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Bagcilar Medical Bulletin is a peer-reviewed English journal aiming to publish original research, current review articles, case reports and letters related to all medical fields. The journal is currently published quarterly as an online publication. The articles will become freely available to all readers in pdf format as soon as they have been accepted after peer review. Accepted articles will immediately appear as a part of the issue belonging to that publication period. The journal uses EjManager online manuscript submission, review and tracking system .

Editorial Policies and Review Process

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

Publication Policy

Bagcilar Medical Bulletin considers for publication papers in the following categories:

- Original researches,
- Brief researches,
- Case reports,
- Reviews,
- Letters to the Editor

The journal gives high priority to original studies in publication because of aims to add the findings of searches in Turkey to international scientific knowledge, to share them within the international science milieu and to constitute the introduction of Turkish scientists. The review articles to be published in the journal are authorized by the editor to the relevant authors working on the subject.

General Principles

Papers that have not been published before or under evaluation by other publications are accepted for evaluation by the journal, if approved by each of the authors. The publication board may amend manuscripts upon informed consent of authors. Editors and redactors are fully empowered to correct mistakes related to orthography, citation as given in National Library of Medicine MEDLINE/PubMed Resources.

For quoted texts, tabulated data and graphics from published papers, the author has to obtain permission from the author(s) or the owner of the publishing rights of the source article and indicate the allowance in the paper. Author(s) is responsible for obtaining such permissions.

Short presentations that took place in scientific meetings can be referred to if announced in the article. The editor hands over the formally acceptable papers to at least two national/international referees for evaluation and gives the green light for publication upon modification by the authors in accordance with the referees' claims. Changing the name of an author (omission, addition or order) in papers submitted to the journal requires thepermission of all declared authors. Refused papers and graphics are not returned to the author.

Author Rights

Authors transferring the copyright of their article to the journal retain their right to use the article in its published form in their other work, in part or whole, without any revision or modification and to expand it into a book form on condition that they give appropriate attribution to the publication in the journal explicitly as stated in Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License and in the journal's open-access policy. When the article is to be re-used by the author

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as a book chapter or in a collection or compilation or expanded into a book for commercial purposes, permission is required to be sought from the journal, which reserves its right to levy or waive a fee for such re-use, and appropriate attribution is required to be given to the original publication in the journal explicitly.

Author Responsibilities

It is authors' responsibility to ensure that the article is in accordance with scientific and ethical standards and rules. And authors should ensure that the submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere in any language. Applicable copyright laws and conventions should be followed. Copyright material (e.g. tables, figures or extensive quotations) should be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources should be appropriately credited and referenced. The author(s) must have contributed to the submitted manuscript and must declare that they were involved in substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and 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. Those who do not meet all the above criteria should be named in the acknowledgements. Fundraising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The order of names in the author list of an article should be a co-decision, and it should be indicated in the Copyright Transfer Form. The individuals who do not meet the authorship criteria but contributed to the study should take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing general support, providing material or financial support are examples to be indicated in the acknowledgement section. Written informed consent should be taken from the persons whose participation are indicated in the acknowledgement section.

All authors must disclose all issues concerning financial relationships, conflict of interest, and competing interests that may potentially influence the results of the research or scientific judgment. All financial contributions, supports or sponsorship of projects must be clearly explained.

When an author discovers a significant error or inaccuracy in his/her own published paper, it is the author's obligation to promptly cooperate with the Editor-in-Chief to provide retractions or corrections of mistakes. The Author Contribution Form, indicating the authors' contribution to the manuscript and the ICJME Form for Potential Conflicts of Interest should be sent together with the manuscript. Please read ICMJE recommendations on roles and responsibilities of authors.

Responsibility for the Editors, Reviewers and Review Process

Editors evaluate manuscripts for their scientific content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. They provide a fair double-blind peer-review of the submitted articles for publication. They ensure that all the information related to submitted manuscripts is kept as confidential before publishing.

Editors are responsible for the contents and overall quality of the publication. They should publish errata pages or make corrections when needed. Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for the final decision for the publication of the manuscripts in Bagcilar Medical Bulletin.

Please review the COPE publication ethics guidelines by clicking here.

