgz.ydn@hotmail.com

Abstract

Cardiac localization of hydatid cyst, which is a parasitic disease, is rare. In this article, a case of mediastinal hydatid cyst invading the left atrium is presented. A 62-year-old male patient with risk factors for coronary artery disease presented with epigatric pain, nausea and vomiting. Coronary imaging was performed because ongoing epigatric pain was accompanied by ischemic changes and elevated troponin on electrocardiography. No occlusive lesion was observed in the epicardial coronary arteries. Mesenteric embolism was detected in the patient whose epigatric pain continued. The patient, who did not accept surgery after the initial diagnosis, developed peripheral and cerebral emboli in the following period, and the patient was referred for surgery.

Keywords: Intracardiac hydatid cyst, Acute coronary syndrome, Mesenteric ischemia, Echinococcus granulosus, Left atrium

Dear Editor,

Hydatid cyst is a zoonotic disease caused by Echinococcus granulosus larvae. Human infection most commonly occurs in the liver and lungs. Mediastinal involvement is extremely rare, there are a few case examples in the literature [1,2]. Cardiac involvement can be observed through the adjacent mediastinal hydatid cyst. The incubation period of the disease may last for many years until the hydatid cyst grows large enough to trigger clinical symptoms. Cysts of cardiac origin may present with tamponade or systemic embolism findings, mimicking acute coronary syndrome [3]. We aimed to present our case of mediastinal hydatid cyst, which presented with peripheral and cerebral multiple emboli following mesenteric ischemia.

Patient Information

A 62-year-old man with a known history of hypertension and coronary artery disease presented to the emergency department with epigastric pain and nausea and vomiting. His electrocardiogram (ECG) was in sinus rhythm with ST depression and T negativity in the anterior leads. The patient with persistent pain, ischemia findings on ECG and elevated troponin was taken to the coronary angiography laboratory, but no occlusive lesion was observed in the epicardial coronary arteries. Mesenteric computed tomography angiography (CTA) was performed because of persistent epigastric pain during post-angiography follow-up. The superior mesenteric artery (SMA) was occluded on CTA. In addition, a mass containing cystic-necrotic areas invading the atrium was observed in the mediastinum. The patient was operated for mesenteric ischemia. The patient who was scheduled for surgery for intracardiac hydatid cyst refused the operation. One month after the initial presentation, the patient presented to the emergency room with speech disturbance, numbness in the legs and syncope. Diffusion magnetic resonance imaging (MRI) showed diffusion restrictions

in the right cerebellar region and bilateral cerebral hemispheres (Figure 1). Lower extremity CTA showed total occlusion of the right popliteal artery (Figure 2). Cardiac MRI showed a 65*50 mm hydatid cyst lesion in the mediastinum above the left atrium, projecting into the lumen, smoothly circumscribed, with small cysts of daughter vesicles. (Figure 3). The patient was referred for surgery.

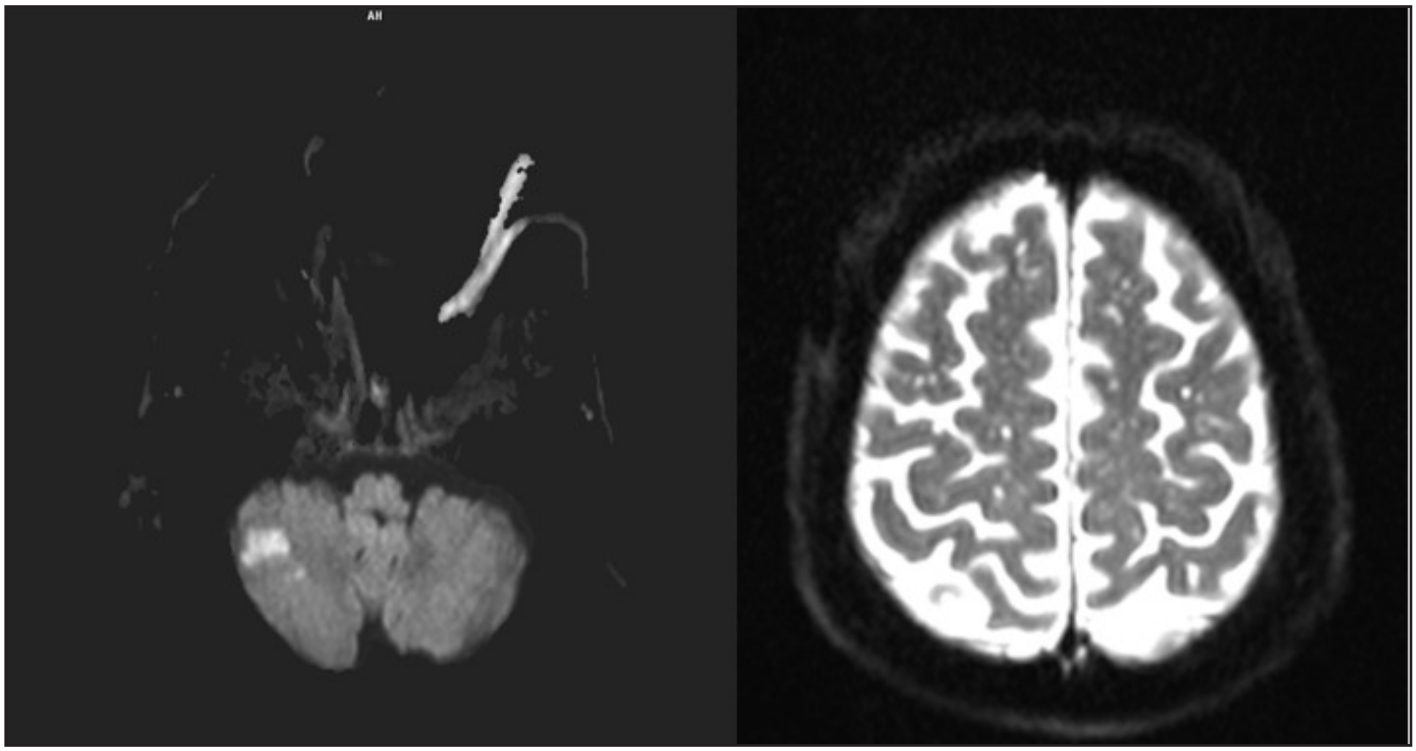


Figure 1.**A.** Diffusion restriction in the right cerebellar region, **1.B.** Diffusion restrictions in bilateral cerebral hemispheres

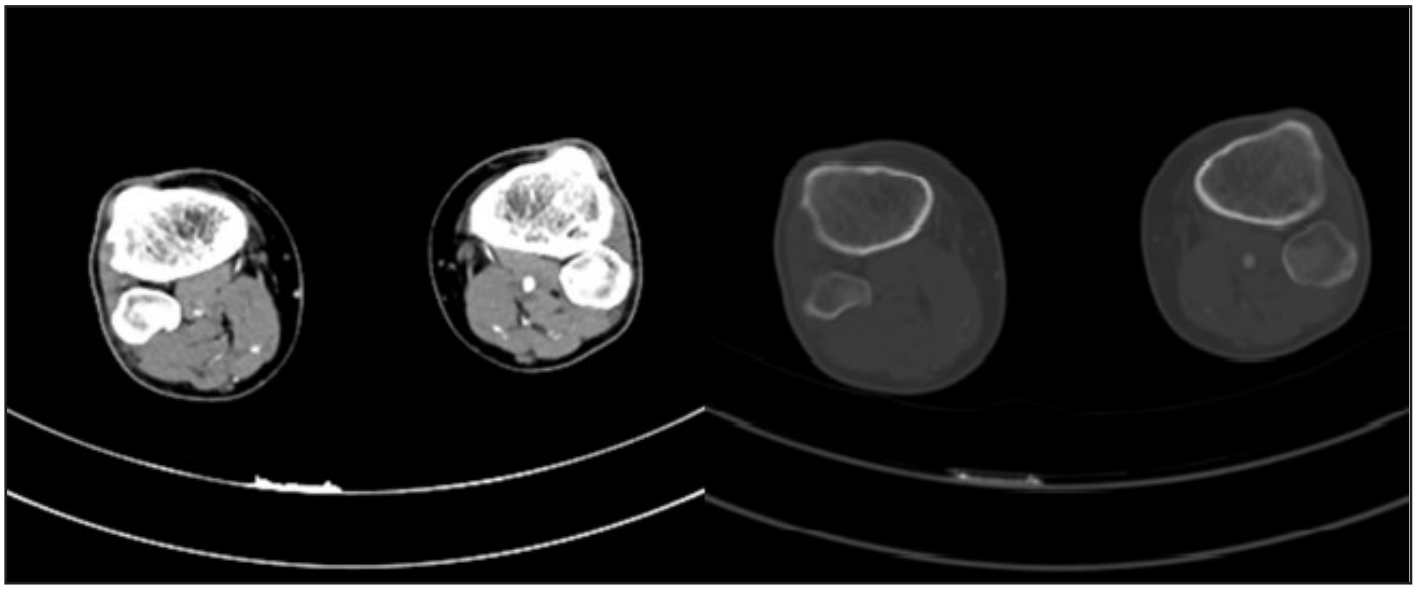


Figure 2. Right popliteal artery occlusion

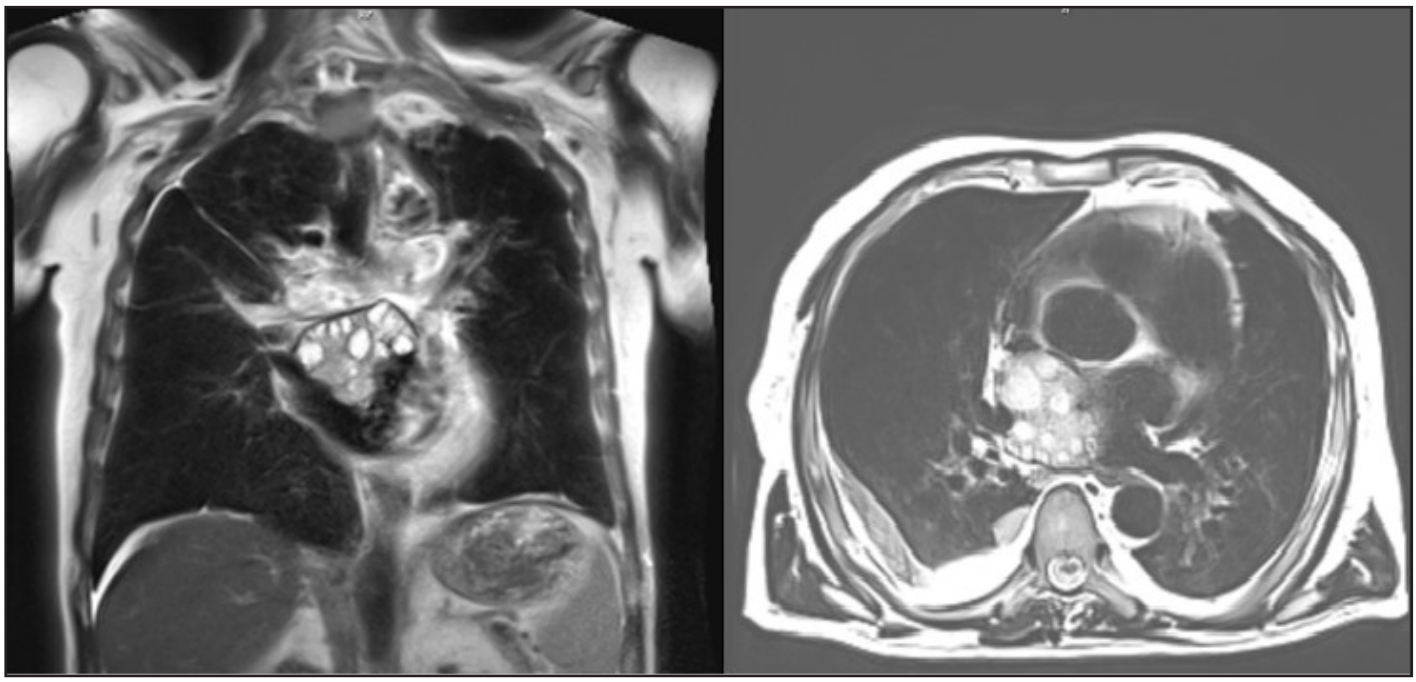


Figure 3. Coronal and axial sections of a 65*50 mm hydatid cyst lesion in the mediastinum above the left atrium with small cysts of daughter vesicles projecting into the lumen, smoothly circumscribed.

DISCUSSION

Cardiac hydatid cysts account for 0.5% to 2% of cases. This is due to the continuous contraction of the heart, which prevents invasion of parasite eggs into the myocardium despite the presence of viable cysts [4]. The left ventricle and right ventricle are most commonly affected, while the pericardium, left atrium, right atrium and interventricular septum are less common locations. Most patients with cardiac hydatid cysts are asymptomatic due to the slow growth of hydatid cysts (~1 cm per year), with symptoms occurring in approximately 10% of patients [5]. In symptomatic cases, symptoms are non-specific and vary depending on the number, size, location and local damage of the cysts. They may mimic symptoms of valvular diseases. Cardiac hydatid cyst-related bundle branch block, arrhythmias, myocardial infarction and sudden cardiac death have been reported [6]. There is a tendency to cause pulmonary embolism and CTEPH [7]. Intracardiac hydatid cyst cases may mimic acute coronary syndrome [8,9]. Cases presenting with neurologic symptoms have been reported [10]. Chest pain and dyspnea are the most common symptoms, precordial pain is usually vague. It may occur due to compression of the myocardium by hydatid cysts or by coronary emboli with typical angina. This may lead to misdiagnosis, especially in elderly patients with risk factors for coronary artery disease. In our case, coronary angiography was performed to exclude the possibility of coronary artery disease because epigatric pain was accompanied by ischemic changes on electrocardiography. The diagnosis of cardiac hydatid cyst is usually made by echocardiography and serologic tests. However, computed tomography and magnetic resonance imaging are sometimes needed when echocardiography is insufficient for the initial diagnosis. Patients with cardiac echinococcosis may present with a wide range of clinical findings, including typical angina. Especially in endemic areas, cardiac hydatid cyst should be considered in the differential diagnosis of patients with chest pain, even in those without a history of hydatid disease.

Yours sincerely,

Funding: This study received no funding.

Conflict of Interest: The authors report no conflict of interest.

Each author takes responsibility for all aspects of there liability and freedom from bias of the data presented and their discussed interpretation. Written informed consent was obtained from patient.

Author Contributions: Literature search: NA, ALS, YA ; Article writing: NA, ALS, YA

In our article, no support was received from artificial intelligence-based assistive technologies.

REFERENCES

[1] Mohammadi A, Khodabakhsh M (2011) Multiple mediastinal hydatic cyst: a case report. Tuberk Toraks 59:70-72. https://doi.org/10.5578/tt.2431

[2] Souhi H, Zegmout A, Janah H, El Ouazzani H, Rhorfi IA, Abid A (2016) [A rare cause of posterior mediastinal tumors: mediastinal hydatid cyst]. Pan Afr Med J 25:122. https://doi.org/10.11604/pamj.2016.25.122.9949

[3] Demircan A, Keles A, Kahveci FO, Tulmac M, Ozsarac M (2010) Cardiac tamponade via a fistula to the pericardium from a hydatid cyst: case report and review of the literature. J Emerg Med 38:582-586. https://doi.org/10.1016/j.jemermed.2007.07.017

[4] Giorgadze, Nadareishivili A, Goziridze M, Zodelava E, Nachkepia M, Grigolia G, Chekanov V (2000) Unusual recurrence of hydatid cysts of the heart: report of two cases and review of the clinical and surgical aspects of the disease. J Card Surg 15:223-228. https://doi.org/10.1111/j.1540-8191.2000.tb00460.x

[5] Akrim Y, Babokh F, El Hakkouni A (2022) Cardiac Echinococcosis With Hepatic Involvement in a Child: A Case Report. Cureus 14:e30390. https://doi.org/10.7759/cureus.30390

[6] Sarli B, Ugurlu M, Baktir AO, Tekin AI, Tok A, Yagmur B (2016) Lone, Mobile Left Atrial Hydatid Cyst. Tex Heart Inst J 43:261-263. https://doi.org/10.14503/THIJ-15-5261

[7] Kaskar A, Shetty V, Shetty D (2020) Chronic pulmonary thromboembolism due to intracardiac and pulmonary hydatidosis. Asian Cardiovasc Thorac Ann 28:610-612. https://doi.org/10.1177/0218492320957918

[8] Tekin AF, Durmaz MS, Dagli M, Akbayrak S, Akbayrak P, Turgut B (2018) Left ventricular hydatid cyst mimicking acute coronary syndrome. Radiol Case Rep 13:697-701. https://doi.org/10.1016/j.radcr.2018.03.019

[9] Sogunuru G, Murty DS, Chinta VR, Vuddanda K, Moka N (2010) Cardiac hydatidosis presenting as an acute coronary syndrome. BMJ Case Rep 2010. https://doi.org/10.1136/bcr.02.2010.2752

[10] Derbel B, Ziadi J, Besbes T, Dougaz W, Mleyhi S, Zairi I, Denguir R (2019) Intracardiac echinococcosis cyst mimicking a septal cardiac tumor with neurological symptoms. Int J Infect Dis 88:152-153. https://doi.org/10.1016/j.ijid.2019.08.024

How to Cite;

Aydın N, Sertdemir AL, Alsancak Y (2024) Ghost Passenger in the Heart: The Story of an Intracardiac Cyst Dancing with Coronary and Peripheral Embolisms. 30(2):207-210. Eur J Ther. https://doi.org/10.58600/eurjther2020

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):211-212.
https://doi.org/10.58600/eurjther2057

Letter to Editor

Evaluating RDW's Role in Heart Failure Mortality: Insights and Implications

Yunus Emre Yavuz [1], Fatih Kahraman [2]

[1]Department of Cardiology, Siirt Training and Research Hospital, Siirt, Türkiye
[2]Department of Cardiology, Kütahya Evliya Çelebi Training and Research Hospital, Kütahya, Türkiye

Received: 2024-02-19 **Accepted**: 2024-03-017 **Published Online**: 2024-03-18

Corresponding Author
Yunus Emre Yavuz
Address: Department of Cardiology, Siirt Training and Research Hospital, Siirt, Türkiye
E-mail: yemre91@icloud.com

To the Editor,

I am writing to express my appreciation for the recent publication by Umit Yuksek, "Red Cell Distribution Width Is an Independent Predictor of 1-Year Mortality in a Turkish Patient Population with Acute Decompensated Heart Failure" [1]. This study contributes significantly to our understanding of prognostic factors in acute heart failure, highlighting the importance of red cell distribution width (RDW) as an independent predictor of 1-year mortality in patients with acute decompensated heart failure. The methodology used in the study, which involved a cohort of 101 patients, provides an analysis of the predictive value of RDW as well as traditional clinical predictors. The finding that a 1% increase in RDW is associated with a 44% increase in 1-year mortality is particularly striking and emerging as a simple but powerful prognostic marker in clinical practice.

In addition to the limitations mentioned by the author, there are a few other factors that could potentially impact the results. First, studies on the effect of demographic characteristics on the value of RDW show that RDW is associated with various clinical conditions and demographic factors [2]. It has been reported that RDW can be affected by a number of factors, such as age, gender, inflammation, coronary artery disease, heart failure, hyperlipidemia, diabetes mellitus, pneumonia, and chronic obstructive pulmonary disease. Patients with acute decompensated heart failure may also be frequently intertwined with these diseases during their initial admission. The fact that some of these important demographic characteristics were not clearly explained in the patient population of the study may be important in terms of influencing the results of the study. The criteria for inclusion or exclusion in the study are also not comprehensive and clear. We think that these should be specified in more detail. In addition, the non-invasive diagnosis of heart failure with preserved ejection fraction (HFpEF) is difficult and controversial. For this reason, it is recommended to use scoring systems like H_2FPEF and HFA-PEFF for the diagnosis of HFpEF [3,4]. We believe that if any echocardiography or laboratory parameters other than the EF were evaluated while considering this patient group, it would be good to mention the methodology section. However, mentioning this issue in the limitations section may be useful if it is not mentioned.

Second, when we look at the comparison of the clinical and laboratory characteristics of the

subgroups with normal, high, and very high RDW values, it is noteworthy that factors such as Killip classification, mitral insufficiency, atrial fibrillation, cardiogenic shock, inotropic drug requirement, which may have significant effects on mortality in acute HEART FAILURE, do not have a significant relationship with high RDW. It also appears that even if it is not statistically significant, the EF value is positively correlated with RDW. As a result, despite this important success of RDW in showing a 1-year mortality estimate, it also has a weak relationship with many other mortality predictor parameters in acute heart failure, suggesting that unforeseen clinical conditions or parameters may potentially affect RDW in this study group.

Statistically significant findings may not always be clinically or biologically significant. RDW may indicate that it is a clinically important variable, but this effect may be small and not make a significant difference in practice. The reason for coming to this conclusion is that the important limitations mentioned above may affect the study results. In conclusion, we believe that further research is necessary to investigate the mechanisms underlying the association between RDW and mortality in acute heart failure patients and to examine the potential of RDW to guide therapeutic interventions. We commend the author of this study, which not only enriches our understanding but also opens avenues for future research in acute heart failure management, and we thank the journal for publishing it.

Yours sincerely,

Acknowledgment: The authors declare that they have not received any support from artificial intelligence tools for this article.