Reviewers evaluate manuscripts based on content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. They should have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments should be objective.

Reviewers should identify the relevant published work that has not been cited by the authors. They must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the Editor-in-Chief if they are aware of copyright infringement and plagiarism on the author's side.

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A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the Editor-in-Chief and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The reviewers are not allowed to have copies of the manuscripts for personal use and they cannot share manuscripts with others. Unless the authors and editor permit, the reviews of referees cannot be published or disclosed. The anonymity of the referees is important. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point. Please review the COPE publication ethics guidelines by clicking here.

Standards and Principles

Bagcilar Medical Bulletin is committed to upholding the highest standards of publication ethics and observes the following guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously. Each manuscript is reviewed by one of the editors and at least two referees under double-blind peer review process. We reserve the right to use plagiarism detecting software to screen submitted papers at all times. We check for plagiary and fraudulent data, falsification (fabrication or manipulation of research data, tables, or images) and improper use of humans or animals in research. All manuscripts not in accordance with these standards will be removed from the publication. This also contains any possible malpractice discovered after the publication. In accordance with the code of conduct we will report any cases of suspected plagiarism or duplicate publishing.

We follow the COPE Ethics Flowcharts for dealing with cases of possible scientific misconduct and breach of publication ethics.

Human and Animal Rights, Informed Consent, Conflict of Interest

The Bagcilar Medical Bulletin adopts highest ethical and scientific standards and ensures that it is free of influences regarding commercial interests. It is authors' responsibility that the articles are in accordance with ethical codes of conduct. Bagcilar Medical Bulletin takes as principle to comply with the ethical standards of Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects as revised in 2013.

For this reason, regarding the subjects of clinical experiments, it should be indicated in the submitted manuscripts definitely that the above mentioned codes of conduct were applied. Besides approvals, from national or local ethical committees should be sent together with the papers as well. Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children and those under wardship or with confirmed insanity, authors are asked to include information about whether the legal custodian's assent was obtained. And a letter of affirmation signed by all authors, confirming the collection of informed consents has to be sent to the journal.

Identifying information such as names, initials, hospital numbers, dates, photographs, and family pedigree must be avoided, unless disclosure is allowed by written consent of patient or the legal custodian of the patient. Informed consent for this purpose requires that an identifiable patient be shown in the manuscript to be published. Patient consent should be written and archived either with the journal, the authors, or both, as dictated by local regulations or laws. It must be mentioned in the text that informed consent was obtained from the participants. Especially for case report, identifying information should be avoided as much as possible. Eye masking on photos is not sufficient to conceal the identity of the patient. Authors have to stipulate lack of impact on scientific significance in case of changing the identifying information. Written informed consent should be taken from the patients presented in case studies; and it should be indicated in the manuscript.

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Authors have to confirm in the section "Materials and Methods" that study has been conducted in compliance to above mentioned principles, approvals have been obtained from related institutional ethical committees and informed consents were collected.

When reporting experiments on animals, authors should indicate whether the institutional and national guides for the care and use of laboratory animals were followed as in "Guide for the Care and Use of Laboratory Animals" and approval from ethical committee should be taken. The editor and the publisher do not guarantee or accept responsibility for the published features or definitions of commercial products. If there is direct or indirect grant support, it should be acknowledged in the section titled "declaration of interest" and should include the full name of the sponsor and grant number. Existence or lack of sponsorship of any kind as well as the type of sponsorship (consulting etc.) has to be acknowledged, as well.

Adopts WAME's definition which states that conflict of interest exists when author, peer reviewer or editor has a competing interest that could unduly influence (or be reasonably seen to do so) his or her responsibilities in the publication process. The types of competing interests that should be declared include financial ties, academic commitments, personal relationships, political or religious beliefs, institutional affiliations. The conflict of interest is to be acknowledged in the manuscript.

All manuscripts submitted to the journal for publication are checked by Crossref Similarity Check powered by "iThenticate" software for plagiarism. If plagiarism is detected, relevant institutions may be notified. In this case, the authors might be asked to disclose their raw data to relevant institutions.

Language

The language of the Bagcilar Medical Bulletin is American English. In addition, abstracts of the articles are published in both English and Turkish, and abstracts in both languages are requested from the authour(s).