REFERENCES

[1] Yuksek U (2023) Red Cell Distribution Width Is an Independent Predictor of 1-Year Mortality in a Turkish Patient Population with Acute Decompensated Heart Failure. Eur J Ther 29:829-837. https://doi.org/10.58600/eurjther1803

[2] Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G (2015) Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 52:86-105. https://doi.org/10.3109/10408363.2014.992064

[3] Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA (2018) A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation 138:861-870. https://doi.org/10.1161/CIRCULATIONAHA.118.034646

[4] Pieske B, Tschope C, de Boer RA, et al. (2020) How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail 22:391-412. https://doi.org/10.1002/ejhf.1741

How to Cite;

Yavuz YE, Kahraman F (2024) Evaluating RDW's Role in Heart Failure Mortality: Insights and Implications. 30(2):211-212. Eur J Ther. https://doi.org/10.58600/eurjther2057

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):213-216.
https://doi.org/10.58600/eurjther2037

Letter to Editor

Cardiac Memory T Waves After Termination of Fascicular Ventricular Tachycardia in the Emergency Room

Süleyman Cihan Kara [1], Uğur Canpolat [1*]

[1] Hacettepe University, Faculty of Medicine, Department of Cardiology, Ankara, Türkiye

Received: 2024-01-30 **Accepted**: 2024-03-17 **Published Online:** 2024-03-18

Corresponding Author
Ugur Canpolat, MD
Address: Hacettepe University Faculty of Medicine, Department of Cardiology, 06100, Sıhhiye, Ankara/Türkiye
E-mail: dru_canpolat@yahoo.com

Abstract
Left posterior fascicular tachycardia (LPFVT) is a common type of idiopathic ventricular tachycardia that might be misdiagnosed as supraventricular tachycardia. Memory T wave is an inverted T wave that is seen after altered depolarization states such as pacemaker rhythm, ablated accessory pathways, ventricular tachycardia, or intermittent bundle branch blocks. Herein, we presented a young male patient who was admitted to the emergency room with FVT. After termination of tachycardia negative T waves (memory T wave) were seen. Memory T waves might be seen after the termination of FVT and must be differentiated from other causes of inverted T waves such as ischemia.

Keywords: Idiopathic ventricular tachycardia; T-wave inversion; memory T-wave

Dear Editor,

Left posterior fascicular ventricular tachycardia (LPFVT) is the most common type of idiopathic left VT [1]. The presence of the right bundle branch block and the left anterior hemiblock are the main features of electrocardiography (ECG) that are seen in these patients. It is usually hemodynamically well-tolerated, seen in patients without any structural heart disease, and responds well to calcium channel blockers, especially verapamil [2]. Due to its clinical features and ECG findings, it can be misdiagnosed as a supraventricular tachycardia with aberrancy.

Memory T waves, also known as the Chatterjee phenomenon, are one of the rare reasons for diffuse T wave inversion in ECG, seen after previous ventricular tachycardia, pacemaker implantation, bundle branch block, or Wolf-Parkinson-White syndrome. It is a benign process and there is no need for treatment. However, it must be differentiated from other reasons for T wave inversion such as ischemia [3].

Herein, we presented a patient with LPFVT, in which after the termination of tachycardia memory T waves were observed in the emergency room.

A 17-year-old male with no history of any diseases was admitted to the emergency room with a complaint of palpitations. A 12 lead ECG revealed a wide QRS tachycardia with right bundle branch block and left anterior fascicular block, fascicular ventricular tachycardia that originated from the left posterior fascicle was diagnosed (**Figure 1**). After the first examination, intravenous 25 mg diltiazem was administered. Control ECG revealed sinus rhythm with deep symmetrically negative T waves at the V_{3-6}, DII, DIII, and aVF derivations (**Figure 2**). His cardiac markers were within normal reference limits and

transthoracic echocardiography showed no abnormality. The patient underwent catheter ablation of FVT originating from the left posterior fascicle using a 3-dimensional electroanatomical mapping system after induction of the tachycardia during index hospitalization. The remaining hospital stay was unremarkable. He was discharged without any anti-arrhythmic medication.

There are several causes of T-wave inversion in the emergency room. An exact differential diagnosis is critical to avoid unnecessary tests, procedures, and prolonged hospital stay for the patients. In this paper, we presented a young male patient without any history of systemic illness, medication, or illicit drug use who was admitted with a wide QRS complex tachycardia consistent with FVT, and memory T waves were observed after termination of the tachycardia.

Left posterior FVT has a right bundle branch block, and left anterior fascicular block morphology at the ECG. Due to its ECG features, usually being hemodynamically well tolerated, seen in young patients without structural heart disease, and being sensitive to calcium channel blockers, it can be misdiagnosed as supraventricular tachycardia with aberrancy. Michowitz et al. [3] noted four ECG features favor FVT rather than supraventricular tachycardia; (a) presence of atypical V_1 morphology for RBBB, (b) QRS duration <140 milliseconds, (c) R/S ratio ≤1 in V_6 derivation, and (d) presence of positive QRS in aVR derivation. The presence of 3 or more of these features favors FVT. In our patient, all variables (QRS width 130 ms, V6 R/S ratio <1, and positive aVR) except for typical RBBB morphology (0 points) support VT. So the total score of 3 supported the diagnosis of FVT [3].

Memory T waves are one cause of T wave inversions, which are seen in patients' sinus rhythm ECG, when patients have transient abnormal ventricular conduction and turned into sinus rhythms, such as VT, bundle branch blocks, transient ventricular pacing, and intermittent Wolf-Parkinson-White patients [4]. First Chatterjee et al. described transient T wave inversion and ST segment depressions after ventricular pacing. They claimed T wave inversion is caused by artificial depolarization of ventricle changes repolarization and this finding has been seen as T wave inversion [5]. In 1982 Rosenbaum and colleagues postulated electrotonic modulation of ventricular repolarization and described the term, cardiac memory. They implicated, that T waves of the sinus follow the direction of the QRS complex of abnormal activation and its amplitude is proportional to the duration of abnormal activation so called accumulation [6]. In memory, T wave inversion is related to the loss of function of Ito and potassium channels [7].

One of the biggest challenges of T wave inversion in the emergency room is differentiating memory T waves from ischemic T wave inversion. Different algorithms are defined for this purpose. Shvilkin et al. [8] declared that positive T wave in aVL, positive/isoelectric T wave in lead I, and bigger T wave inversion in precordial derivations than inferior derivations favor memory T waves caused by ventricular pacing more than ischemia. Nakagawa et al. [9] also proposed criteria including (i) positive T wave in aVL derivation, (ii) negative or isoelectric T wave in lead II, and (iii) negative T wave in V4-6 derivations, or (iv) QTc <430 ms with a 100% sensitivity and 96% specificity for the cardiac memory compared to ischemic etiology. Based on proposed criteria in previous studies, T-wave

Table 1. Review of the literature about the cardiac memory T waves after termination of the left posterior fascicular ventricular tachycardia (LPFVT).

Article	Year	Patient #	Age	VT type	T wave inversion	Catheter ablation	Disappearance of T-wave inversion
Park et al. [10]	2012	n=1	28 yo	LPFVT	After electrical cardioversion	Yes	3-months later
Sorgente et al. [7]	2012	n=1	26 yo	LPFVT	After verapamil	Yes	Not reported
Kim et al. [13]	2012	n=1	41 yo	LPFVT	After catheter ablation	Yes	1-month later
Josephson et al. [11]	2015	n=1	24 yo	LPFVT	After verapamil	Not reported	Not reported
Nakagawa et al. [9]	2016	n=16	Mean 35 ± 17 yo	LPFVT	9/16 patients after verapamil or electrical cardioversion	Yes	Within 6-weeks
Siroky et al. [12]	2020	n=1	24 yo	LPFVT	After amiodarone	Yes	Not reported
Gunaseelan et al. [4]	2020	n=1	36 yo	LPFVT	After diltiazem	Not reported	Not reported
Kara et al.	2024	n=1	17 yo	LPFVT	After diltiazem	Yes	Not reported

inversions in our patient's sinus rhythm ECG were consistent with cardiac memory (T wave was positive in lead aVL and I, T waves were deeper in precordial derivations than inferior derivations, negative T wave in lead II, and negative T wave in V4-6 derivations).

In Table 1, we reviewed the previously reported patients of cardiac memory T waves after FVT. Park et al. [10] reported a patient with FVT in whom the T-wave inversion was observed after the termination of tachycardia with electrical cardioversion and T-wave inversion disappeared after 3 months. Josephson et al. [11] presented a case in which FVT terminated with intravenous verapamil infusion and also showed inverted T waves after termination of tachycardia. Sirotky et al. [12] and Kim et al. [13] represented other cases of LPVT in which T-wave inversions were observed after catheter ablation and disappeared in the first week and first month of follow-up. In our patient, memory T waves were also observed after termination of the tachycardia with diltiazem administration.

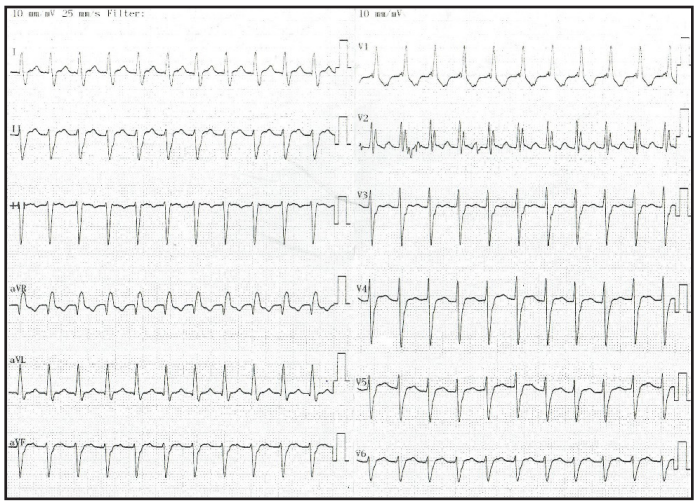


Figure 1. The patient's admitting ECG revealed a wide QRS complex tachycardia with right bundle branch block and left anterior fascicular block morphology, fascicular VT originating from the left posterior fascicle was diagnosed.

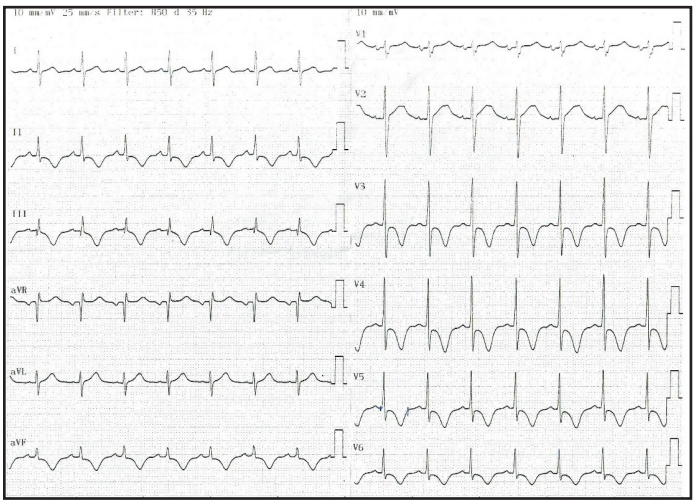


Figure 2. Control ECG after administration of intravenous diltiazem revealed sinus rhythm with deep, symmetrical T wave inversion at the V_{3-6}, DII, DIII, and aVF derivations, and positive T waves at the DI, V_{1-2}, aVL, and aVR.

In conclusion, LPFT is a common type of idiopathic ventricular tachycardia and memory T waves might be seen after its termination. Differentiation of LPFT from supraventricular tachycardias, and memory T waves from ischemic inverted T waves are challenging issues that must be solved.

Kind Regards,

Funding: None.

Conflict of interest: U.C.: Proctoring for Biotronik & Medtronic; S.C.K. and M.D.: None declared.

Written and verbal informed consent was obtained from the patient before the publication of this case report.

REFERENCES

[1] Lerman BB, Stein KM, Markowitz SM (1997) Mechanisms of idiopathic left ventricular tachycardia. J Cardiovasc Electrophysiol 8:571-583. https://doi.org/10.1111/j.1540-8167.1997.tb00826.x

[2] Belhassen B, Rotmensch HH, Laniado S (1981) Response of recurrent sustained ventricular tachycardia to verapamil. Br Heart J 46:679-682. https://doi.org/10.1136/hrt.46.6.679

[3] Michowitz Y, Tovia-Brodie O, Heusler I, Sabbag A, Rahkovich M, Shmueli H, Glick A, Belhassen B (2017) Differentiating the QRS Morphology of Posterior Fascicular Ventricular Tachycardia From Right Bundle Branch Block and Left Anterior Hemiblock Aberrancy. Circ Arrhythm Electrophysiol 10. https://doi.org/10.1161/CIRCEP.117.005074

[4] Gunaseelan R, Sasikumar M, Aswin K, Nithya B, Balamurugan N, Vivekanandan M (2020) Memory T-Waves, a Rare Cause of T-Wave Inversion in the Emergency Department. J Emerg Trauma Shock 13:312-316. https://doi.org/10.4103/JETS.JETS_70_20

[5] Chatterjee K, Harris A, Davies G, Leatham A (1969) Electrocardiographic changes subsequent to artificial ventricular depolarization. Br Heart J 31:770-779. https://doi.org/10.1136/hrt.31.6.770

[6] Rosenbaum MB, Blanco HH, Elizari MV, Lazzari JO, Davidenko JM (1982) Electrotonic modulation of the T wave and cardiac memory. Am J Cardiol 50:213-222. https://doi.org/10.1016/0002-9149(82)90169-2

[7] Sorgente A, Josephson ME (2012) Don't forget the memory: Contribution of the T wave vector in localizing the site of origin of a monomorphic idiopathic ventricular tachycardia. J Cardiol Cases 5:e28-e31. https://doi.org/10.1016/j.jccase.2011.09.003

[8] Shvilkin A, Huang HD, Josephson ME (2015) Cardiac memory: diagnostic tool in the making. Circ Arrhythm Electrophysiol 8:475-482. https://doi.org/10.1161/CIRCEP.115.002778

[9] Nakagawa T, Yagi T, Ishida A, Mibiki Y, Yamashina Y, Sato H, Sato E, Komatsu J, Saijo Y (2016) Differences between cardiac memory T wave changes after idiopathic left ventricular tachycardia and ischemic T wave inversion induced by acute coronary syndrome. J Electrocardiol 49:596-602. https://doi.org/10.1016/j.jelectrocard.2016.04.001

[10] Park C, Gentil P, Carballo D, Tran N, Monnard S, Shah D (2012) Cardiac memory following idiopathic fascicular left ventricular tachycardia. Journal of Cardiovascular Medicine 15:224-225.

[11] Josephson ME, Wellens HJ (2015) A tachycardia showing marked T-wave changes after its termination. Heart Rhythm 12:458-460. https://doi.org/10.1016/j.hrthm.2014.08.025

[12] Siroky GP, Keller S, Suri R (2020) In memory of tachycardia: A wide complex tachycardia in a young male. J Arrhythm 36:801-803. https://doi.org/10.1002/joa3.12385

[13] Kim SH (2012) T Wave Memory Caused by Sustained Idiopathic Left Ventricular Tachycardia. International Journal of Arrhythmia 13:24-27

How to Cite;

Kara SC, Canpolat U (2024) Cardiac Memory T Waves After Termination of Fascicular Ventricular Tachycardia in the Emergency Room. 30(2):213-216. Eur J Ther. https://doi.org/10.58600/eurjther2037

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):217-226.
https://doi.org/10.58600/eurjther1914

Review Article

Dysphagia in Individuals with Huntington's Disease: A Narrative Review

Merve Sapmaz Atalar [1]*, Özlem Oğuz[2], Gençer Genç [3]

[1] Department of Speech and Language Therapy Hamidiye Faculty of Health Sciences, University of Health Sciences, İstanbul, Türkiye
[2] Department of Speech and Language Therapy, Faculty of Health Sciences, Üsküdar University, İstanbul, Türkiye
[3] Department of Neurology, Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, İstanbul, Türkiye

Received: 2023-11-02 **Accepted**: 2024-01-09 **Published Online**: 2024-01-17

Corresponding Author
Merve Sapmaz Atalar, MSc
Address: Department of Speech and Language Therapy Hamidiye Faculty of Health Sciences, University of Health Sciences, İstanbul, Türkiye
E-mail(s): merve.sapmaz@sbu.edu.tr

ABSTRACT

Huntington's disease (HD) is a neurodegenerative autosomal dominant condition characterized by motor, behavioral, and cognitive symptoms. Aspiration pneumonia stands out as a leading cause of death in HD, primarily attributed to dysphagia, which gets more noticeable as the disease progresses. Dysphagia symptoms in individuals with HD are compounded by noticeable movement problems, including Chorean or rigid-bradykinetic patterns. These symptoms manifest in every phase of swallowing and fluctuate with the progression of HD. Lingual chorea, delayed swallowing initiation, and impaired swallowing-respiratory coordination are key indicators of dysphagia in individuals with HD. The negative impact on eating behaviors is further exacerbated by concurrent cognitive and sensory deficits. Consequently, dysphagia leads to social isolation, restrictions on activities and involvement, and a diminished quality of life for individuals with HD. To minimize these adverse effects, a referral to a speech-language therapist (SLT) for swallowing assessment should be initiated immediately upon the diagnosis of HD by a neurologist. Starting from the earliest stages of the disease, both clinical and instrumental swallowing assessments should be employed to minimize the detrimental consequences of dysphagia. Depending on the assessment results, compensatory and/or rehabilitative (restitutive) strategies can be recommended for treatment. Furthermore, the SLT actively collaborates with other team members, including individuals with HD, caregivers, neurologists, otolaryngologists, gastroenterologists, and others, contributing collectively to the decision-making process regarding both oral and non-oral feeding considerations. Despite the negative impact of dysphagia on individuals with HD and its significant role in individuals' deterioration, the evidence for specific dysphagia interventions remains limited. Clinicians, therefore, rely on well-established general swallowing therapy practices. There is a pressing need for evidence-based research on dysphagia in HD. In this study, the literature on dysphagia in individuals with HD will be examined, with a focus on its pathophysiology and the role of SLT in diagnostic and intervention techniques.

Keywords: Huntington's disease, swallowing, dysphagia, chorea

INTRODUCTION

Huntington's disease (HD) is a neurodegenerative and autosomal dominant disease that often manifests as progressive symptoms beginning in adulthood [1,2]. This condition typically emerges between the ages of 30 and 50, impacting 4-10 individuals per 100,000 in the population [3-8]. HD is linked to the huntingtin (HTT) gene on chromosome 4p16.3, arising from an elevated number of cytosine-adenine-guanine (CAG) trinucleotide repeats

within this gene [3,9,10]. In individuals without HD, the number of CAG repeats typically does not exceed 34. However, for those with HD, this number can surpass 40 [9]. The increased count of CAG repeats triggers the production of the huntingtin protein, leading to subsequent neuronal loss [9]. Notably, neuronal loss is more common in the basal ganglia, specifically in the caudate nucleus and putamen, although it is also observable in the cerebral cortex [2]. HD causes motor, cognitive, and psychiatric disorders [11] The most characteristic feature of the disease is chorea, a motor disorder involving dance-like, involuntary, fast, and non-stereotypic hyperkinetic movements [12]. Other motor disorders include muscle stiffness (rigidity), dystonia (involuntary and prolonged muscle contractions), and slowness of movement (bradykinesia) [9,13,14]. Cognitive and psychiatric disorders associated with the disease include dementia, depression, personality changes, and attention deficit [12]. As the disease advances, a genetic test is employed to confirm the diagnosis when clinical symptoms, encompassing a mix of motor, cognitive, and behavioral disorders, raise suspicion [8,13]. While chorea is a common initial experience, dystonia and rigidity also manifest as the disease progresses [13,14]. These motor disruptions in motor function can result in issues like swallowing difficulties (dysphagia) and hyperkinetic dysarthria [15,16]. Alongside motor challenges which contributes to dysphagia, cognitive problems can influence swallowing as well [15]. Dysphagia, in turn, may lead to malnutrition, dehydration, and aspiration pneumonia [17]. Notably, aspiration pneumonia stands as a primary cause of death in HD [18]. Furthermore, dysphagia can contribute to social isolation, limitations in activity and participation, and a decline in overall quality of life [16,17]. Hence, dysphagia not only adversely affects individuals with HD but also may amplifies the burden on caregivers. Therefore, early diagnosis and treatment of dysphagia are of critical importance.

Main Points;

- Dysphagia is a common problem in Huntington's disease, affecting about 90% of individuals with the condition.
- As the disease progresses, symptoms worsen, leading to issues like malnutrition, dehydration, and pneumonia.
- Assessment methods include comprehensive swallowing evaluation like the clinical evaluation and instrumental assessment.
- A team of healthcare professionals, including speech-language therapists, works together to ease dysphagia symptoms using a mix of behavioral and medical approaches, with early involvement of caregivers in the process.

Dysphagia should be managed by a multidisciplinary team for individuals with HD. Members of the team may include, but are not limited to, speech-language therapists (SLTs), neurologists, otolaryngologists, gastroenterologists, nutritionists, physiotherapists, occupational therapists, and nurses. Referral of individuals to SLTs in the early stages of the disease is particularly crucial in terms of providing information and counseling to individuals, according to European HD guidelines [19]. SLTs assist in clinical decision-making for the immediate assessment and intervention for individuals with HD and dysphagia [19]. Individuals with HD and their caregivers are referred to SLTs and then they go through stages such as assessing swallowing safety of individual, identifying current risks for dysphagia, minimizing the individual's and caregiver's concerns, discussing intervention options during the course of the disease, and effectively communicating with needed health professionals [19].