Manuscript Organization And Format

All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the Journal it is being submitted (i.e., original research article,brief research article, review article, case report or letter to the editor). In addition, a Copyright Transfer Form, Author Contribution Form and ICJME Form for Disclosure of Potential Conflicts of Interest must be submitted. Authors will be notified of the receipt of their paper and the number assigned to it. The number should be included in all further correspondence. All parts of the manuscript, including case reports, quotations, references, and tables, must be double-spaced throughout. All four margins must be at least 2.5 cm. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) acknowledgement 5) references, and 6) tables and/or figures. All pages must be numbered consecutively.

Title Page

On the title page, include full names of authors, academic or professional affiliations, and complete address with phone, fax number(s) and e-mail address (es) of the corresponding author. Acknowledgments for personal and technical assistance should be indicated on the title page.

Abstract and Keywords

Title of the manuscript in English should be written in English abstract, and a Turkish title must be for Turkish abstract.. All articles should include abstract and keywords. For abstracts are most distinct parts of an article and take place on the electronic databases, author should be sure that abstract represents the content of the article accurately. Abstract should inform about the basis of the study and include the purpose, basic procedures (selection of cases and laboratory animals, observatory and analytical methods), key findings and conclusions. New and significant apects of the study or observations should be stated. Up to 3-10 key words in English and in Turkish should be in accordance with National Library of Medicine's Medical Subjects Subheadings (MeSH).

Manuscript Types

Original Research

Original research articles report substantial and original scientific results within the journal scope. Original research articles comprised of Abstract, Key Words, Introduction, Material and Methods, Results, Discussion, Conclusion, References and Table/ Figures. The abstract should be structured as the following.

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Abstract

The abstract should be no longer than 500 words and structured as follows: objective, method, results, and conclusions. Objective -the primary purpose of the article; Material and Method(s) -data sources, design of the study, patients or participants, interventions, and main outcome measures; Results -key findings; Conclusions -including direct clinical applications.

Keywords

Up to 3-10 key words in English and in Turkish should be in accordance with National Library of Medicine's Medical Subjects Subheadings (MeSH).

Introduction

This section should contain a clear statement of the general and specific objectives as well as the hypotheses which the work is designed to test. It should also give a brief account of the reported literature. The last sentence should clearly state the primary and secondary purposes of the article. Only, the actual references related with the issues have to be indicated and data or findings related with the current study must not be included in this section.

Material and Methods

This section should contain explicit, concise descriptions of all procedures, materials and methods used in the investigation to enable the reader to judge their accuracy, reproducibility, etc. This section should include the known findings at the beginning of the study and the findings during the study must be reported in results section. Ethics Committee Approval of the research and written Informed Consent obtained from the participants should be indicated.

The selection and description of the participants

The election, source of population, inclusion and exclusion criteria of the people who participate to experimental or clinical study must be clearly defined in this section. The particular study sample must be explained by the authors (i.e., why the study is performed in a definite age, race or sex population, etc.)

Technical information

The methods, apparatus (the manufacturer's name and address in parentheses), and procedures in sufficient detail must be defined to allow others to reproduce the results. References to established methods, including statistical methods (see below) must be given and brief descriptions for methods that have been published but are not well-known must be provided; new or substantially modified methods must be described, the reasons for using them must be given, and their limitations of the methods must be evaluated. The all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration must be identified. Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

Statistics

The statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. If possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size must be avoided. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. The computer software used must be specified.

Results

The results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. The all the data in the tables or illustrations should not be repeated in the text; only the most important observations must

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be emphasized or summarized. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Discussion

The findings of the study, the findings and results which support or do not support the hypothesis of the study should be discussed, results should be compared and contrasted with findings of other studies in the literature and the different findings from other studies should be explained. The new and important aspects of the study and the conclusions that follow from them should be emphasized. The data or other information given in the Introduction or the Results section should not be repeated in detail.

Conclusions

Conclusions derived from the study should be stated. For experimental studies, it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice. The conclusions should be linked with the goals of the study but unqualified statements and conclusions not adequately supported by the data should be avoided. New hypotheses should be stated when warranted, but should be labeled clearly as such.