Little is known about HD-related dysphagia despite the physical, psychological, social, and even deadly consequences. This study aims to provide a wide framework for SLTs and learners through reviewing the literature on the etiology, prevalence, symptoms, assessment, and treatments of dysphagia associated with HD. The goal is also to guide clinical practice and improve awareness of the role of SLTs in HD-related dysphagia among other health professionals on the team.

In order to access the findings of the literature to be included in the review, PubMed, Scopus, and Google Scholar were consulted. Conference papers, seminar proceedings, and symposium papers were excluded from the review. Moreover, books were consulted to gather additional information. The article title, abstract, and keyword fields were examined using the following search *'dysphagia in Huntington's disease, dysphagia assessment in Huntington's disease, dysphagia therapy/ intervention in Huntington's disease.* The search encompassed recent publications, specifically those released post-2000, with the exception of four publications including dysphagia-related scales and focusing on HD and serving as primary sources for information on the disease.

Prevalence, Pathophysiology and Symptoms-Findings of Huntington's Disease Related Dysphagia

Dysphagia, a common disorder in neurodegenerative diseases like Parkinson's, Amyotrophic lateral sclerosis and Alzheimer's, is also prevalent in HD [20-23]. Dysphagia is reported in around 90% of IwHD [21]. It is observed in 35% of people in the early stage, 94% of people in the middle stage, and 100% of people in the late stage [24]. Neuropathological changes in HD involve neurodegeneration in regions such as the striatum, pallidum, cerebral neocortex and allocortex, brainstem, thalamus, and cerebellum [25]. A study highlighted the compromise of swallowing safety due to atrophy in a network comprising parietotalamocerebellar areas [26]. This network is associated with sensory processing, sensorimotor transformation, and cognitive control. Neurodegeneration in these areas leads to the emergence of sensory, motor, cognitive, and psychiatric disorders [26].

It is well known that dysphagia can manifest in the oral, pharyngeal, and esophageal phases in HD [27]. Neuromuscular dyscoordination in the oral and pharyngeal phases is thought to originate from basal ganglia or cerebellar dysfunction [24,25]. The impact of mutant huntingtin on oro-pharyngeal muscles is also presumed [24]. Silent aspiration, as observed in individuals with HD, may arise from sensory disturbances in the epiglottis and posterior wall of the hypopharynx, similar to other neurodegenerative disorders (e.g., Parkinson's disease) [24,28]. Motor and sensory problems affecting swallowing can worsen with motor problems in the upper extremities in individuals with HD, leading to severe restrictions in self-feeding [29]. Dysphagia symptoms in individuals with HD can be hyperkinetic or akinetic-rigid motor symptoms, varying according to the stage of HD [15,30]. Involuntary movements observed in HD can complicate the eating and drinking process by making postural control challenging, increasing the risk of aspiration [15,31]. Rapid lingual chorea and lingual dysfunction associated with swallowing coordination issues result in problems with bolus preparation and delivery [15,32,33]. Weak lingual control of the bolus can lead to premature spilling into the laryngeal vestibule [29]. Coughing due to laryngeal chorea is an early clinical symptom of HD [27]. Loss of voluntary feeding control is associated with late-stage symptoms such as aspiration pneumonia, choking, unintentional weight loss, and cachexia [30,27,34].

In the oral phase of swallowing, in addition to lingual dysfunction, impaired and involuntary lip and jaw movements can be observed [35]. In the pharyngeal phase of swallowing in individuals with HD, coordination disorders, airway protection issues, prolonged laryngeal elevation, decreased pharyngeal clearance, pharyngeal residue, and penetration/aspiration problems may arise [15,29,30]. Postural instability in HD contributes to problems in both the oral and pharyngeal phases [29]. In the esophageal phase, there may be gastroesophageal inflammation such as gastritis or esophagitis and esophageal dysmotility [15,36].

Psychiatric and cognitive problems can also impact nutrition in addition to motor and sensory issues. Cognitive and psychiatric changes pose the greatest burden on families, are associated with functional decline, and can predict hospitalization [37,38]. Individuals with HD may not be aware of social eating behaviors, may fragment meals during anger bursts, and may struggle to maintain the social aspects of eating [27]. Cognitive inhibition deficiencies affecting eating speed lead to insatiable appetite, impulsively fast eating (tachyphagia), and increased hunger in individuals with HD, resulting in ineffective transportation of food into the oral cavity and inadequate lip closure [33].

Common oral health issues observed among individuals with HD include gum inflammation, tooth decay, poor oral hygiene, and bruxism in a recent review [39]. Additionally, many medications used for psychiatric symptoms induce dry mouth [40]. Early referral to a dentist is essential for maintaining oral health, as dental procedures become more challenging as the disease progresses [39].

In summary, involuntary movements can impact all phases of swallowing in individuals with HD. Symptoms such as throwing food from containers, pushing food out of the mouth with the tongue, breathing during laryngeal swallowing, and regurgitation can occur [27]. Although dysphagia symptoms and findings emerge in all three phases, they are typically observed in the oral and pharyngeal phases [32,36]. Figure 1 emphasizes dysphagia symptoms and findings in individuals with HD based on swallowing stages [15,27,32].

Assessment of Huntington's Disease Related Dysphagia

It is now established that dysphagia is prevalent in HD. Various symptoms associated with dysphagia can manifest during different stages of the swallowing process. For instance, aspiration, even in the early stages of HD, has been reported to

be prevalent, with a notable incidence of silent aspiration [26]. Although individuals with HD may not self-report dysphagia symptoms during assessment, it is crucial for neurologists to address these symptoms explicitly and refer to SLT for a comprehensive swallowing evaluation, such as a clinical evaluation and instrumental assessment. The comprehensive swallowing evaluation, aligned with the International Classification of Functioning, Disability, and Health (ICF) framework, should commence the evaluation from the early stages of the disease [19,31]. The ICF framework emphasizes that dysphagia assessment should encompass (1) the evaluation of body structures and functions that may influence swallowing, eating, or drinking behaviors, (2) swallowing activities and participation, (3) eating or drinking activities and participation, and (4) personal and environmental factors that may affect swallowing [9,41].

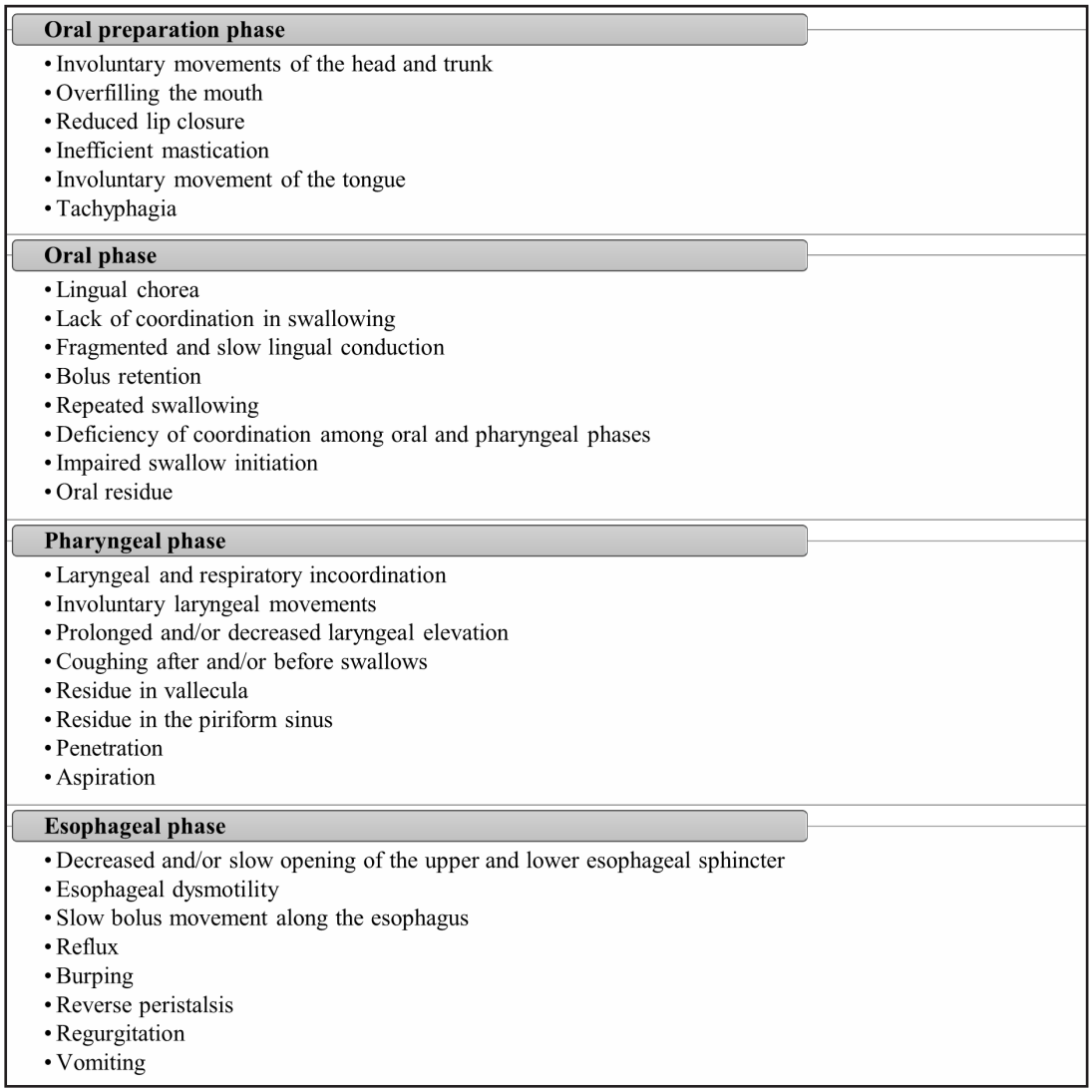


Figure 1. Dysphagia symptoms and findings in individuals with Huntington's disease

Clinical evaluation of swallowing includes medical history, complaints about swallowing and drooling, physical examination (observation, oral motor assessment, respiration, phonation and resonance assessment, feeding assessment, test swallows) [42]. Dysphagia assessment includes a clinical evaluation (including formal and informal assessments). Information collected during the informal (pre-assessment/preliminary) assessment should adhere to the standards recommended by assessment guidelines [19]. A comprehensive preliminary assessment should include case history, medical history, dysphagia symptoms, nutrition/swallowing history, and patient-specific information at the beginning of the clinical evaluation [42]. Medical reports, discussions with healthcare professionals, and verbal information from the individual or caregiver can be utilized to obtain a thorough medical history [42]. The formal assessment aims to identify the presence of dysphagia symptoms, such as mealtime

performance and accompanying environmental factors, during the clinical evaluation [9]. Patient-reported scales that provide preliminary information for advanced assessments can be employed as screening tools to assess the risk of dysphagia [31]. Widely used scales include the Eating Assessment Tool (EAT-10) and Swallowing Related Quality of Life (SWAL-QOL) [43-45]. Self-assessment tools specifically designed for individuals with HD, such as the Huntington Disease Dysphagia Scale (HDDS) and Huntington Disease Health-Related Quality of Life (HDQLIFE), can also be utilized [16,46]. A 90 mL water swallow test and bedside swallowing assessment, including clinician observation, can provide preliminary information for more advanced assessments [31,47]. Additionally, observing feeding in the home environment can be beneficial for assessing the impact of environmental factors [19]. When clinical evaluation symptoms in the digestive/upper respiratory tract, an appropriate medical referral should be made. In the final stage of clinical assessment, should use the gathered information to decide on further assessment procedures and determine the safety of food trials [19].

Fiberoptic Endoscopic Evaluation of Swallowing (FEES) and Videofluoroscopic Swallowing Study (VFSS) / Modified Barium Swallow Study (MBSS) are the most used instrumental methods for diagnosing dysphagia in individuals with HD [26,27,29]. However, these diagnostic approaches may be contraindicated if the individual cannot collaborate or participate due to involuntary movements or cognitive issues [19]. FEES may be more challenging to use in individuals with HD because it does not visualize the oral phase, and choreic movements may complicate evaluation [19]. However, various scales and procedures can be employed and integrated for specific purposes. In some studies where FEES is used for dysphagia in individuals with HD, it has been combined with the Penetration Aspiration Scale (PAS), Dysphagia Outcome and Severity Scale (DOSS), or Yale Pharyngeal Residue Severity Rating Scale [24,26,31,48-50]. Oral intake can be recorded based on the Functional Oral Intake Scale (FOIS) [51]. In a study using VFSS for dysphagia in individuals with HD, the Penetration Aspiration Scale and Bethlehem Assessment Scale (BAS) were used [29]. Additionally, high-resolution pharyngeal impedance manometry (HRIM) and surface electromyograph (sEMG) can be used [32,52]. The advantage of pharyngeal HRIM is that it allows the objective evaluation of swallowing biomechanics, contributing to understanding the pathogenesis of dysphagia and developing a treatment plan. Surface electromyography (sEMG) can be used to measure the activity of the submental muscles during swallowing and as a biofeedback tool. Methods and scales that can be used in swallowing assessments in individuals with HD are provided in Figure 2.

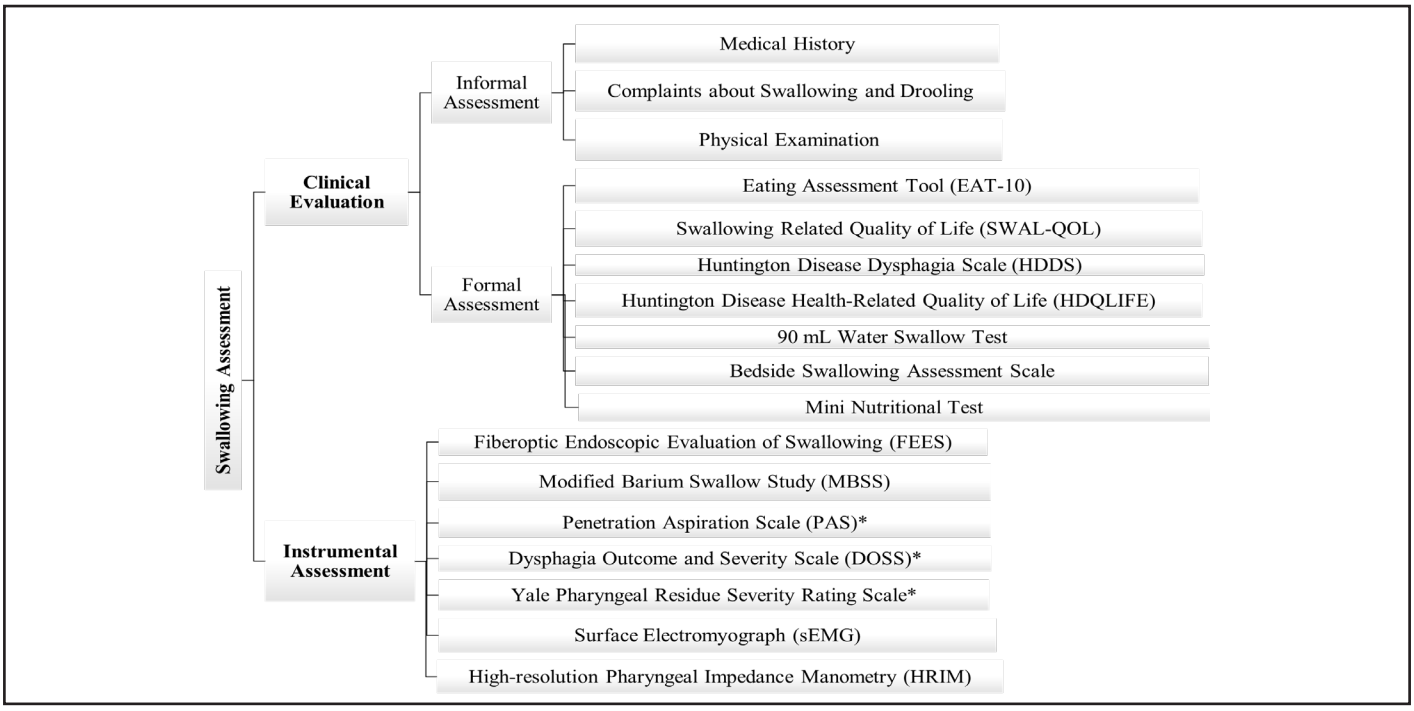


Figure 2. Swallowing assessment in individuals with Huntington's disease.
*Scales that are used during the instrumental assessment.

Collaborative analysis of the information obtained from swallowing assessments with medical professionals can enhance the effectiveness of diagnosis, appropriate food selection, postural modification, and maneuver or exercise options. Gaining insights into the impact of dysphagia on eating and drinking activities and participation, as well as the burden it places on caregivers, will provide a foundation for a holistic, sensitive, and collaborative intervention. Certainly, the assessment process should involve a multidisciplinary team comprising a neurologist, SLT, and other relevant professionals. Each opinion and perspective are crucial for planning the therapy phase.

Intervention of Huntington's Disease Related Dysphagia

Behavioral, medical interventions and a combination of both can be employed in the management of dysphagia among individuals with HD. SLTs play a pivotal role, particularly in addressing oral and pharyngeal dysphagia. Their responsibilities encompass tailoring treatment plans for swallowing disorders based on individual performance, delivering treatment, and establishing criteria for concluding interventions. Furthermore, their coordination with other healthcare professionals facilitates the selection of the most effective intervention method for the individual [42].

In the context of managing dysphagia in individuals with HD the primary objective is to alleviate symptoms rather than tackling the underlying cause [27]. As the disease advances, considerations for cognitive levels and behaviors become increasingly vital. Consequently, the treatment plan should be adjusted according to the individual's cognitive level. Behavioral treatment for dysphagia falls into two categories: compensatory or rehabilitative (restitutive) intervention [42]. Compensatory intervention involves a range of strategies such as postural adjustments, proper equipment utilization, oral hygiene practices, considerations for meal quantity and frequency, bolus size and placement, maneuvers, feeding rate, nutritional modifications, and caregiver support. It is crucial to customize and apply these strategies with a specific focus on individuals with HD [19,27]. Creating a conducive feeding environment also contributes to improving swallowing function and safety [31]. Exercises and maneuvers aimed at enhancing swallowing function are integral components of rehabilitative treatment [42]. Exercises that enhance airway closure could be helpful [52-54]. A randomized controlled pilot study, for instance, examined the impact of a 4-month respiratory muscle strength training on 18 participants with HD, revealing benefits for pulmonary function in individuals with HD but no effect on swallowing function [53].

Speech-language therapists can offer recommendations and implement compensatory and rehabilitative interventions for both individuals and caregivers early on [19]. These recommendations may encompass raising awareness about swallowing, reducing concerns related to swallowing and eating, providing guidance on postural adjustments, alerting about hazardous foods and textures, minimizing distractions during mealtime, and establishing a comfortable environment [19]. Recommendations pertaining to diet modifications are incorporated in addition to early-stage interventions. Importantly, safe swallowing advice and information should be communicated effectively, considering both oral and written formats for individuals and caregivers of individuals with HD. Furthermore, SLTs are crucial in providing suggestions to modify the viscosity, textures, and temperatures of food and liquids for enhanced swallowing safety [19].

Active collaboration of SLTs in the multidisciplinary decision-making process regarding non-oral nutrition (e.g., nasogastric tube [NG], percutaneous endoscopic gastrostomy [PEG]) is important. However, this decision-making process should be initiated with due consideration of the cognitive abilities of the individual, involving individuals with HD and their caregivers. Until advanced stages, oral feeding is generally feasible in HD. Even in advanced stages, efforts can be made to continue diet modifications, compensatory, and rehabilitative swallowing maneuvers as much as possible. Additionally, maintaining oral hygiene and ensuring that caregivers possess knowledge about safe nutrition for individuals are emphasized [19,39].

Medical interventions encompass pharmacological treatments and non-oral nutrition alternatives. Pharmacological treatments (e.g., antipsychotics, valbenazine, and tetrabenazine) can be advantageous in managing motor and behavioral symptoms in HD. However, their usage should be approached cautiously in individuals with mid to late-stage dysphagia [31]. Especially for individuals facing challenges with swallowing pills and capsules, alternative administration methods may be explored. Data from controlled laboratory studies suggest that the crushed content of valbenazine capsules can be incorporated into soft foods or liquids, including acidic ones, or administered through a G-tube. This holds promise for patients struggling with capsule

ingestion, and further evaluation in a clinical setting is warranted [55]. Generally, in scenarios where oral intake becomes problematic, and airway protection is uncertain, nutritional options like NG or PEG are discussed with the collaboration of other team members. Dysphagia intervention recommendations for individuals with HD are given in Figure 3 [19,27,39,52-54].

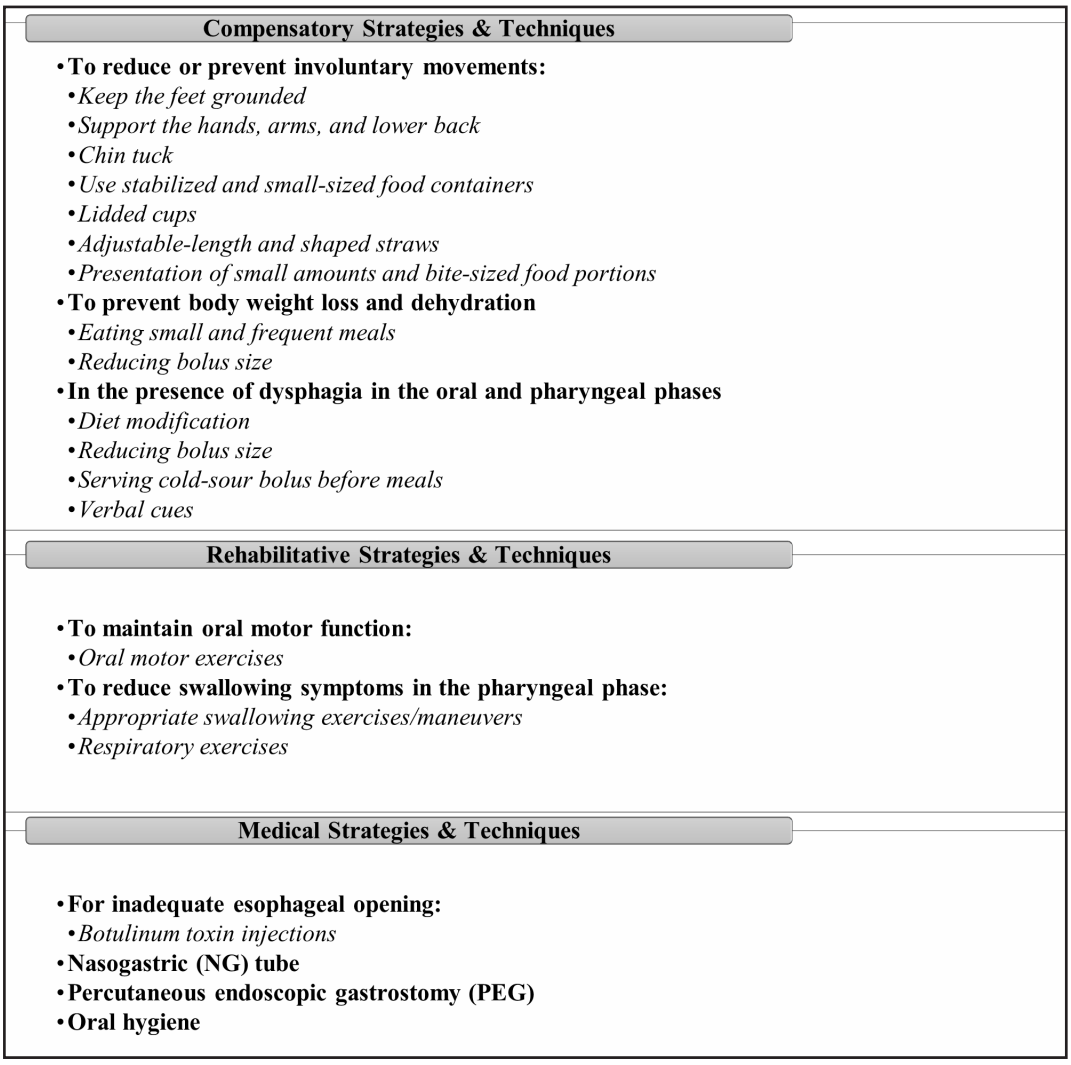


Figure 3. Recommendations for dysphagia intervention in Huntington's Disease

CONCLUSION

A referral and a teamwork are crucial for a thorough assessment of swallowing upon the neurologist's confirmation of HD diagnosis, regardless of the presence of symptoms, while clinical evaluations and patient-reported scales are preferred for comprehensive swallowing assessments, they cannot replace instrumental evaluations. Given the neurodegenerative nature of the disease, MBSS should be utilized early in the progression of HD to assess and monitor the individual's advancement. Even in the early stages, proactive swallowing maneuvers and exercises can be beneficial, with modifications adjusted over time based on the individual's condition and preferences. The inclusive involvement of caregivers in the dysphagia management process at every stage can provide valuable support. Collaborating with experts from various disciplines is essential when making decisions about dysphagia management, especially in situations where oral intake is not possible. Considering the limited nature of existing literature summaries on dysphagia interventions in interventions in individuals with HD, further evidence-based research on this subject is necessary.

Conflict of interest: No conflict of interest was experienced.

Funding: No financial support was received for this study.

Author Contributions: Conception: M, S, A; Ö, O - Design:

M, S, A; Ö, O - Supervision: Ö, O; G, G- Literature: M, S, A; Ö, O - Review: M, S, A; Ö, O; G, G - Writing: M, S, A; Ö, O; G, G - Critical Review: G, G.

REFERENCES

[1] Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ, Tabrizi SJ (2015) Huntington disease. Nat Rev Dis Primers. 23(1):15005. https://doi.org/10.1038/nrdp.2015.5

[2] Freed DB (2020) Motor speech disorders: diagnosis and treatment. Plural Publishing.

[3] A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes (1993) The Huntington's Disease Collaborative Research Group. Cell, 72(6):971–983. https://doi.org/10.1016/0092-8674(93)90585-e

[4] Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, Scahill RI, Leavitt BR, Stout JC, Paulsen JS, Reilmann R, Unschuld PG, Wexler A, Margolis RL, Tabrizi SJ. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol. 2014 Apr;10(4):204-16. https://doi.org/10.1038/nrneurol.2014.24

[5] Squitieri F, Griguoli A, Capelli G, Porcellini A, D'Alessio B. Epidemiology of Huntington disease: first post-HTT gene analysis of prevalence in Italy. Clin Genet. 2016 Mar;89(3):367-70. https://doi.org/10.1111/cge.12574

[6] Evans SJ, Douglas I, Rawlins MD, Wexler NS, Tabrizi SJ, Smeeth L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. J Neurol Neurosurg Psychiatry. 2013 Oct;84(10):1156-60. https://doi.org/10.1136/jnnp-2012-304636

[7] Medina A, Mahjoub Y, Shaver L, Pringsheim T (2022) Prevalence and Incidence of Huntington's Disease: An Updated Systematic Review and Meta-Analysis. Mov Disord. 37(12):2327–2335. https://doi.org/10.1002/mds.29228

[8] Roos RA (2010) Huntington's disease: a clinical review. Orphanet J Rare Dis. 5:40. https://doi.org/10.1186/1750-1172-5-40

[9] Murry T, Carrau R, Chan K (2020) Clinical management of swallowing disorders, 5th ed. Plural Publishing.

[10] Nance MA (2017) Genetics of Huntington disease. Handb Clin Neurol. 144: 3–14. https://doi.org/10.1016/B978-0-12-801893-4.00001-8

[11] Bachoud-Lévi AC (2020) On behalf the Multicentric Intracerebral Grafting in Huntington's Disease Group. Human Fetal Cell Therapy in Huntington's Disease: A Randomized, Multicenter, Phase II Trial. Mov Disord. 35(8):1323-1335. https://doi.org/10.1002/mds.28201

[12] Duffy J (2013) Motor Speech Disorders: Substrates, Differential Diagnosis, and Management. 3 ed. St. Louis: Elsevier Mosby.

[13] Walker FO (2007) Huntington's disease. Lancet. 369(9557):218–228. https://doi.org/10.1016/S0140-6736(07)60111-1

[14] Mahant N, McCusker EA, Byth K, Graham S (2003) Huntington Study Group. Huntington's disease: clinical correlates of disability and progression. Neurology. 61(8):1085-92. https://doi.org/10.1212/01.wnl.0000086373.32347.16

[15] Kagel MC, Leopold NA (1992) Dysphagia in Huntington's disease: a 16-year retrospective. Dysphagia. 7(2):106-14. https://doi.org/10.1007/BF02493441

[16] Carlozzi NE, Schilling SG, Lai JS, Perlmutter JS, Nance MA, Waljee JF, Miner JA, Barton SK, Goodnight SM, Dayalu P (2016) HDQLIFE: the development of two new computer adaptive tests for use in Huntington disease, Speech Difficulties, and Swallowing Difficulties. Qual Life Res. 25(10):2417-2427. https://doi.org/10.1007/s11136-016-1273-y

[17] Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A, Ortega P (2002) Social and psychological burden of dysphagia: its impact on diagnosis and treatment. Dysphagia. 17(2):139-46. https://doi.org/10.1007/s00455-001-0113-5

[18] Heemskerk AW, Roos RA (2012) Aspiration pneumonia and death in Huntington's disease. PLoS Curr. 30;4:RRN1293. https://doi.org/10.1371/currents.RRN1293

[19] Hamilton A, Heemskerk AW, Loucas M, Twiston-Davies R, Matheson KY, Simpson SA, Rae D (2012) Oral feeding

in Huntington's disease: a guideline document for speech and language therapists. Neurodegener Dis Manag. 2(1), 45-53.

[20] Parlak MM, Babademez MA, Alicura Tokgöz S, Bizpınar Ö, Saylam G (2022) Evaluation of Swallowing Function according to the Stage of Alzheimer's Disease. Folia Phoniatr Logop. 74(3):186-194. https://doi.org/10.1159/000519263

[21] Kalkers K, Schols JMGA, van Zwet EW, Roos RAC (2022) Dysphagia, Fear of Choking and Preventive Measures in Patients with Huntington's Disease: The Perspectives of Patients and Caregivers in Long-Term Care. J Nutr Health Aging. 26(4):332-338. https://doi.org/10.1007/s12603-022-1743-6

[22] Sapmaz Atalar M, Genç G (2022) Parkinson Hastalığında Yutma Bozukluklarına Yaklaşım. Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi. 9(2), 189-203.

[23] Perry BJ, Nelson J, Wong JB, Kent DM (2021) The cumulative incidence of dysphagia and dysphagia-free survival in persons diagnosed with amyotrophic lateral sclerosis. Muscle Nerve. 64(1):83-86. https://doi.org/10.1002/mus.27244

[24] Schindler A, Pizzorni N, Sassone J, Nanetti L, Castaldo A, Poletti B, Solca F, Pirola F, Lazzari L, Stramba-Badiale M, Rossi A, Silani V, Mariotti C, Ciammola A (2020) Fiberoptic endoscopic evaluation of swallowing in early-to-advanced stage Huntington's disease. Sci Rep. 10(1):15242. https://doi.org/10.1038/s41598-020-72250-w

[25] Rüb U, Seidel K, Heinsen H, Vonsattel JP, den Dunnen WF, Korf HW (2016) Huntington's disease (HD): the neuropathology of a multisystem neurodegenerative disorder of the human brain. Brain Pathol. 26(6):726-740. https://doi.org/10.1111/bpa.12426

[26] Schumann-Werner B, Dogan I, Mirzazade S, Mall B, Overbeck R, Honrath P, Schulz JB, Reetz K, Werner CJ (2021) Clinical predictors and neural correlates for compromised swallowing safety in Huntington disease. Eur J Neurol. 28(9):2855-2862. https://doi.org/10.1111/ene.14953

[27] Stewart C (2012). Dysphagia Symptoms and Treatment in Huntington's Disease: Review. Perspectives on Swallowing and Swallowing Disorders (Dysphagia). 21(4): 126. https://doi.org/10.1044/sasd21.4.126

[28] Rodrigues B, Nóbrega AC, Sampaio M, Argolo N, Melo A (2011) Silent saliva aspiration in Parkinson's disease. Mov Disord. 26(1):138-41. https://doi.org/10.1002/mds.23301

[29] Keage M, Baum S, Pointon L, Lau J, Berndt J, Hopkins J, Maule R, Vogel AP (2020) Imaging and Clinical Data on Swallowing Function of Individuals with Huntington's Disease and Dysphagia. J Huntingtons Dis. 9(2):163-171. https://doi.org/10.3233/JHD-190390

[30] Heemskerk AW, Roos RA (2011) Dysphagia in Huntington's disease: a review. Dysphagia. 26(1):62-6. https://doi.org/10.1007/s00455-010-9302-4

[31] Pizzorni N, Pirola F, Ciammola A, Schindler A (2020) Management of dysphagia in Huntington's disease: a descriptive review. Neurol Sci. 41(6):1405-1417. https://doi.org/10.1007/s10072-020-04265-0

[32] Lee TH, Lee JS, Kim WJ (2012) High resolution impedance manometric findings in dysphagia of Huntington's disease. World J Gastroenterol. 18(14):1695-9. https://doi.org/10.3748/wjg.v18.i14.1695

[33] Hamakawa S, Koda C, Umeno H, Yoshida Y, Nakashima T, Asaoka K, Shoji H (2004) Oropharyngeal dysphagia in a case of Huntington's disease. Auris Nasus Larynx. 31(2):171-6. https://doi.org/10.1016/j.anl.2003.11.001

[34] Trejo A, Tarrats RM, Alonso ME, Boll MC, Ochoa A, Velásquez L (2004) Assessment of the nutrition status of patients with Huntington's disease. Nutrition. 20(2):192-6. https://doi.org/10.1016/j.nut.2003.10.007

[35] Manor Y, Oestreicher-Kedem Y, Gad A, Zitser J, Faust-Socher A, Shpunt D, Naor S, Inbar N, Kestenbaum M, Giladi N, Gurevich T (2019) Dysphagia characteristics in Huntington's disease patients: insights from the Fiberoptic Endoscopic Evaluation of Swallowing and the Swallowing Disturbances Questionnaire. CNS Spectr. 24(4):413-418. https://doi.org/10.1017/S1092852918001037

[36] Andrich JE, Wobben M, Klotz P, Goetze O, Saft C (2009) Upper gastrointestinal findings in Huntington's disease: patients suffer but do not complain. J Neural Transm (Vienna). 116(12):1607-11. https://doi.org/10.1007/s00702-009-0310-1

[37] Ishihara L, Oliveri D, Wild EJ.(2021) Neuropsychiatric comorbidities in Huntington's and Parkinson's Disease: A United States claims database analysis. Ann Clin Transl Neurol. 8(1):126-137. https://doi.org/10.1002/acn3.51252

[38] Paulsen JS (2011) Cognitive impairment in Huntington disease: diagnosis and treatment. Curr Neurol Neurosci Rep. 11:474–483.

[39] Munhoz L, Jabbar AQ, Silva Filho WJE, Nagai AY, Arita ES (2023) The oral manifestations of Huntington's disease: A systematic review of prevalence. Oral Dis. 29(1):62-74. https://doi.org/10.1111/odi.14076

[40] Rada RE (2008) Comprehensive dental treatment of a patient with Huntington's disease: literature review and case report. Spec Care Dentist. 28(4):131-5. https://doi.org/10.1111/j.1754-4505.2008.00027.x

[41] Threats TT (2007) Use of the ICF in dysphagia management. Semin Speech Lang. 28(4):323–333.

[42] Groher ME, Crary MA (2016) Dysphagia: Clinical Management in Adults and Children. 2nd ed. USA: Elsevier Health Sciences.

[43] Belafsky PC, Mouadeb DA, Rees CJ, Pryor JC, Postma GN, Allen J, Leonard RJ (2008) Validity and reliability of the Eating Assessment Tool (EAT-10). Ann Otol Rhinol Laryngol. 117(12):919-24. https://doi.org/10.1177/000348940811701210

[44] Cordier R, Joosten A, Clavé P, Schindler A, Bülow M, Demir N, Arslan SS, Speyer R (2017) Evaluating the Psychometric Properties of the Eating Assessment Tool (EAT-10) Using Rasch Analysis. Dysphagia. 32(2):250-260. https://doi.org/10.1007/s00455-016-9754-2

[45] McHorney CA, Robbins J, Lomax K, et al. (2002) The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. Dysphagia. 17 (2): 97–114.

[46] Heemskerk A, Verbist BM (2014) The Huntington's disease dysphagia scale. Mov Disord 29:1312–1316.

[47] de Tommaso M, Nuzzi A, Dellomonaco AR, Sciruicchio V, Serpino C, Cormio C, Franco G, Megna M (2015) Dysphagia in Huntington's disease: correlation with clinical features. Eur Neurol 74:49–53.

[48] Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL (1996) A penetration-aspiration scale. Dysphagia. 1996 Spring;11(2):93-8. https://doi.org/10.1007/BF00417897

[49] O'Neil KH, Purdy M, Falk J, Gallo L. (1999) The Dysphagia Outcome and Severity Scale. Dysphagia. 14(3):139-45. https://doi.org/10.1007/PL00009595

[50] Neubauer PD, Rademaker AW, Leder SB (2015) The Yale Pharyngeal Residue Severity Rating Scale: An Anatomically Defined and Image-Based Tool. Dysphagia. 30(5):521-8. https://doi.org/10.1007/s00455-015-9631-4

[51] Crary MA, Mann GD, Groher ME (2005) Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil. 86(8):1516-20. https://doi.org/10.1016/j.apmr.2004.11.049

[52] Reyes A, Cruickshank T, Thompson J, Ziman M, Nosaka K (2014) Surface electromyograph activity of submental muscles during swallowing and expiratory muscle training tasks in Huntington's disease patients. J Electromyogr Kinesiol. 24(1):153-8. https://doi.org/10.1016/j.jelekin.2013.09.009

[53] Reyes A, Cruickshank T, Nosaka K, Ziman M (2015) Respiratory muscle training on pulmonary and swallowing function in patients with Huntington's disease: a pilot randomised controlled trial. Clin Rehabil. 29(10):961-73. https://doi.org/10.1177/0269215514564087

[54] Clark J (2021) A practical approach to movement disorders: diagnosis and management. In: Fernandez, H. H., Walter, B. L., Rush, T., & Ahmed, A. (eds.), Springer Publishing Company.

[55] Sajatovic M, Patel A, Hebert M, Mar A, Moore R, Bristow A, Farahmand K, Siegert S (2023) Crushing the Contents of Valbenazine Capsules for Potential Addition to Soft Foods or Administration via Gastrostomy Tube. Clin Ther. 45(12):1222-1227. https://doi.org/10.1016/j.clinthera.2023.09.024

How to Cite;

Sapmaz Atalar M, Oğuz Ö, Genç G (2024). Dysphagia in Indivuduals with Huntington's Disease: A Narrative Review. 30(2):217-226. Eur J Ther. https://doi.org/10.58600/eurjther1914

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):227-239.
https://doi.org/10.58600/eurjther1978

Review Article

Current Pharmacological Treatment for Sleep Disorders in Children and Adolescents with Autism Spectrum Disorder

Hatice Altun [1], Semiha Cömertoğlu Arslan [1]

[1] Department of Child and Adolescent Psychiatry, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Türkiye

Received: 2023-12-23 **Accepted**: 2024-02-11 **Published Online**: 2024-02-12

Corresponding Author
Hatice Altun, MD
Address: Department of Child and Adolescent Psychiatry, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Türkiye
E-mail: drhaticealtun@gmail.com

ABSTRACT

Sleep disorders are very common in children and adolescents with Autism Spectrum Disorder (ASD) and can negatively impact their lives, mental health, developmental processes, families' lives, and emotional well-being. It is essential to determine the specific sleep disorder and its underlying cause in treatment planning. Currently, nonpharmacological and pharmacological interventions are the main treatments for improving sleep disorders in children and adolescents with ASD. If nonpharmacological strategies are unsuccessful or difficult to implement, medications should be considered and used in conjunction with them. Melatonin, behavioral interventions, and parent education are the most effective treatments to improve sleep, relative to other pharmacological treatments. Medications used to treat sleep disorders in these children are used off-label. Melatonin appearing to be safe and effective may be an evidence-based and efficacious first-line treatment for treating insomnia symptoms in children and adolescents with ASD. Antipsychotics (e.g.low dose quetiapine), antidepressants with strong sedative effects such as trazodone and mirtazapine, antihistamines (e.g.diphenhydramine, niaprazine), alpha-adrenergic drugs (e.g. clonidine), benzodiazepines (e.g.clonazepam) and other hypnotic drugs, anticonvulsants (e.g. gabapentin), Alzheimer's drugs (e..g donepezil), superoxide and iron treatment are other drugs used in pharmacological treatment. Depending on the type of sleep disorders and the presence of comorbidities, the most effective pharmacological treatment should be selected on a case-by-case basis.

Keywords: Autism Spectrum Disorder, Sleep, Sleep Initiation and Maintenance Disorders, Pharmacological Treatment, Melatonin

INTRODUCTION

Autism spectrum disorders (ASD) are neurodevelopmental disorders that cause difficulties with social interactions, communication, and stereotyped behavior patterns. ASD affects approximately one in 36 children [1]. It is common for individuals with ASD to have comorbid psychiatric disorders, including sleep disorders. Sleep is vital for a child's overall growth and well-being. It plays a vital role in regulating many biological functions in children such as metabolism, mood regulation, learning, and memory [2, 3]. Sleep disorders are very common in ASD. According to a recent review, children with ASD have a higher likelihood of experiencing sleep-related disorders, with a prevalence ranging from 50% to 80%, in contrast to 9% to 50% among typical children [4]. Insomnia is the most frequently

reported sleep problem. Sleep disorders such as parasomnias, sleep-disordered breathing, movement disorders during sleep, and excessive sleepiness during the day are also observed in children and adolescents with ASD [4, 5].

Studies show that children with ASD undergo more bedtime resistance, sleep onset delay, and difficulties maintaining sleep. They often wake up frequently at night and have irregular sleep patterns, a shorter sleep duration, and early morning awakening. Besides they suffer from sleep anxiety, excessive sleepiness during the day, parasomnias, and sleep-disordered breathing [5-10]. Sleep problems in children with ASD seem to be related to age. Younger children experience more difficulty going to bed, higher levels of bedtime resistance, bedtime anxiety, night wakings, and parasomnias. However, older children are more prone to sleeplessness [11].
Sleep problems in ASD children are commonly linked to conditions such as anxiety, attention problems, impulsivity, oppositional behavior, sensory sensitivities, digestive problems, and medication use [4, 12].