Tables, Graphics and Illustrations

Tables, graphics and illustrations should be numbered in Arabic numerals in the text. The places of the illustrations should be signed in the text. Detailed information is under the related heading in below.

Brief Research

Brief researches are similar to original research in that they follow the same format and guidelines, but they consider small-scale research or research that is in early stages of development. These may include preliminary studies that has a simple research design or a small sample size and that have produced limited pilot data and initial findings that indicate need for further investigation. Brief researches are much shorter than manuscripts associated with a more advanced, larger-scale research project. They are not meant to be used for a short version of an article about research that would otherwise qualify for a full original research manuscript or for publishing material on research that lacks significance, is not rigorous or, if expanded, would not qualify for a full article or for research.

Case Report

Case reports consider new, interesting and intriguing case studies in detail. They should be unique and present methods to overcome any health challenge by use of novel tools and techniques and provide a learning source for the readers. Case reports comprise of: Abstract (unstructured summary), Key-words, Introduction, Case Report, Discussion, Reference, Tables and Figures. Written informed consent of the patient should be obtained and indicated in the manuscript.

Review

Review articles are written by individuals who have done substantial work on the subject or are considered experts in the field. The Journal invites authors to write articles describing, evaluating and discussing the current level of knowledge regarding a specific subject in the clinical practice.

The manuscript should have an unstructured abstract representing an accurate summary of the article, key words, introduction, conclusion. Authors submitting review article should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

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Letter to the Editor

Letter to the Editor is short and decisive manuscript. They should be preferably related to articles previously published in the Journal or views expressed in the Journal. The letter should not include preliminary observations that need a later study for validation.

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text. Each table should be typed or printed with double spacing on a separate sheet of paper. The tables should be numbered consecutively in the order of their first citation in the text and a brief title for each table should be supplied. Any internal horizontal or vertical lines should not be used and a short or an abbreviated heading should be given to each column. Authors should place explanatory matter in footnotes, not in the heading. All nonstandard abbreviations should be explained in footnotes, and the following symbols should be used in sequence: *,†,‡,§,ǁ,¶,**,††,‡‡. The statistical measures of variations, such as standard deviation and standard error of the mean should be identified. Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully. Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text. Such tables should be submitted for consideration with the paper so that they will be available to the peer reviewers.

Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as digital prints in photographic-quality. In addition to requiring a version of the figures suitable for printing, authors are asked for electronic files of figures in a format (for example, JPEG or GIF) that will produce high-quality images in the Web version of the journal; authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, sharp, glossy, black-and-white or color photographic prints should be sent, usually 127 x 173 mm. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends--not on the illustrations themselves. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Photographs of potentially identifiable people must be accompanied by written permission to use the photograph. Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, the original source should be acknowledged and written permission from the copyright holder should be submitted to reproduce the figure. Permission is required irrespective of authorship or publisher except for documents in the public domain. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. We publish illustrations in color only if the author pays the additional cost.

Legends for Illustrations (Figures)

The legends for illustrations should be typed or printed out using one spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each one clearly should be identified and explained in the legend. The internal scale should be explained and the method of staining in photomicrographs should be identified.

Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be in degrees Celsius, blood pressures should be in millimeters of mercury. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International

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System of Units (SI). Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Acknowledgement(s)

All forms of support, including individual technical support or material support must be acknowledged in the author's footnote before references.

Case Reports and Word Limitation

Original papers and reviews have no specific word limitation. A case report must be strictly limited to 1000 words excluding abstract and have minimal figures, tables, and references. Letters to the Editor (maximum of 500 words, including references; no tables or figures) will be considered if they include the notation "for publication." A letter must be signed by all of its authors. Letters critical of an article published in the journal must be received within 12 weeks.

Preparation of Manuscripts

The Bagcilar Medical Bulletin follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals". Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.),

STROBE statement-checklist of items that should be included in reports of observational studies,

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.)

References

Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can

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now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently. Using abstracts as references should be avoided.

References to papers accepted but not yet published should be designated as “in press” or “forthcoming”; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as “unpublished observations” with written permission from the source. Citing a “personal communication” should be avoided unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, written permission and confirmation of accuracy from the source of a personal communication must be obtained.