Sleep problems in children with ASD tend to last longer and endure when compared to typical children. Typical children's sleep problems typically fade with age [13]. As well as being prevalent and persistent, sleep issues have a significant impact on various aspects of children's and family's lives. Poor sleep has been shown to negatively affect ASD symptoms and their daytime functioning. Sleep problems can lead to difficulties in social communication, increased stereotypical behavior, more dysfunctional routines, lower cognitive and academic performance, lower learning capacities and memory, poorer quality of life, higher stress and mood disorders for family members. Insufficient sleep has also been associated with increased social, emotional/behavioral problems, such as tantrums, defiance, aggression, irritability, self-harm, low mood, anxiety, fluctuations in mood, attentional deficits, and hyperactivity. For this reason, it is very important to recognize and treat sleep problems in children with ASD [2, 7, 14-17].

Main Points:

- Sleep disorders, one of the most common comorbid disorders in children and adolescents with ASD, negatively affect the lives of both children and families in many ways.
- Melatonin appearing to be safe and effective may be an evidence-based and efficacious first-line treatment for insomnia in children and adolescents with ASD.
- Antipsychotics, antidepressants, antihistamines, alpha-adrenergic drugs, benzodiazepine and other hypnotic drugs, anticonvulsants, Alzheimer's drugs, superoxide and iron treatment are other drugs used in pharmacological treatment.
- Depending on the type of sleep disorders and the presence of comorbidities, the most effective pharmacological treatment should be selected on a case-by-case basis.

The causes of sleep problems in ASD have not yet been definitively established. Sleep disorder has been linked to biological factors, irregularities in circadian genes, abnormalities in the melatonin system, psychological, social and environmental factors, sensory hyperarousal, comorbid medical conditions, and medications [2, 4, 5, 17].

Clinical Assessment and Management of Sleep Disorders in ASD

The first clinical assessment of sleep problems is vital and frequently disregarded. Before using any medicines or other treatments for sleep problems, it is crucial to recognize and treat the underlying medical conditions causing them. To diagnose sleep disorders properly in ASD, Rana et al. 2021 advise following these steps: (1) taking a detailed history of sleep patterns, sleep times, wake-up times, and sleep schedules; (2) identifying any behavioral factors, such as struggling to understand affectionate expectancies ascribed to communication difficulties (3) screen for sleep disorders, such as nightmares, sleep apnea, night terrors, restless leg syndrome, sleep-related movements, and sleepwalking; (4) diagnosing psychiatric disorders that occur at the same time, like discomfort or notice attention deficiency hyperactivity disorder (ADHD); (5) diagnosing medical conditions that occur at the same time, such as seizures, nocturia, gastrointestinal reflux disease, eczema, night cough, and pain [5].

Currently, most treatments for improving sleep problems in children with ASD involve behavioral or pharmacological interventions. The National Institute for Health and Care Excellence (NICE) recommends that a behavioral sleep plan be developed in conjunction with parents or carers for individuals with ASD under 19 years old who have sleep problems. [18]. The evaluation should also consider any comorbidities, medication use, and environmental or psychological factors (like nearby

injury or bullying) that could be causing the sleep problem. It is suggested that drug treatments are only attempted if behavioral interventions have failed or if the impact on the child or their family is long-lasting. Similarly, in the recently published practice guideline of the American Academy of Neurology for sleep disturbance in children and adolescents with ASD, pharmacological treatments are recommended only when non-pharmacological treatments do not work and all relevant factors have been addressed [19].

Non-pharmacological treatments, which are the mainstay of treatment of sleep disorders, include establishing sleep routines, sleep training, and direct behavioral intervention. These methods are safer and can be just as efficient as drugs, mainly for mild or ordinary cases [4, 19].

Malow and colleagues [20] analyzed 1,518 children aged 4-10 and found that 46% of those diagnosed with a sleep disorder were prescribed sleep medications. To this day, the Food and Drug Administration (FDA) has not approved any medication for treating insomnia in children with ASD.

There are important conditions to keep in mind before starting a new medication in the treatment of sleep disorders in children with ASD [5, 20, 21]. (see Table 1).

Table 1. Important conditions to keep in mind before starting a new medication in the treatment of sleep disorders in children with ASD

- Prescription and non-prescription medications that the child may take should be reviewed.
- The child's age and clinical history, along with any associated medical conditions, should be evaluated in detail.
- The right choice of sleep-enhancing drugs should be made. Since there is insufficient scientific evidence for sleep-enhancing medications, the choice should be made based on the main sleep complaint and associated symptoms. Treatment approaches vary depending on the sleep problem.
- Sleep drugs should be started at the lowest effective dose, increased when necessary, and the side effects of the medications should be taken into account.
- To reduce the risk of rebound insomnia, drugs should be closely monitored and slowly reduced. Sudden discontinuation of sleeping medications should be avoided.
- Treatment goals should be determined together with parents and should be realistic and measurable. Potential side effects such as daytime sedation and tolerance should be discussed.
- It is important to screen adolescents for alcohol and drug use due to the additive impacts of sedative-hypnotic and entertaining drugs.
- Correct timing is vital when managing sleep disorders, as most hypnotic drugs take effect within half an hour and reach their highest point within one or two hours. Therefore, administering medication too soon or too late will result in reduced effectiveness

The Pharmacological Treatment of Insomnia and Disrupted Sleep Behavior

Melatonin is frequently used in the pharmacological treatment of sleep disorders in children with ASD. However, if behavioral and melatonin treatments are insufficient, other psychotropic drugs may be prescribed off-label. This includes drugs like antipsychotics, antidepressants with strong sedative effects such as trazodone and mirtazapine, antihistamines, alpha-adrenergic drugs like clonidine, benzodiazepines, and other hypnotic drugs, anticonvulsants such as gabapentin, Alzheimer's drugs like donepezil, superoxide and iron treatment [2, 4, 10, 20, 21]. Currently, there is not enough research on these medications and their clinical effectiveness and safety profile in treating sleep problems. However, surveys examining the effectiveness of psychotropic medication prescribed for various reasons on the sleep of individuals with ASD throughout their lifetime have been informative.

1. Melatonin

Melatonin is the most common pharmacological medication prescribed for insomnia and circadian rhythm sleep-wake disorders in ASD [10, 22]. Melatonin is a hormone synthesized principally in the pineal gland, has an important function in the regulation of circadian rhythm and core body temperature rhythms, and is regulated by the suprachiasmatic nucleus of the hypothalamus [23]. It is thought that melatonin may help relieve anxiety and improve overall health [24]. Several studies have been carried out on patients with ASD, demonstrating the effectiveness of melatonin. These studies encompassed open-label data, randomized controlled trials, uncontrolled trials, control trials, retrospective studies, and meta-analyses. The overall consensus is that melatonin decreases sleep onset latency (SoL), proceeds the sleep phase, and increases total sleep time (TST) while reducing night wakings [10, 20, 22, 25-27]. However, the reduction in night wakings has been reported to occur with sustained/prolonged-release melatonin formulations

rather than immediate-release melatonin [28]. A recent review reported that prolonged-release melatonin formulation treatment effectively improved both sleep onset, duration, and consolidation, and externalizing behaviors during the day in children and adolescents with ASD, as well as caregivers' quality of life and gratification with their children's sleep [22].

In a study of 125 children with ASD aged 2-17.5 years who had sleep problems for more than three months and did not benefit from behavioral intervention for four weeks, it was found that TST increased by 57.5 minutes and SoL decreased by 39.6 minutes after taking melatonin mini tablets at a dose of 2 to 5 mg for 13 weeks [26]. In a meta-analysis of 35 researchers, the findings show that melatonin increases TST by 73 minutes and reduces SoL by 66 minutes from the standard level. Unfortunately, the melatonin did not present any significant improvement in night wakings [29]. Open-label study determined the effectiveness of melatonin in 24 (aged 3 to 10 years) children using doses up to 9 mg. The research showed that reduced SoL (on average 21.3 minutes less, from 42.9 to 21.6 minutes), but there was no significant change in the TST, sleep quality, or night wakings after receiving therapy for 14 weeks. The study also displayed better behavior and less stereotypical and compulsive behavior [30]. A significant retrospective study investigating the use of melatonin with a dosage range of 3-6 mg in 107 participants aged 2-18 years demonstrated the absence of sleep concerns for around 25% of parents after 1.8 years of follow-up, based on objective evaluation [31]. In contrast, a different phase III trial, which was randomized and placebo-controlled, was carried out to evaluate a variety of immediate-release melatonin doses (0.5-12 mg) for the treatment of severe sleep problems in children with neurodevelopmental disorders. This study revealed that administering melatonin resulted in limited extra sleep (increase of 23 minutes in TST, decrease of 38 minutes in SoL, earlier waking times) and also did not improve behavioral outcomes and night wakings [32].

Generally, the application of melatonin is fairly well-tolerated and the side effects are rare and mild. Most published research studies have not disclosed any significant safety concerns. Commonly reported adverse effects of melatonin include headache, dizziness, hypothermia, increased enuresis, and morning drowsiness. A few children reported experiencing nightmares [17, 22, 25, 26, 29, 30]. In a recent study comprising 80 children and adolescents who were administered melatonin for 104 weeks, it was concluded that melatonin is safe with minor side effects such as fatigue (6.3%), daytime sleepiness (6.3%), and mood swings (4.2%) [28]. Long-term use of melatonin has been found to have no negative effects on height, body mass index, or pubertal development, as shown by the lack of evidence of delay or withdrawal effects [22]. Although there are concerns that long-term use of melatonin may cause a delay in pubertal development in children, the results are inconsistent and there are not enough studies on this subject according to some findings obtained from a small number of animal studies [33]. However, it is important to consider metabolic phenotypes and potential drug interactions that may increase the risk of side effects in individuals with ASD. Melatonin is metabolized via the hepatic microsomal P450 pathway. Drug interactions of melatonin are mostly with inhibitors and enhancers of CYP1A2, this condition is resulting in the increase or the decrease in melatonin bioavailability. There is a theoretical concern that antiepileptic drugs that act as enzyme inducers, such as phenobarbital, phenytoin, and carbamazepine, may accelerate the elimination of melatonin [34].

Melatonin is available in immediate, sustained, and prolonged-release oral tablets, intranasal spray, liquid, transdermal, and sublingual formulations that range from 1-10 milligrams. After oral administration, melatonin is absorbed rapidly, and peak plasma levels are observed after 40-60 minutes, which persists for up to 1.5 hours (depending on dosage) before declining [35]. It is presumed that the immediate release formulations are more helpful for sleep-onset insomnia and controlled-release forms for sleep maintenance, due to immediate-release melatonin has a short half-life (40 minutes) [19]. The generally recommended dose for administration 30-60 minutes before bedtime is 1-3 mg [19, 29]. The expert opinion of the European Society of Pediatric Neurology is that it can be administered at doses of 1-5 mg approximately 30 minutes before bedtime as sleep inductor, and it can be started at doses of 0.2-0.5 mg 3-4 hours before bedtime as kronobiyotic in delayed sleep phase syndrome. (It can be increased by 0.2-0.5 mg every week as needed until the effect is seen (maximum 3 mg; adolescents: 5 mg)) [36]. However, dose adjustments of up to 10 mg/day are possible for sleep disorders in ASD and age or weight is not related to an effective dose [19, 22].

As it is classified as a dietary supplement, the safety of melatonin has not been subject to thorough evaluation by the FDA. Although the use of melatonin is generally considered safe, there is a shortage of rigorous data supporting its use. In addition, recommendations concerning the usage of melatonin in children

and adolescents are inconsistent. The availability of various brands, combined with the lack of strict regulations imposed by the FDA on over-the-counter medications, raises concerns about the actual content of melatonin in different formulations. While melatonin has been demonstrated to be effective in treating ASD in children according to numerous studies, these studies are not without limitations. These limitations comprise small study sizes, comorbid neurodevelopmental disabilities confounding factors, imprecision in sleep aspects differentiation, varied drug dosages administered, lack of long-term monitoring data, and absence of a placebo group [5].

Melatonin receptor agonists, such as agomelatine and ramelteon, selectively act on MT1 and MT2 melatonin receptors and are utilized for treating sleep problems in children with ASD. Administering agomelatine (25 mg/day) for three months has resulted in a significant increase in TST and has improved the sleep phase and stability of sleep in ASD children [37]. Ramelteon (dose: 2-8 mg/day), a melatonin agonist administered to treat three ASD children, has been discovered to alleviate sleep problems, particularly insomnia, and lead to concurrent enhancements in behavior [38]. Ramelteon is the exclusive drug in this category that has received endorsement from the FDA for insomnia treatment in adults. Adverse effects primarily comprise dizziness and fatigue, and it is recommended to exercise caution when co-administering with Fluvoxamine.

Finally, pharmacological treatments for sleep disorders in children with ASD have revealed robust evidence supporting the effectiveness of melatonin supplementation, including the melatonin receptor agonist ramelteon. Nevertheless, there has been limited evidence for the use of other pharmacological treatments. Melatonin treatment for children with ASD has been discovered to be more effective and safer than sedatives and hypnotic medications [5].

2. Antipsychotics

Antipsychotic medication is commonly prescribed to address mood and behavioral comorbidities, such as aggression, irritability, and self-injurious behaviors found in individuals with ASD. These medications have a secondary benefit for sleep, although there is limited data on their efficacy and tolerability for treating insomnia in children. A study has demonstrated the efficacy of atypical antipsychotic drugs, specifically risperidone, in reducing SoL but not sleep duration. Nevertheless, considering the side effects and associated health risks related to risperidone treatment, it should not be prescribed for insomnia alone [39]. A six-month open-label extension study was conducted on 56 children and adolescents with ASD (ages 5 to 17), which revealed that those on higher doses of risperidone reported significant improvements in their sleep quality based on a sleep visual analog scale [40]. Children with ASD benefit from low-dose quetiapine to manage sleep disturbances and behavioral problems including aggression and irritability. During an 8-week open-label study involving 18 patients aged between 13-17 years old, quetiapine effectively alleviated their aggression and sleep problems [41]. Risperidone, quetiapine, and olanzapine are among the atypicals prescribed to treat sleep disorders in children [42]. However, it should be noted that while these drugs are often prescribed off-label to treat insomnia, they are not generally recommended as the first-line pharmacotherapeutic agent for this indication.

3. Antidepressants

There is limited data on the use and effectiveness of sedative antidepressants, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs) for sleep disorders in children with ASD. These medications have the potential to help with sleep problems, especially those associated with concomitant psychiatric conditions. Sedative antidepressants, mirtazapine, and trazodone may be advantageous for a child with concurrent symptoms of depression. SSRIs and TCAs may be prescribed in patients whose sleep onset is significantly impaired by obsessive thoughts and anxiety. These antidepressants promote sleep by counteracting wake-promoting neurotransmitters, like serotonin, noradrenaline, histamine, and acetylcholine. The majority of these antidepressants can cause suppression of REM sleep and daytime sedation [42]. An open-label trial investigated the effectiveness and tolerability of mirtazapine (at a dosage range of 7.5-45 mg/day) in adults with ASD suffering from related symptoms. Out of the 26 participants, nine individuals (34.6%) were deemed as responders (‘much improved’ or ‘very much improved’ on the Clinical Global Impression-Improvement Scale) following the alleviation of various symptoms, such as aggression, self-harm, depression, anxiety, hyperactivity, irritability, and insomnia [43]. Trazodone is a frequently utilized medication in psychiatric practice. While it is commonly prescribed for insomnia, only a small number of case reports have demonstrated its efficacy [44]. Its effectiveness has primarily been established in adults with psychiatric illness. Trazodone acts as a 5-HT2A/C antagonist and is among the most sedative antidepressants, which is accompanied by a notable morning hangover effect. Although there is currently no concrete evidence to support the use of

trazodone in children with ASD, it is prescribed to children and adolescents who struggle with sleep disorders [5, 42]. The TCAs, amitriptyline, imipramine, and doxepin are frequently prescribed for their sedative effects and are often used to treat insomnia in adults. [45]. No evidence supports the use of amitriptyline or trimipramine in children with ASD. Nevertheless, amitriptyline has been administered to children with neurodevelopmental impairments in doses ranging from 5 to 50 mg [5].

4. Antihistamines

Antihistamines are the primary non-prescription medicine for childhood sleep disorders. However, they carry a risk of adverse effects ranging from sedation to severe anticholinergic symptoms, which include blurred vision, constipation, urinary retention, dry mouth, tachycardia, fever, and confusion [10, 21]. Diphenhydramine, a first-generation antihistamine, is frequently used by practitioners to treat sleep problems (dosing range: 0.5 mg/kg up to a maximum of 25 mg per day). It functions as a histamine (H1) receptor antagonist in the peripheral and central nervous system resulting in a sedative and hypnotic effect [46]. In addition, Trimeprazine, another H1 receptor antagonist (dosing range: 45–90 mg per day), has been demonstrated to improve night wakings in children with chronic sleep disorders [47]. However, an open-label study has found niaprazine (an H1-receptor antagonist and piperazine derivative) to be effective in ameliorating sleep problems in children who had ASD and mild/moderate intellectual disability (dosage: 1 mg/kg/day, three times daily) [48]. Although antihistamines are widely used for patients with ASD, limited clinical trials have investigated their efficacy.

5. Alpha-2-adrenergic agonists

In cases of ASD, off-label use of the two main alpha agonists, Clonidine and Guanfacine, has increased despite the lack of any randomized controlled trial evidence of their effectiveness, particularly in anxiety and sleep disorders. In a case series of six cases with neurodevelopmental disorders, the findings showed that clonidine (dose range: 0.05-0.225 mg/day) effectively improves sleep onset and sleep maintenance in severe and unmanageable sleep problems. Hypotension, bradycardia, dry mouth, irritability, and REM suppression are potential side effects of clonidine and may lead to rebound hypertension and rebound REM if abruptly discontinued [49]. An open retrospective study investigated the efficacy of clonidine for treating insomnia, aggressive behaviors, hyperactivity, inattention, mood disorder, and in a cohort of 19 children with ASD. Oral clonidine was administered at 50 µg with a gradual increase up to 100 µg, 30 minutes before bedtime. Results showed that clonidine significantly reduced SoL and night waking, while its effectiveness in improving ADHD, mood instability, and aggression in this population has been limited. The adverse effects were generally tolerable [50].

Despite the frequent off-label use of immediate-release guanfacine (dosage range: 0.5–2 mg/day) to treat sleep problems in the young population, its efficacy has not been scientifically established [51]. A recent randomized placebo-controlled trial of extended-release guanfacine reported that it failed to significantly improve sleep patterns in individuals with ASD [52]. There is a shortage of placebo-controlled double-blind clinical trials that can offer a greater understanding of the clinical effectiveness and safety of these medications in ASD.

6. Benzodiazepines and non-benzodiazepine sedative-hypnotics

Benzodiazepines exhibit inhibitory actions through GABA receptors, leading to sedative, anxiolytic, and muscle-relaxing effects [53]. Although benzodiazepines are often prescribed for insomnia in adult patients, they are not frequently prescribed for the pediatric population due to their adverse effects such as headaches, cognitive impairment, dizziness, sedation, rebound insomnia, physical and behavioral dependence. Studies in children are limited, but they have shown the potential for benzodiazepines to improve sleep disorders [21].

Clonazepam is the only benzodiazepine that has been studied for sleep disorders in ASD. Clonazepam, an intermediate-acting benzodiazepine, demonstrated efficacy in managing parasomnias, periodic limb movement disorder (PLMD), nocturnal biting, and partial arousals in children with developmental disabilities. In a case series involving 11 children with ASD, 0.5-1 mg of clonazepam successfully resolved sleep-related REM behavioral disorder in 75% of the participants. The intervention has been generally well-tolerated among the participants. However, one child exhibited a paradoxical response, experiencing increased activity and agitation [54]. A study examining the use of clonazepam in children who had developmental disabilities revealed its efficacy in reducing nightmares and abnormal motor behavior during sleep [55]. However, limitations of clonazepam usage include concerns over its tolerability profile, potential for drug dependence, and lack of evidence-based data in the pediatric population.

The sedative-hypnotics, zaleplon, zolpidem, and eszopiclone, collectively referred to as the ‘Z-drugs’, have a pharmacology

similar to that of benzodiazepines but are not chemically related to them. They act by binding to the benzodiazepine-1 subtype within the GABA receptor complex and have a relatively short half-life. Unlike benzodiazepines, these drugs do not cause persistent sedation, cognitive or memory impairments throughout the day [56]. Additionally, these medications usually do not result in rebound insomnia (an increase in insomnia when a sleep aid is abruptly stopped), a negative consequence of benzodiazepines. Although zaleplon and zolpidem are used in children, information about eszopiclone is not extensive. There have been few studies on children, and there are no clinical trials available on the use of this type of medication for ASD. Clearance of non-benzodiazepine receptor agonist medications is three times higher in children than adults, resulting in drug inefficiency and potentially inducing frightening sleep states such as sleepwalking and sleep-related hallucinations [42]. Due to their low efficacy and high incidence of adverse reactions, these drugs have limited practical application and should only be considered for use in this population when all other options have been exhausted. However, they may be taken into consideration for patients who are in late adolescence or early adulthood.

7. Anticonvulsants

Concerning the treatment of insomnia in children, there is limited data on the effectiveness of anticonvulsants. Most studies have focused on examining aggression and irritability, and have reported improvements in these areas. Adverse events observed in these studies have ranged from insomnia to sedation. Sedation is typically dose-dependent, and tolerance is known to develop [42]. Gabapentin (3-7.5 mg/kg, maximum of 15 mg/kg) administered 30 to 45 minutes before bedtime has resulted in enhanced sleep among 18 out of 23 (78%) children. However, adverse effects, such as agitated night wakings and feeling peculiar, have been reported. Gabapentin is not commonly used as a first-line agent [57]. Nevertheless, it may have potential benefits for children. It could be advantageous for children and adolescents with ASD who have comorbid symptoms of restless leg syndrome (RLS), excessive PLMD, or nighttime seizures [5].

8. Alzheimer's medications

Donepezil is used to treat Alzheimer's disease, acting as a reversible acetylcholinesterase inhibitor and enhancing cholinergic transmission. A nonblinded study in a limited number of children with ASD demonstrated the effectiveness of donepezil in increasing REM sleep, improving related behavioral and attention problems, and reducing REM sleep onset latency [58]. However, the trial is impeded by its small sample size. Possible side effects of donepezil usage include hypotension, vivid dreams, insomnia, bradycardia, and gastrointestinal symptoms (nausea, vomiting, and diarrhea) [42]. There are no sufficient studies on the use of donepezil in sleep problems in children with ASD.

9. Suvorexant

Suvorexant is a dual orexin receptor agonist that binds selectively to orexin-1 and -2 receptors, leading to the inactivation of wakefulness. The tolerability, efficacy, and safety of suvorexant (20 mg/kg) in treating insomnia among 30 adolescents approximately 6 months after commencing treatment was assessed by Kawabe and colleagues. Of these patients, seven had ASD. Out of the thirty patients, seventeen (56.7%) have continued to take suvorexant, leading to a noteworthy decrease on the Clinical Global Impression-Severity Scale as well as an improvement in their overall sleep quality. The lack of a control group and the small sample size are important limitations of the study. Nevertheless, it indicates that suvorexant could be a viable treatment option for adolescents grappling with insomnia and conceivably ASD [59]. In a recent study of 3 children (2 with ASD) and 1 adult patient with neurodevelopmental disorders, has been reported one patient showed a strong improvement in sleep onset and maintenance, and another showed a significant improvement in insomnia symptoms in combination therapy with trazodone, and two patients have shown a slight benefit or no benefit from suvorexant treatment [60].

10. Oral Iron Supplement

Iron is a cofactor for tyrosine hydroxylase, the enzyme responsible for converting the amino acid tyrosine into dopamine. It is common for children with ASD to have low serum ferritin levels. In a treatment study of 33 children with ASD and RLS, iron supplementation (6 mg/kg/day, elemental iron) for 8 weeks reported a significant improvement in sleep quality. The baseline mean ferritin level was 15.72 mcg/L (4.2-39.0 mcg/L). The mean ferritin level after treatment was 28.8 mcg/L (6.6-103 mcg/L), indicating a correlation between iron deficiency and sleep disorder in children with ASD. This study is limited by a small sample size and a lack of controls. Oral iron supplementation has adverse effects such as vomiting, nausea, diarrhea, constipation, metallic taste, and black/green stools [61]. In a retrospective analysis of medical records from 9,791 children with ASD, the study has found significantly low levels of serum ferritin linked to various sleep disorders, such as PLMD (27 ng/mL), disrupted

sleep (24 ng/mL), and substandard sleep efficiency (7 ng/mL) [62]. Serum ferritin, which is an iron storage protein (level <50 ng/mL), was also linked with RLS. Iron therapy is recommended for ferritin levels below 50 ng/mL. Iron supplementation has been proven to be an effective treatment for low ferritin levels in individuals with sleep disorders [63].

The Pharmacological Treatment for Sleep-Disordered Breathing

In the treatment of sleep-disordered breathing, medical devices, and surgical interventions are primarily used. Adenotonsillectomy is typically the preferred first-line surgical treatment for pediatric obstructive sleep apnea (OSA). Some children may need continuous positive airway pressure (CPAP) or further surgical procedures following an adenotonsillectomy, particularly those who are obese or have underlying medical conditions like craniofacial anomalies. Focusing on reducing weight and utilizing positional therapy can also help alleviate obstructive sleep apnea in children [64]. Pharmacological treatment of OSA, particularly for mild OSA, may involve nasal corticosteroids, leukotriene antagonists, or a combination of both [64-66]. However, the primary course of treatment for OSA ought not to include medication, particularly for children with ASD due to limited evidence on the effectiveness of these treatments, which have been exclusively tested on typical children. Pharmacological treatment strategies for OSA in children with ASD require further research.

The Pharmacological Treatment for Sleep-Related Movement Disorders

Restless legs syndrome (RLS) and PLMD, both sleep-related movement disorders, have been linked to low levels of iron. Children with ASD may have idiosyncratic dietary preferences, causing iron deficiencies. Therefore, if ferritin levels are low (less than 50 ng/dl), replenishing iron is recommended, particularly if sleep is disrupted [61]. As well as iron supplements, gabapentin is sometimes used off-label to treat RLS that begins in childhood. A recent study has found that gabapentin is generally well-tolerated with no serious side effects and improves sleep quality or resolves insomnia in children with RLS [67]. Dopamine agonists are also medications used to treat RLS in older teens and adults [66]. The safety and efficacy of anticonvulsants and dopamine agonists have not been trialed in children with ASD.

The Pharmacological Treatment for Parasomnias

Parasomnias are unwanted events that occur during sleep, including sleepwalking, night terrors, confusional arousals, nightmares, REM sleep behavior disorder, and bruxism. When treating parasomnias, it is crucial to identify the primary diagnosis. Benzodiazepines and TCAs such as imipramine are generally used in the pharmacological treatment of parasomnias [66]. Clonazepam is a benzodiazepine that significantly suppresses third and fourth-stage NREM sleep. If sleep terrors (parasomnia) are frequent and severe or cause functional impairment such as fatigue, daytime sleepiness, and distress, clonazepam may be used briefly at bedtime. It is recommended to use clonazepam in the early hours of the night when sleep terrors predominate, at least 90 minutes before the child goes to sleep, for an effective drug level [68]. In a case series of children with ASD, it was reported that clonazepam could also be used in the REM sleep behavior disorder [54].

Limitations

In this review, many studies evaluating different medical treatments and differing methodologically in the treatment of sleep disorders in children with ASD have been examined. However, when these studies are evaluated in general; reasons such as small sample size, limited number of studies on specific sleep disorders, limited number of randomized placebo-controlled studies on medical treatments other than melatonin, differences in drug doses and methodological differences between treatment methods have made it difficult to establish a standard treatment protocol, in these population. Additionally, complementary and alternative treatments used by families were not evaluated in this review.

CONCLUSIONS

In summary, sleep disorders are very common in children and adolescents with ASD. Although sleep drugs are frequently prescribed, evidence regarding the use and effectiveness of drugs in these children is limited. No medications are approved by the FDA for sleep disorders in children who have ASD. Melatonin has shown good effectiveness in many studies. However, the long-term effects of melatonin still need to be studied extensively. Depending on the type of sleep disorders and the presence of comorbidities, the most effective pharmacological treatment should be selected on a case-by-case basis. Future randomized controlled trials are needed to elucidate the effectiveness of pharmacological drugs that can be used in young children and to examine possible side effects and drug-drug interactions for this population group.

Funding: This manuscript was not funded.

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

Acknowledgements: No acknowledgements.

Author Contribution: The authors confirm contribution to the paper as follows: study Conception and Design: HA, SCA; Supervision. HA, SCA; Analysis and interpretation of results: HA, SCA; Literature review: HA, SCA; Writing: HA, SCA; Critical review: HA, SCA. All authors reviewed the results and approved the final version of the manuscript.

REFERENCES

[1] Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, Durkin MS, Fitzgerald RT, Furnier SM, Hughes MM (2023) Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2020. MMWR Surveil Summ. 72(2): 1–14. https://doi.org/10.15585/mmwr.ss7202a1

[2] Karthikeyan R, Cardinali DP, Shakunthala V, Spence DW, Brown GM, Pandi-Perumal SR (2020) Understanding the role of sleep and ıts disturbances in autism spectrum disorder. Int J Neurosci. 130 (10): 1033-1046. https://doi.org/10.1080/00207454.2019.1711377

[3] Dahl RE (2007) Sleep and the developing brain. Sleep. 30(9):1079-1080. https://doi.org/10.1093/sleep/30.9.1079

[4] Burman D, Ramanujam K, Manzar D, Chattu VK, Spence DW, Zaki NF, Jahrami H, Pandi-Perumal SR (2023) Sleep and autism spectrum disorder: a comprehensive review of diagnosis, markers, ınterventions, and treatments. Sleep Vigil. 7: 9-22. https://doi.org/10.1007/s41782-022-00222-3

[5] Rana M, Kothare S, DeBassio W (2021) The assessment and treatment of sleep abnormalities in children and adolescents with autism spectrum disorder: a review. J Can Acad Child Adolesc Psychiatry. 30(1):25-35.

[6] Chen H, Yang T, Chen J, Chen L, Dai Y, Zhang J, Li L, Jia F, Wu L, Hao Y (2021) Sleep problems in children with autism spectrum disorder: a multicenter survey. BMC psychiatry. 21 (1):406. https://doi.org/10.1186/s12888-021-03405-w

[7] Mazurek MO, Sohl K (2016) Sleep and behavioral problems in children with autism spectrum disorder. J Autism Dev Disord. 46 (6): 1906-1915. https://doi.org/10.1007/s10803-016-2723-7

[8] Wiggs L, Stores G (2004) Sleep patterns and sleep disorders in children with autistic spectrum disorders: insights using parent report and actigraphy. Dev Med Child Neurol. 46: 372-380. https://doi.org/10.1017/s0012162204000611

[9] Inthikoot N, Chonchaiya W (2021) Sleep problems in children with autism spectrum disorder and typical development. Pediatr Int. 63: 649-657. https://doi.org/10.1111/ped.14496

[10] Cortese S, Wang F, Angriman M, Masi G, Bruni O (2020) Sleep disorders in children and adolescents with autism spectrum disorder: diagnosis, epidemiology, and management. CNS drugs. 34: 415-423. https://doi.org/10.1007/s40263-020-00710-y

[11] Goldman SE, Richdale AL, Clemons T, Malow BA (2012) Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. J Autism Dev Disord.42: 531-538. https://doi.org/10.1007/s10803-011-1270-5

[12] Hollway JA, Aman MG, Butter E (2013) Correlates and risk markers for sleep disturbance in participants of the autism treatment network. J Autism Dev Disord. 43: 2830-2843. https://doi.org/10.1007/s10803-013-1830-y

[13] Hodge D, Carollo TM, Lewin M, Hoffman CD, Sweeney DP (2014) Sleep patterns in children with and without autism spectrum disorders: developmental comparisons. Res Dev Disabil. 35: 1631-1638 https://doi.org/10.1016/j.ridd.2014.03.037

[14] Taylor MA, Schreck KA, Mulick JA (2012) Sleep disruption as a correlate to cognitive and adaptive behavior problems in autism spectrum disorders. Res Dev Disabil. 33: 1408-1417. https://doi.org/10.1016/j.ridd.2012.03.013

[15] Martin CA, Papadopoulos N, Chellew T, Rinehart NJ, Sciberras E (2019) Associations between parenting stress, parent mental health and child sleep problems for children with ADHD and ASD: Systematic review. Res Dev Disabil. 93: 103463. https://doi.org/10.1016/j.ridd.2019.103463

[16] Sikora DM, Johnson K, Clemons T, Katz T (2012) The relationship between sleep problems and daytime behavior in children of different ages with autism spectrum disorders. Pediatrics. 130: 83-90. https://doi.org/10.1542/peds.2012-0900f

[17] Seo WS (2021) An update on the cause and treatment of sleep disturbance in children and adolescents with autism spectrum disorder. Yeungnam Univ J Med. 38: 275-281. https://doi.org/10.12701/yujm.2021.01410

[18] Recommendations. Autism spectrum disorder in under 19s: support and management | Guidance | NICE. https://www.nice.org.uk/guidance/cg170/chapter/1-Recommendations. Last updated: 14 June 2021 Accessed

[19] Buckley AW, Hirtz D, Oskoui M, Armstrong MJ, Batra A, Bridgemohan C, Coury D, Dawson G, Donley D, Findling RL (2020) Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 94: 392-404. https://doi.org/10.1212/wnl.0000000000009033

[20] Malow BA, Katz T, Reynolds AM, Shui A, Carno M, Connolly HV, Coury D, Bennett AE (2016) Sleep difficulties and medications in children with autism spectrum disorders: a registry study. Pediatrics. 137: 98-104. https://doi.org/10.1542/peds.2015-2851h

[21] Bruni O, Angriman M, Calisti F, Comandini A, Esposito G, Cortese S, Ferri R (2018) Practitioner review: treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. J Child Psychol Psychiatry. 59: 489-508. https://doi.org/10.1111/jcpp.12812

[22] Schroder CM, Banaschewski T, Fuentes J, Hill CM, Hvolby A, Posserud M-B, Bruni O (2021) Pediatric prolonged-release melatonin for insomnia in children and adolescents with autism spectrum disorders. Expert Opin Pharmacother. 22: 2445-2454. https://doi.org/10.1080/14656566.2021.1959549

[23] Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP (2007) Role of the melatonin system in the control of sleep: therapeutic implications. CNS drugs. 21: 995-1018. https://doi.org/10.2165/00023210-200721120-00004

[24] Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F, Warner DS (2010) Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. Anesthesiology. 113: 968-976. https://doi.org/10.1097/aln.0b013e3181e7d626

[25] Hayashi M, Mishima K, Fukumizu M, Takahashi H, Ishikawa Y, Hamada I, Sugioka H, Yotsuya O, Yamashita Y (2022) Melatonin treatment and adequate sleep hygiene interventions in children with autism spectrum disorder: a randomized controlled trial. J Autism Dev Disord. 52(6):2784-2793. https://doi.org/10.1007/s10803-021-05139-w

[26] Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL (2017) Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 56(11):948-957.e4. https://doi.org/10.1016/j.jaac.2017.09.414

[27] Xiong M, Li F, Liu Z, Xie X, Shen H, Li W, Wei L, He R (2023) Efficacy of Melatonin for Insomnia in Children with Autism Spectrum Disorder: A Meta-analysis. Neuropediatrics. 54: 167-173. https://doi.org/10.1055/s-0043-1761437

[28] Maras A, Schroder CM, Malow BA, Findling RL, Breddy J, Nir T, Shahmoon S, Zisapel N, Gringras P (2018) Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder J Child Adolesc Psychopharmacol. 28: 699-710. https://doi.org/10.1089/cap.2018.0020

[29] Rossignol DA, Frye RE (2011) Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 53(9):783-792. https://doi.org/10.1111/j.1469-8749.2011.03980.x

[30] Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, Burnette C (2012) Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. J Autism Dev Disord. 42: 1729-1737. https://doi.org/10.1007/s10803-011-1418-3

[31] Andersen IM, Kaczmarska J, McGrew SG, Malow BA (2008) Melatonin for insomnia in children with autism spectrum disorders. J Child Neurol. 23(5):482-485. https://doi.org/10.1177/0883073807309783

[32] Gringras P, Gamble C, Jones A, Wiggs L, Williamson P, Sutcliffe A, Montgomery P, Whitehouse W, Choonara I, Allport T (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. BMJ. 5:345:e6664. https://doi.org/10.1136/bmj.e6664

[33] Boafo A, Greenham S, Alenezi S, Robillard R, Pajer K, Tavakoli P, De Koninck J (2019) Could long-term administration of melatonin to prepubertal children affect timing of puberty? A clinician's perspective. Nat Sci Sleep. 31(11):1-10. https://doi.org/10.2147/nss.s181365

[34] Zisapel N (2022) Assessing the potential for drug interactions and long term safety of melatonin for the treatment of insomnia in children with autism spectrum disorder. Expert Review of Clinical Pharmacology Expert Rev Clin Pharmacol. 15 (2): 175-185. https://doi.org/10.1080/17512433.2022.2053520

[35] Waldhauser F, Waldhauser M, Lieberman HR, Deng M-H, Lynch HJ, Wurtman RJ (1984) Bioavailability of oral melatonin in humans. Neuroendocrinology. 39 (4): 307-313. https://doi.org/10.1159/000123997

[36] Bruni O, Alonso-Alconada D, Besag F, Biran V, Braam W, Cortese S, Moavero R, Parisi P, Smits M, Van der Heijden K (2015) Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol. 19 (2): 122-133. https://doi.org/10.1016/j.ejpn.2014.12.007

[37] Ballester P, Martínez MJ, Inda M-d-M, Javaloyes A, Richdale AL, Muriel J, Belda C, Toral N, Morales D, Fernández E (2019) Evaluation of agomelatine for the treatment of sleep problems in adults with autism spectrum disorder and co-morbid intellectual disability. J Psychopharmacol. 33(11): 1395-1406. https://doi.org/10.1177/0269881119864968

[38] Kawabe K, Horiuchi F, Oka Y, Ueno S-i (2014) The melatonin receptor agonist ramelteon effectively treats insomnia and behavioral symptoms in autistic disorder. Case Rep Psychiatry. 2014:561071. https://doi.org/10.1155/2014/561071

[39] Aman MG, Arnold M, L Eugene, McDougle CJ, Vitiello B, Scahill L, Davies M, McCracken JT, Tierney E, Nash PL, Posey DJ (2005) Acute and long-term safety and tolerability of risperidone in children with autism J Child Adolesc Psychopharmacol. 15 (6):869-884. https://doi.org/10.1089/cap.2005.15.869

[40] Kent JM, Hough D, Singh J, Karcher K, Pandina G (2013) An open-label extension study of the safety and efficacy of risperidone in children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol. 23 (10): 676-686. https://doi.org/10.1089/cap.2012.0058

[41] Golubchik P, Sever J, Weizman A (2011) Low-dose quetiapine for adolescents with autistic spectrum disorder and aggressive behavior: open-label trial. Clin Neuropharmacol. 34 (6): 216-219. https://doi.org/10.1097/wnf.0b013e31823349ac

[42] Relia S, Ekambaram V (2018) Pharmacological approach to sleep disturbances in autism spectrum disorders with psychiatric comorbidities: a literature review. Med Sci (Basel). 6 (4): 95. https://doi.org/10.3390/medsci6040095

[43] Posey DJ, Guenin KD, Kohn AE, Swiezy NB, McDougle CJ (2001) A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. J Child Adolesc Psychopharmacol. 11(6): 267-277. https://doi.org/10.1089/10445460152595586

[44] Parker RA, Hartman EE (2002) An 8-year-old boy with autism, 1 year later. JAMA. 287 (4): 504. https://doi.org/10.1001/jama.287.4.504

[45] Wichniak A, Wierzbicka A, Jernajczyk W (2012) Sleep and antidepressant treatment. Curr Pharm Des. 18 (36): 5802-5817. https://doi.org/10.2174/138161212803523608

[46] Russo RM, Gururaj VJ, Allen JE (1976) The effectiveness of diphenhydramine HCI in pediatric sleep disorders. J Clin Pharmacol. 16 (5-6): 284-288. https://doi.org/10.1002/j.1552-4604.1976.tb02406.x

[47] France KG, Blampied NM, Wilkinson P (1999) A multiple-baseline, double-blind evaluation of the effects of trimeprazine tartrate on infant sleep disturbance Exp Clin Psychopharmacol. 7(4):502-513. https://doi.org/10.1037/1064-1297.7.4.502

[48] Rossi PG, Posar A, Parmeggiani A (1999) Niaprazine in the treatment of autistic disorder. J Child Neurol. 14 (8): 547-550. https://doi.org/10.1177/088307389901400814

[49] Ingrassia A, Turk J (2005) The use of clonidine for severe and intractable sleep problems in children with

neurodevelopmental disorders: a case series. Eur Child Adolesc Psychiatry. 14 (1): 34-40. https://doi.org/10.1007/s00787-005-0424-4

[50] Ming X, Gordon E, Kang N, Wagner GC (2008) Use of clonidine in children with autism spectrum disorders. Brain Dev. 30 (7): 454-460. https://doi.org/10.1016/j.braindev.2007.12.007

[51] Fiks AG, Mayne SL, Song L, Steffes J, Liu W, McCarn B, Margolis B, Grimes A, Gotlieb E, Localio R (2015) Changing patterns of alpha agonist medication use in children and adolescents 2009–2011. J Child Adolesc Psychopharmacol. 25 (4): 362-367. https://doi.org/10.1089/cap.2014.0122

[52] Politte LC, Scahill L, Figueroa J, McCracken JT, King B, McDougle CJ (2018) A randomized, placebo-controlled trial of extended-release guanfacine in children with autism spectrum disorder and ADHD symptoms: an analysis of secondary outcome measures. Neuropsychopharmacology. 43 (8): 1772-1778. https://doi.org/10.1038/s41386-018-0039-3

[53] Griffin CE, Kaye AM, Bueno FR, Kaye AD (2013) Benzodiazepine pharmacology and central nervous system–mediated effects. Ochsner J. 13 (2): 214-223.

[54] Thirumalai SS, Shubin RA, Robinson R (2002) Rapid eye movement sleep behavior disorder in children with autism. J Child Neurol. 17 (3): 173-178. https://doi.org/10.1177/088307380201700304

[55] Lloyd R, Tippmann-Peikert M, Slocumb N, Kotagal S (2012) Characteristics of REM sleep behavior disorder in childhood. J Clin Sleep Med. 8 (2): 127-131. https://doi.org/10.5664/jcsm.1760

[56] Olson L (2008) Hypnotic hazards: adverse effects of zolpidem and other z-drugs. Aust Prescr. 31:146–9. https://doi.org/10.18773/austprescr.2008.084

[57] Robinson AA, Malow BA (2013) Gabapentin shows promise in treating refractory insomnia in children. J Child Neurol. 28 (2): 1618-1621. https://doi.org/10.1177/0883073812463069

[58] Buckley AW, Sassower K, Rodriguez AJ, Jennison K, Wingert K, Buckley J, Thurm A, Sato S, Swedo S (2011) An open label trial of donepezil for enhancement of rapid eye movement sleep in young children with autism spectrum disorders. J Child Adolesc Psychopharmacol. 21 (4): 353-357. https://doi.org/10.1089/cap.2010.0121

[59] Kawabe K, Horiuchi F, Ochi M, Nishimoto K, Ueno S-I, Oka Y (2017) Suvorexant for the treatment of insomnia in adolescents. J Child Adolesc Psychopharmacol. 27 (9): 792-795. https://doi.org/10.1089/cap.2016.0206

[60] Besterman AD, Jeste SS (2023) Dual orexin receptor antagonists for insomnia in youth with neurodevelopmental disorders: a case series and review. Eur Child Adolesc Psychiatry. 32(3): 527-531. https://doi.org/10.1007/s00787-021-01883-7

[61] Dosman CF, Brian JA, Drmic IE, Senthilselvan A, Harford MM, Smith RW, Sharieff W, Zlotkin SH, Moldofsky H, Roberts SW (2007) Children with autism: effect of iron supplementation on sleep and ferritin. Pediatr Neurol. 36 (3): 152-158. https://doi.org/10.1016/j.pediatrneurol.2006.11.004

[62] Youssef J, Singh K, Huntington N, Becker R, Kothare SV (2013) Relationship of serum ferritin levels to sleep fragmentation and periodic limb movements of sleep on polysomnography in autism spectrum disorders. Pediatr Neurol. 49: 274-278. https://doi.org/10.1016/j.pediatrneurol.2013.06.012

[63] Trotti L, Bhadriraju S, Becker L (2012) Iron for restless legs syndrome. Cochrane Database Syst Rev. 5(5):CD007834. https://doi.org/10.1002/14651858.cd007834.pub2

[64] Daftary AS, Kotagal S (2010) Treatment of childhood obstructive sleep apnea. Curr Treat Options Neurol. 12 (5): 369-378. https://doi.org/10.1007/s11940-010-0084-7

[65] Kheirandish L, Goldbart AD, Gozal D (2006) Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. Pediatrics. 117: e61-e66. https://doi.org/10.1542/peds.2005-0795

[66] Kotagal S (2012) Treatment of dyssomnias and parasomnias in childhood. Curr Treat Options Neurol. 14 (6): 630-649. https://doi.org/10.1007/s11940-012-0199-0

[67] Kanney ML, Durmer JS, Trotti LM, Leu R (2020) Rethinking bedtime resistance in children with autism: is restless legs syndrome to blame? J Clin Sleep Med. 16 (12): 2029-2035. https://doi.org/10.5664/jcsm.8756

[68] Leung AK, Leung AA, Wong AH, Hon KL (2020) Sleep terrors: an updated review. Curr Pediatr Rev. 16 (3): 176-182. https://doi.org/10.2174/1573396315666191014152136

How to Cite;

Altun H, Cömertoğlu Arslan S (2024) Current Pharmacological Treatment for Sleep Disorders in Children and Adolescents with Autism Spectrum Disorder. 30(2):227-239. Eur J Ther. https://doi.org/10.58600/eurjther1978

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):240-247.
https://doi.org/10.58600/eurjther1979

Case Report

ChatGPT Guided Diagnosis of Ameloblastic Fibro-Odontoma: A Case Report with Eventful Healing

Ömer Uranbey [1], Ferhat Ayrancı [1], Büşra Erşan Erdem [2]

[1] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ordu University, Ordu, Türkiye
[2] Department of Medical Pathology, Faculty of Medicine, Ordu University, Ordu, Türkiye

Received: 2023-12-25 **Accepted**: 2024-01-22 **Published Online**: 2024-01-29

Corresponding Author
Ömer Uranbey DDS, MSc,
Address: Ordu University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery
Cumhuriyet Campus, Mustafa Kemal Boulevard. No: 254, 52200, Altınordu Ordu, Türkiye
E-mail: eomeruranbey@gmail.com

ABSTRACT

Ameloblastic Fibro-Odontoma (AFO) defined by the World Health Organization as a mixed odontogenic tumor. It's rare and representing 1% to 3% of odontogenic tumors. Due to AFO's rarity and poorly understood etiopathology, clinicians and pathologists may face difficulties in its differential diagnosis. This case report explores the diagnosis and treatment of this uncommon maxillofacial condition in a juvenile patient, also showcasing ChatGPT's potential to assist clinicians by providing diagnosis and recommendations. In parallel to the treatment processes, an external researcher described the case and simulated possible diagnostic and treatment scenarios using ChatGPT 3.5. Although the diagnosis and recommendations obtained are not taken into account in the evaluation of the case, the aim is to draw attention to these tools, which depict a scenario similar to clinical reality. The use of Artificial Intelligence in healthcare, including ChatGPT, is still evolving, and more research is needed to understand its full potential in analyzing clinical information, providing diagnoses, and recommending treatments.

Keywords: Ameloblastic Fibro-Odontoma, Odontogenic Neoplasm, ChatGPT

INTRODUCTION

The use of artificial intelligence (AI) in medicine has shown promising results in improving diagnostic accuracy and streamlining the decision-making process [1]. One of them, Chat Generative Pre-Trained Transformer (ChatGPT), released to the public on November 30, 2022, is the largest artificial intelligence language model and a prototype developed by OpenAI, specializing in dialogue [2]. ChatGPT uses machine learning on extensive human-generated data to generate text responses [3]. The main advantages are that it reduces human error, provides assistance and guidance to doctors and other healthcare professionals, and is always accessible for patient services [4]. This tool holds the potential to function as a valuable aid and guide for clinicians, particularly in rare conditions [1].

Ameloblastic Fibro-Odontoma (AFO) is a uncommon benign odontogenic tumor, sharing similar histologic features with Ameloblastic Fibroma (AF) [5]. Histologically, it also includes enamel and dentin components [5]. AFO's typically occur in the posterior regions of the mandible and maxilla and usually present as painless, slow-growing swellings accompanied by tooth eruption failure [6]. Its higher prevalence is particularly observed in the pediatric population [6]. AFO exhibits less aggressive behavior than AF although numerous case reports have documented locally aggressive involvement of AFO [7-9]. Treatment varies from only the removal of the tumor to the

removal of the tumor, curettage, and extraction of the associated teeth [8]. Most recurrences reported in the literature are the result of inadequate removal, therefore surgical planning is critical [8].

In this case report, we investigated a scenario where the direct assessment from diagnosis to treatment was considered complicated and evaluated the suggestions of artificial intelligence during these stages. This exemplified the utility of ChatGPT in detailing the diagnosis, treatment, and follow-up process of a rare tumoral case. At this point, an external researcher described the scenario of our case and asked ChatGPT 3.5 for appropriate prompts and possible diagnoses. The appropriate prompts were selected based on the study of Khurana and Vaddi [10]. The diagnoses and recommendations obtained were not taken into consideration in the evaluation of the case. However, it is intended to draw attention to these tools, which are quite relevant to clinical reality.

CASE REPORT

An 8-year-old girl with no history of systemic disease presented to our clinic with pain and swelling in the region of the right lower premolar. Clinical examination revealed a lesion in the premolar region of the right mandible, extending from tooth number 42 to tooth number 85, characterized by a painful, mild swelling of the vestibular mucosa and erythematous appearance of the adherent gingiva in the relevant region. Radiological examination revealed the presence of a radiopaque and radiolucent mixed lesion in the premolar region, localized into the bone, causing displacement of the erupting permanent teeth. A 3D cone beam tomography examination revealed that the lesion was bicompartmentalized, separated from the surrounding tissue by a soft tissue capsule and contained tooth-like hard tissues (Figure 1). Histologic examination of the lesion by excisional biopsy was planned. Written consent has been obtained from the family. After receiving parental consent, the hard tissue lesion measuring approximately 1.5 x 2.5 cm (horizontal x vertical) was surgically excised under general anesthesia with the aid of local anesthesia, by osteotomy and odontoectomy with surgical motor and burs. Tooth number 42, which was located into the lesion without any bone support, and tooth number 43, which was displaced excessively towards the base of the mandible by the lesion and had no chance of eruption, were extracted. The mental nerve, which emerged from the foramen, was identified, and its continuity was preserved. Care was taken to avoid any damage to teeth 44 and 41, which were in close anatomical proximity to the lesion. After the lesion enucleation was completed, the cavity was curetted and the retentive areas were removed (Figs. 2,3). Bleeding was controlled and the area was closed primary tension-free. Standard medication was prescribed to control postoperative infections after the surgery with antibiotics (Augmentin BID; 625 mg, 2x1, GS, London, UK), analgesics for pain control (Parol; 500 mg, 2x1, Atabay, Türkiye), and an antibacterial mouthwash (Oroheks Plus %0.15, 3x1, Tripharma, Istanbul, Türkiye). At the end of the first postoperative week, unsatisfactory healing of the erythematous and edematous vestibular gingiva was observed in the wound area. The patient was instructed on proper oral hygiene procedures with wound site care and was scheduled for a follow-up visit the subsequent week. During the follow-up visit, it was observed that local infection findings such as edema and erythema increased in the vestibular flap and that it was traumatized by the contralateral occlusion (Figure 4). Due to the presence of purulent fluid in the cavity, tooth 83 was extracted and the cavity drained through the socket. Antibiotic therapy using a combination of Augmentin-BID 625 mg (2x1, GSK, London, UK) and Flagyl 250 mg tablets (2x1, Sanofi, Paris, France) was initiated. Irrigation of the socket was maintained every three days using saline and povidone iodine. The subsequent week showed a resolution of the local infection and the appearance of normal tissues in the wound area (Figure 5). AFO diagnosed according to pathology report (Figure 6). The wound area has healed as intended, and the patient is currently being monitored for the potential recurrence of lesions and correct eruption of the teeth. Orthodontic consultation was also obtained to rehabilitate the patient's further occlusion.

Main Points:

- Ameloblastic Fibro-Odontoma (AFO) is a rare odontogenic tumor representing 1% to 3% of odontogenic tumors.
- The diagnosis and treatment of AFO in a pediatric patient illustrates the unique challenges and considerations dentists may face in rare tumor cases.
- At the same time, it aims to highlight the clinical utility of ChatGPT as a tool for diagnostic assistance and guidance in rare pathological conditions, underscoring the potential of AI to assist dentists in decision-making.
- The integration of AI in dentistry increases diagnostic accuracy and improves clinicopathologic correlation, representing a significant advancement in the field

Simultaneously with the procedures, another researcher used ChatGPT 3.5 to make the queries. The medical history and clinical findings of the patient were used to generate a case scenario; then, a diagnosis and treatment recommendations were made on October 25, 2023 (Figure 7). The diagnostic and treatment procedures were monitored by an external observer and compared to the promised scenario and treatment management of ChatGPT.

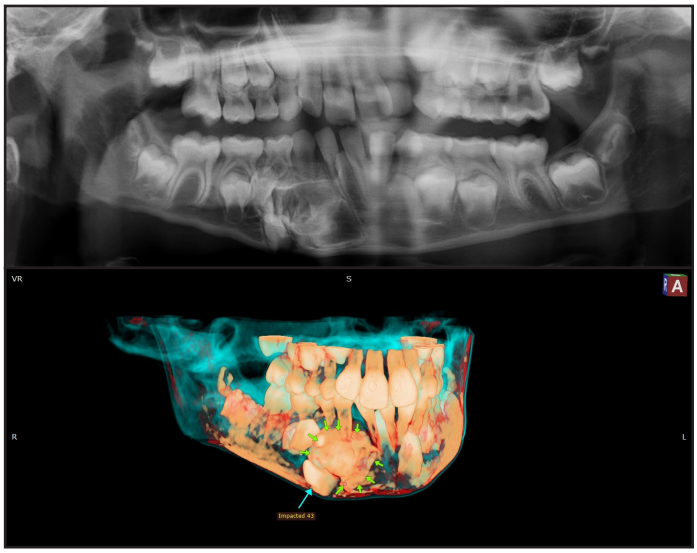


Figure 1. a. Preoperative view on panoramic radiography, **b**: 3D reconstruction of the lesion (Green arrows)

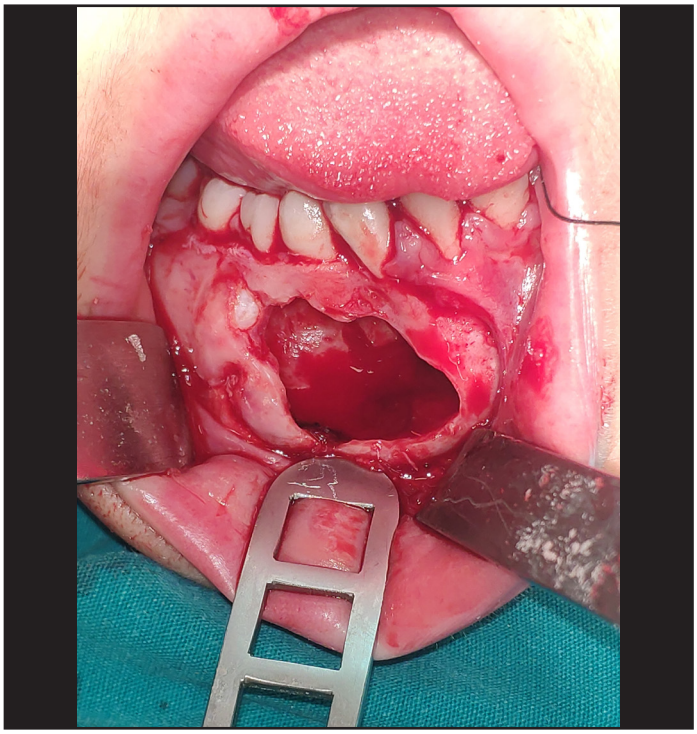


Figure 2. Viewing the cavity after the lesion is enucleated

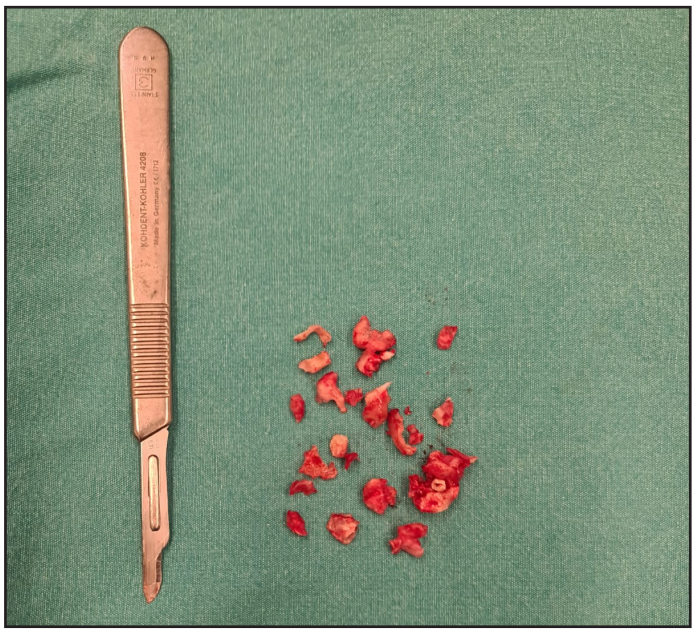


Figure 3. Fragmented hard tissue specimens

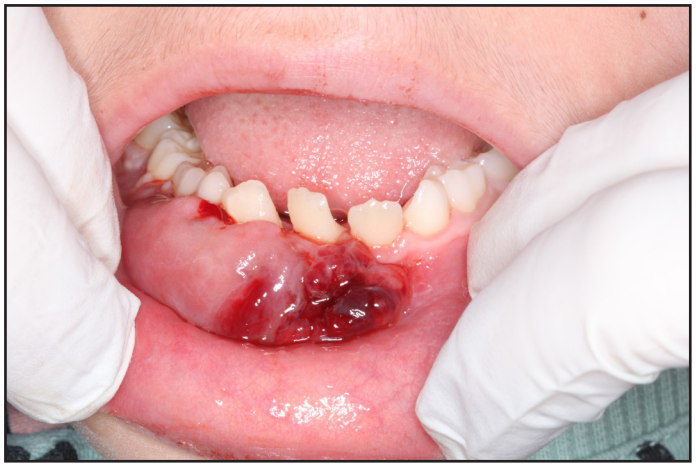


Figure 4. Secondary infection at the site of the wound

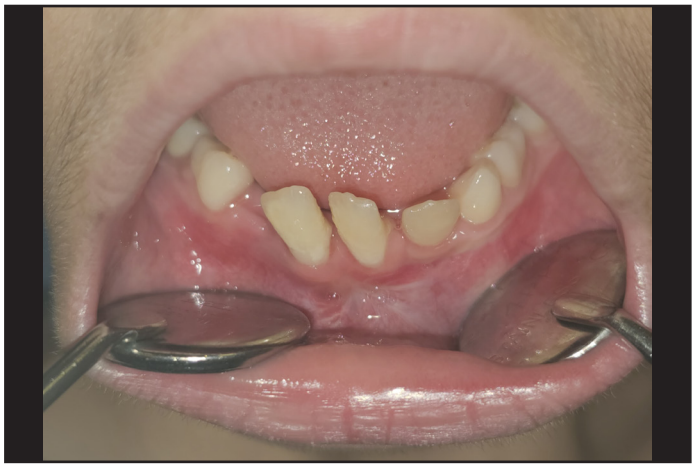


Figure 5. Ensuring complete recovery after the resolution of local infection findings.

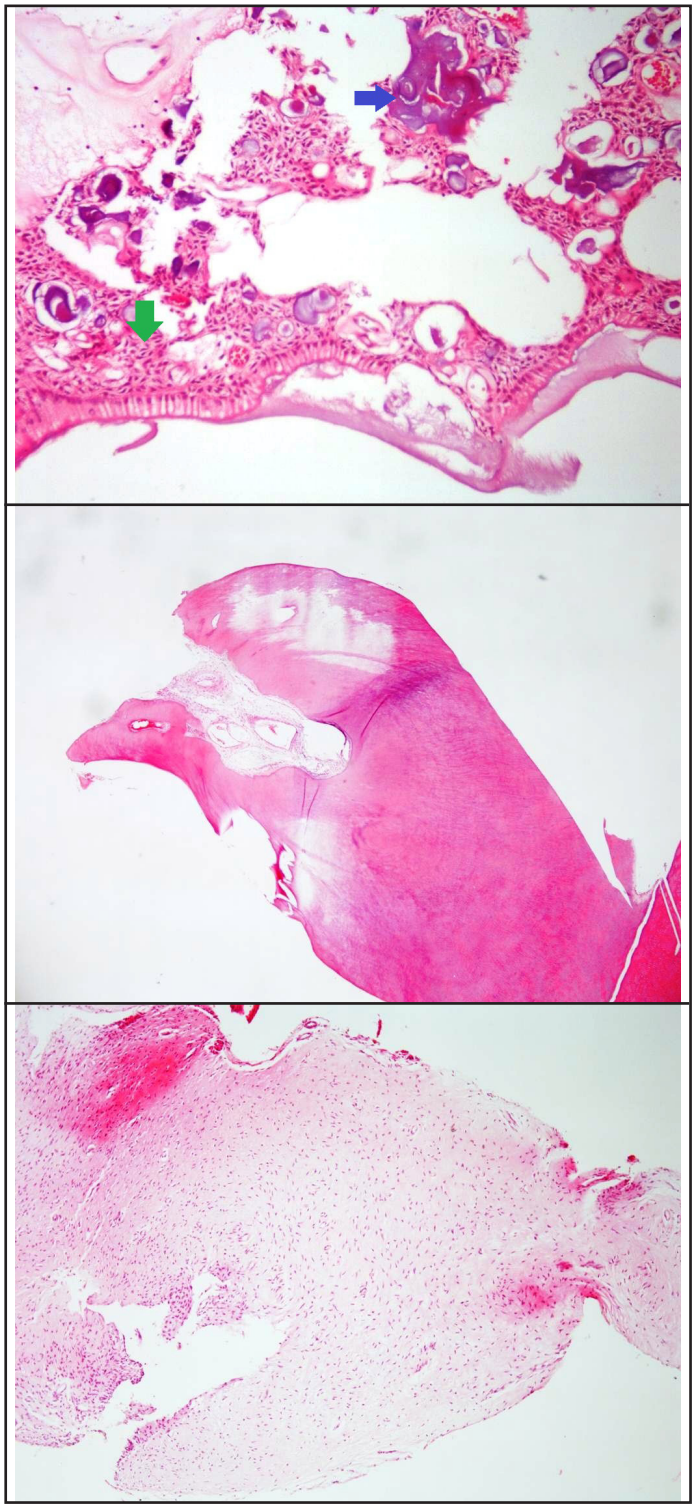


Figure 6. a. In histopathological examination of decalcified tissue samples, both mineralized-calcified foci (blue arrow) and odontogenic epithelium (green arrow) are observed. (Hematoxylin&Eosinx100), **b**: In histopathological sections, enamel-dentin structures and pulp tissue were observed. (Hematoxylin&Eosinx40), and **c**: In this photomicrograph, there is primitive ectomesenchyme that resembled the dental papilla. (Hematoxylin&Eosinx100)

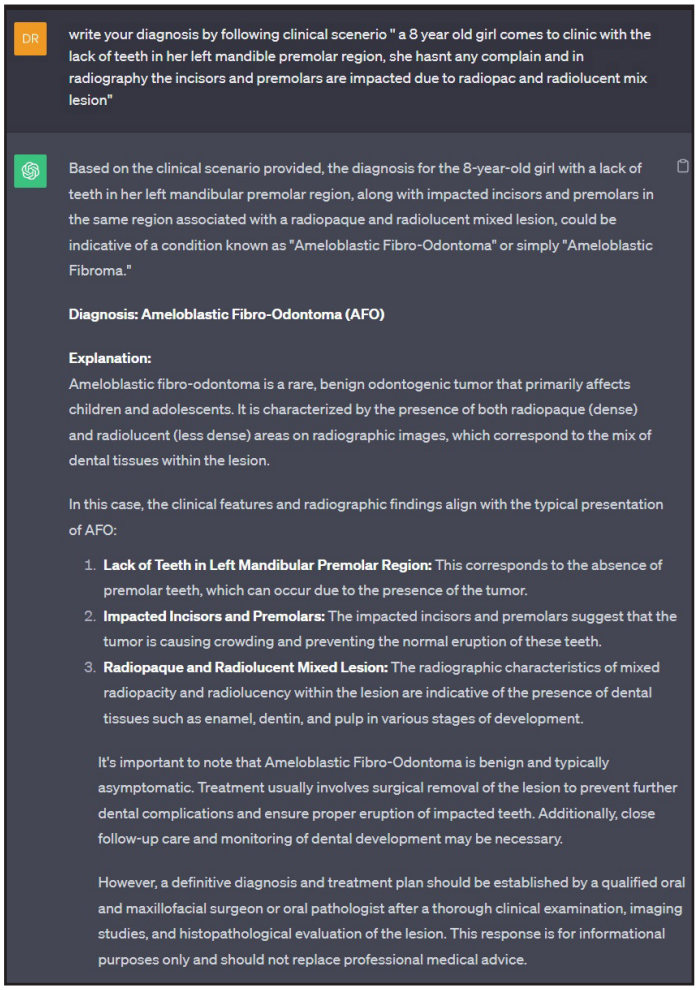
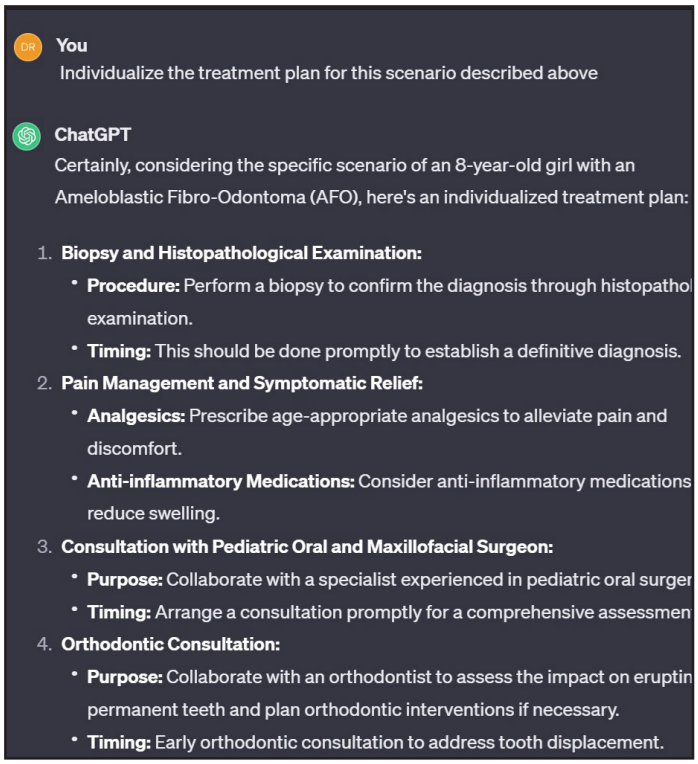


Figure 7. a. Diagnostic prompt with ChatGPT 3.5



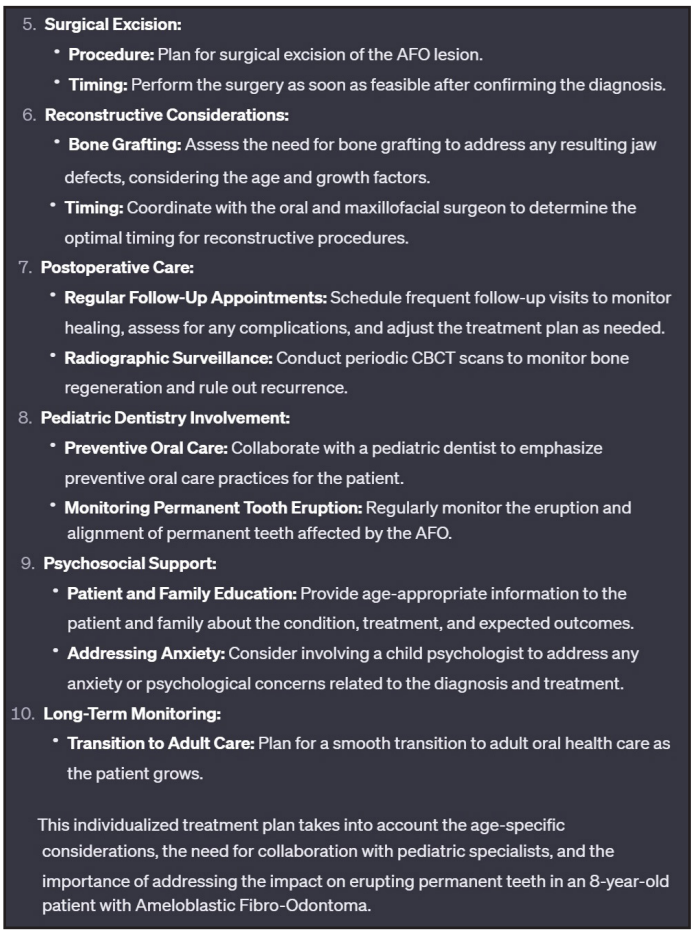


Figure 7. b. Treatment prompt with ChatGPT 3.5

DISCUSSION

AFO is a rare, benign odontogenic tumor with a disputed etiopathogenesis [9]. The proper classification, specifically the differentiation between hamartoma and neoplasm, is still a controversial subject [9]. According to the World Health Organization (WHO), ameloblastic fibro-odontoma (AFO) is recognized as a mixed odontogenic tumor [11]. AFO is composed of odontogenic epithelium and ectomesenchyme, which demonstrate hard tissue formation. It is characterized by ectomesenchyme resembling dental papilla, dental lamina, epithelial strands and nests that resemble the enamel organ, and the presence of both enamel and dentin [11]. Histopathological features of AFO may overlap with those of an immature complex odontoma [9]. Additionally, studies suggest a close relationship between AF, AFO, and odontoma (both compound and complex), suggesting that they may represent different stages of the same lesion [9]. Some propose that AF and AFO may be precursor stages of odontoma [12]. AFO's diagnostic challenges arise from its similarity to Adenomatoid Odontogenic Tumor (AOT) and AF [13]. Distinguishing between AFO and AF relies on the presence of tooth germ differentiation elements (enamel or dentin), with AFO showing evidence and AF lacking such features [13]. Adenomatoid odontogenic tumors, which are benign growths, can present as a "snowflake" opacity on imaging [5]. It is typically located in the anterior part of the maxilla that may help exclude with AFO [5]. Despite its rare incidence, AFO should be considered in the differential diagnosis of intraoral radiolucencies containing radiopaque material, especially in young patients. However, considering that AFO is a rare condition, representing 1% to 3% of odontogenic tumors [6], it should be noted that there is a lack of evidence in the literature regarding the tumor's prognosis post-excision and the necessity of long-term follow-up for potential malignant transformation. Although malignant transformation of AFO is rare, there are cases reported in the literature [14, 15].

For practitioners, especially in busy clinical settings diagnostic uncertainty is common and challenging [16]. At this point, the AI evaluating these pathological conditions has major advantages over the human evaluators. For instance, the human brain, limited in data storage, tends to perceive rare medical conditions and treatments as more challenging [1]. AI has no such limitations and can instantly access countless data sources, such as articles and reviews, deriving conclusions from their content [3]. It is not sensitive to factors present in human evaluators, such as fatigue, sleep deprivation, cognitive overload, noise, or psychological conditions [17]. It also eliminates the effects of cognitive biases, minimizing human error, which is important for diagnosis and treatment [18, 19]. However, the use of ChatGPT and similar language models for direct diagnosis and patient management raises ethical issues. These concerns arise when using ChatGPT, including potential issues of trustworthiness, intellectual property infringement, copyright violations, and bias. It is critical to conduct a careful evaluation and address any limitations or ethical dilemmas before integrating ChatGPT into practice [20]. According to the study by Balel, the use of ChatGPT as a patient information tool in oral and maxillofacial surgery is safe [21]. In addition, there are studies in the literature that suggest that its use in medical education or practice is questionable [2, 4].

One of the conclusions drawn from this case presentation is to exemplify that ChatGPT can serve as an auxiliary tool in complex scenarios, albeit not suitable for forming a preliminary diagnosis. Physicians can use artificial intelligence to prioritize

or generate diagnostic hypotheses previously unexplored [22]. Another conclusion to highlight in this section is that the initial diagnosis by the surgeon on the specimens for histological examination significantly reflects the patient's medical history, clinical, radiological, and laboratory findings. This pre-diagnosis acts as a connection between the clinician and pathologist. In this context, ChatGPT may shows promise in enhancing clinicopathologic correlation.

The responsibility lies with clinicians to accurately and thoroughly identify the lesion, possess sufficient knowledge of it, and differentiate between normal and pathologic conditions. The pathologist's role is significantly facilitated when the specimen is described in the appropriate medical jargon. In a study by Mehnen comparing the diagnostic abilities of ChatGPT and physicians, ChatGPT proved successful in 90% of presented scenarios, establishing it as a valuable assistant tool [23]. In the literature, ChatGPT has been very successful in scenario- and diagnosis-based studies in the fields of psychiatry, ophthalmology, and otolaryngology, achieving high levels of physician agreement [1, 24, 25].

However, there are still concerns regarding the clinical reliability due to its several limitations [4]. It tends to hallucinate, generating responses that may lack a factual basis [26, 27]. The model's knowledge cut-off in September 2021 poses a risk of outdated information [28]. Inconsistency in responses over time and the potential for false references further challenge the reliability of the information provided [28]. Users must approach ChatGPT with caution, verifying information independently and acknowledging its constraints in handling complex, dynamic, and controversial topics. For ChatGPT or similar language models to be routinely used in maxillofacial surgery, clinical reliability, accurate referencing of the information it provides, appropriate guidelines and a framework of practice are required [29]. It should be noted that ChatGPT's questioning on the case scenario was not considered in the surgical planning and was done separately. The required biopsy was taken as planned without any alteration to the excision margins. Given that pathologists are now striving to digitize their data, workflows, and interpretations, AI will definitely be able to assist the development of clinicopathologic correlation strategies [30].

CONCLUSION

In conclusion, this study sheds light on the pediatric presentation of ameloblastic fibro odontoma (AFO) through the case of an 8-year-old girl and emphasizes its relevance for dentists faced with uncommon conditions in young patients. The diagnostic challenges encountered in pediatric cases, particularly in rare tumoral instances like AFO, underscore the distinctive obstacles and considerations faced by clinicians. Furthermore, the study introduces a noteworthy aspect by exploring the potential of AI, specifically ChatGPT, as a valuable diagnostic aid in dentistry. The use of ChatGPT to provide support and guidance in the diagnosis and treatment decision-making process for rare pediatric conditions demonstrates the promising role of artificial intelligence in assisting pediatric dentists in their clinical endeavors. The integration of AI in dentistry has the potential to increase diagnostic accuracy and contribute to improved patient care, marking a significant step forward in the field.

Ethical Approval

The patient provided informed consent to receive the treatment and for the publication of the data in this report.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding

The authors declare that no funding was provided for this study.

Author Contributions

Ömer Uranbey was involved in the conception, management of case, management of complications, and writing of the manuscript.

Ferhat Ayrancı was involved in the conception, management of case, management of complications, and writing of the manuscript.

Büşra Erşan Erdem was involved in the examination of the specimen and writing the final manuscript.

Acknowledgment

The authors would like to thank Leyla Koç, DDS, of the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Ordu University, Türkiye, for her valuable help in performing ChatGPT queries.

REFERENCES

[1] Qu RW, Qureshi U, Petersen G, Lee SC (2023) Diagnostic and Management Applications of ChatGPT in Structured

Otolaryngology Clinical Scenarios. OTO Open 7:e67. https://doi.org/10.1002/oto2.67

[2] Sallam M (2023) ChatGPT Utility in Healthcare Education, Research, and Practice: Systematic Review on the Promising Perspectives and Valid Concerns. Healthcare (Basel) 11. https://doi.org/10.3390/healthcare11060887

[3] Gala D, Makaryus AN (2023) The Utility of Language Models in Cardiology: A Narrative Review of the Benefits and Concerns of ChatGPT-4. Int J Environ Res Public Health 20. https://doi.org/10.3390/ijerph20156438

[4] Liu J, Wang C, Liu S (2023) Utility of ChatGPT in Clinical Practice. Journal of Medical Internet Research 25:e48568. https://doi.org/10.2196/48568

[5] Peters SM, Bergen MS, Philipone EM, Yoon AJ (2018) Ameloblastic Fibro-Odontoma in an Adolescent: A Case Report and Review of Literature. J Clin Pediatr Dent 42:458-460. https://doi.org/10.17796/1053-4625-42.6.10

[6] Safavi M, Mohammadi F (2023) Ameloblastic Fibro-Odontoma. Fetal and Pediatric Pathology 42:281-284. https://doi.org/10.1080/15513815.2022.2088910

[7] Zouhary KJ, Said-Al-Naief N, Waite PD (2008) Ameloblastic fibro-odontoma: expansile mixed radiolucent lesion in the posterior maxilla: a case report. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 106:e15-e21. https://doi.org/https://doi.org/10.1016/j.tripleo.2008.05.038

[8] Omar N, Ullah A, Ghleilib I, Patel N, Abdelsayed RA (2021) A Locally Aggressive Ameloblastic Fibro-Odontoma: A Case Report and Literature Review. Cureus. https://doi.org/10.7759/cureus.20366

[9] Lúcio PSC, Cavalcante RB, Maia RN, Santos ES, Godoy GP (2013) Aggressive ameloblastic fibro-odontoma assessment with CBCT and treatment. European Archives of Paediatric Dentistry 14:179-184. https://doi.org/10.1007/s40368-013-0032-9

[10] Khurana S, Vaddi A (2023) ChatGPT From the Perspective of an Academic Oral and Maxillofacial Radiologist. Cureus 15:e40053. https://doi.org/10.7759/cureus.40053

[11] Soluk-Tekkesin M, Vered M (2021) Ameloblastic Fibro-Odontoma: At the Crossroad Between "Developing Odontoma" and True Odontogenic Tumour. Head and Neck Pathology 15:1202-1211. https://doi.org/10.1007/s12105-021-01332-6

[12] Pontes HA, Pontes FS, Lameira AG, Salim RA, Carvalho PL, Guimarães DM, Pinto Ddos S, Jr. (2012) Report of four cases of ameloblastic fibro-odontoma in mandible and discussion of the literature about the treatment. J Craniomaxillofac Surg 40:e59-63. https://doi.org/10.1016/j.jcms.2011.03.020

[13] Kale SG, Shetty A, Balakrishnan J, Purvey P (2017) Ameloblastic Fibro-odontoma with a Predominant Radiopaque Component. Ann Maxillofac Surg 7:304-307. https://doi.org/10.4103/ams.ams_84_17

[14] Howell RM, Burkes EJ, Jr. (1977) Malignant transformation of ameloblastic fibro-odontoma to ameloblastic fibrosarcoma. Oral Surg Oral Med Oral Pathol 43:391-401. https://doi.org/10.1016/0030-4220(77)90326-7

[15] Gatz S, Thway K, Mandeville H, Kerawala C, MacVicar D, Chisholm J (2015) Chemotherapy responsiveness in a patient with multiply relapsed ameloblastic fibro-odontosarcoma of the maxilla. Pediatric blood & cancer 62. https://doi.org/10.1002/pbc.25627

[16] Hatch S (2017) Uncertainty in medicine. Bmj 357:j2180. https://doi.org/10.1136/bmj.j2180

[17] Croskerry P (2009) A universal model of diagnostic reasoning. Acad Med 84:1022-1028. https://doi.org/10.1097/ACM.0b013e3181ace703

[18] Norman GR, Monteiro SD, Sherbino J, Ilgen JS, Schmidt HG, Mamede S (2017) The Causes of Errors in Clinical Reasoning: Cognitive Biases, Knowledge Deficits, and Dual Process Thinking. Acad Med 92:23-30. https://doi.org/10.1097/acm.0000000000001421

[19] Kuhn GJ (2002) Diagnostic errors. Acad Emerg Med 9:740-750. https://doi.org/10.1111/j.1553-2712.2002.tb02155.x

[20] Dave T, Athaluri SA, Singh S (2023) ChatGPT in medicine: an overview of its applications, advantages, limitations, future prospects, and ethical considerations. Front Artif Intell 6:1169595. https://doi.org/10.3389/frai.2023.1169595

[21] Balel Y (2023) Can ChatGPT be used in oral and maxillofacial surgery? J Stomatol Oral Maxillofac Surg

124:101471. https://doi.org/10.1016/j.jormas.2023.101471

[22] Pelaccia T, Forestier G, Wemmert C (2019) Deconstructing the diagnostic reasoning of human versus artificial intelligence. Canadian Medical Association Journal 191:E1332-E1335. https://doi.org/10.1503/cmaj.190506

[23] Mehnen L, Gruarin S, Vasileva M, Knapp B (2023) ChatGPT as a medical doctor? A diagnostic accuracy study on common and rare diseases. Cold Spring Harbor Laboratory

[24] Delsoz M, Raja H, Madadi Y, Tang AA, Wirostko BM, Kahook MY, Yousefi S (2023) The Use of ChatGPT to Assist in Diagnosing Glaucoma Based on Clinical Case Reports. Ophthalmology and Therapy 12:3121-3132. https://doi.org/10.1007/s40123-023-00805-x

[25] Franco D'Souza R, Amanullah S, Mathew M, Surapaneni KM (2023) Appraising the performance of ChatGPT in psychiatry using 100 clinical case vignettes. Asian J Psychiatr 89:103770. https://doi.org/10.1016/j.ajp.2023.103770

[26] Eysenbach G (2023) The Role of ChatGPT, Generative Language Models, and Artificial Intelligence in Medical Education: A Conversation With ChatGPT and a Call for Papers. JMIR Medical Education 9:e46885. https://doi.org/10.2196/46885

[27] Ji Z, Lee N, Frieske R, Yu T, Su D, Xu Y, Ishii E, Bang YJ, Madotto A, Fung P (2023) Survey of Hallucination in Natural Language Generation. ACM Computing Surveys 55:1-38. https://doi.org/10.1145/3571730

[28] Lecler A, Duron L, Soyer P (2023) Revolutionizing radiology with GPT-based models: Current applications, future possibilities and limitations of ChatGPT. Diagnostic and Interventional Imaging 104:269-274. https://doi.org/https://doi.org/10.1016/j.diii.2023.02.003

[29] Alhaidry HM, Fatani B, Alrayes JO, Almana AM, Alfhaed NK (2023) ChatGPT in Dentistry: A Comprehensive Review. Cureus 15:e38317. https://doi.org/10.7759/cureus.38317

[30] Nakagawa K, Moukheiber L, Celi LA, Patel M, Mahmood F, Gondim D, Hogarth M, Levenson R (2023) AI in Pathology: What could possibly go wrong? Seminars in Diagnostic Pathology 40:100-108. https://doi.org/https://doi.org/10.1053/j.semdp.2023.02.006

How to Cite;

Uranbey Ö, Ayrancı F, Erşan Erdem B. (2024) ChatGPT Guided Diagnosis of Ameloblastic Fibro-Odontoma: A Case Report with Eventful Healing. 30(2):240-247. Eur J Ther. https://doi.org/10.58600/eurjther1979

European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024;30(2):248.
https://doi.org/10.58600/eurjther2088

CORRECTION

Correction to: Determination of Reference Intervals of Biochemistry Parameters in healthy individuals in Gaziantep Province

Mustafa Örkmez [1], Mehmet Tarakçıoğlu [1]

[1] Department of Medical Biochemistry, Gaziantep University, Faculty of Medicine, Gaziantep, Türkiye

Published Online: 2024-03-15

Corresponding Author
Mustafa Örkemz, MD,
Address: Department of Medical Biochemistry, Faculy of Medicine, Osmangazi, Ünv.Tıp Fakültesi 27850 Şahinbey, Şehitkamil Gaziantep/Türkiye
E mail: dorkmez@gmail.com

In the first published version of this article [1], the authors stated that **"Funding: The authors declare no funding"** was misspelled. This has been changed to "**Funding: The study was supported by Gaziantep University Scientific Research Projects Unit with project number TF.11.36"**. The authors take full responsibility for this confusion, and they apologize for the confusion.

Publisher's Note: The original article has been corrected, and a correction note was added.

REFERENCES

[1] Örkmez M, Tarakcıoglu M (2023) Determination of Reference Intervals of Biochemistry Parameters in healthy individuals in Gaziantep Province. Eur J Ther. 29(2):173-178. https://doi.org/10.58600/eurjther.20232902-1343.y

The original article can be find online at; https://doi.org/10.58600/eurjther.20232902-1343.y