Reference Style and Format

The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the National Library of Medicine for its databases. Authors should consult NLM’s Citing Medicine for information on its recommended formats for a variety of reference types. References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in the list of Journals in National Library of Medicine sources. Accuracy of citation is the author’s responsibility. All references should be cited in text. Type references in the style shown below. If there are more than 6 authors, list them followed by et al. Abbreviations of journal names should conform to the style used in National Library of Medicine. If a journal is not indexed in National Library of Medicine’s MEDLINE/PubMed, it should not be abbreviated.

Examples for References:

1. For articles in journals:

For the published article from the journal which placed and abbreviated in MEDLINE:

Crow SJ, Peterson CB, Swanson SA, Raymond NC, Specker S, Eckert ED, et al. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009;166(12):1342-1346.

For the published article from the journal which is not placed and is not abbreviated in MEDLINE:

Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3:171-178.

2. For the supplement:

For the published article from the journal which placed and abbreviated in MEDLINE:

Sharan P, Sundar AS. Eating disorders in women. Indian J Psychiatry 2015:57(Suppl 2):286-295.

For the published article from the journal which is not placed and is not abbreviated in MEDLINE:

Maner F. Yeme bozukluklarının tedavisi. Anadolu Psikiyatri Dergisi 2009;10(Ek 1):55-56.

3. For articles in press:

Cossrow N, Pawaskar M, Witt EA, Ming EE, Victor TW, Herman BK, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 criteria. J Clin Psychiatry, 2016. (in press).

4. For the citations from books:

Books edited by one editor:

McKnight TL. Obesity Management in Family Practice. 1st ed., NewYork: Springer, 2005:47-51.

For the citation from a section of book edited by editor(s):

Jebb S, Wells J. Measuring body composition in adults and children. In Clinical Obesity in Adults and Children, Copelman P, Caterson I, Dietz W (editors). 1st ed., London: Blackwell Publishing, 2005:12-18.

If the authors of the cited section are the editors of the book:

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Eckel RH (editor). Treatment of obesity with drugs in the new millennium. In Obesity Mechanisms and Clinical Management. First ed., Philadelphia: Lippincott Williams & Wilkins, 2003:449-476.

For the citation from a translated book:

McGuffin P, Owen MJ, Gottsman II. Psikiyatri Genetiği ve Genomiği. Abay E, Görgülü Y (Çevirenler) 1st ed., Istanbul: Nobel Tıp Kitabevleri, 2009:303-341.

5. For the citation from thesis:

Keçeli F. Yeme bozukluğu hastalarında obsesif kompulsif bozukluk ve kişilik bozukluğu. Thesis, T.C. Sağlık Bakanlığı Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Istanbul:2006.

6. For the citation from posters:

Akbaş Öncel D, Akdemir A. Üniversite öğrencilerinde diyet, beden algısı ve kendilik algısı arasındaki ilişkiler. 47. Ulusal Psikiyatri Kongresi Özet Kitabı, 26-30 Ekim 201, Antalya, 2011:102.

7. Online Article:

Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med [Internet]. 2006 Jul 4 [cited 2007 Jan 4];145(1):62-9. Available from:http://www.annals.org/cgi/reprint/145/1/62.pdf

SUBMISSION TO JOURNAL

All new manuscripts must be submitted through the Bagcilar Medical Bulletin online manuscript submission and peer review system. Complete instructions are available at the website (). A cover letter should accompany with manuscripts, including the knowledge of:

•The findings of previous same studies should be informed and should be cited. The copies of previous same studies should be sent with manuscripts that might help to the editor in the decision process.

•The knowledge of "all authors have read and accepted the study in its form, all authors meet the criteria for being in authorship" should be stated.

•All helpful things for editorial ship should be stated: The comments of previous editor/reviewers and the response of authors should be added if the manuscript has been sent to another journal for consideration, previously. The editor requested this information to accelerate the publication process.

SUBMISSION CHECKLIST

It is hoped that this list will be useful during the final checking of an article prior to sending it to the journal's editor for review. Please consult this Guide for Authors, for further details of any item.

Ensure that the following items are present:

• Cover letter to the editor

- The category of the manuscript
- Acknowledgement of "the paper is not under consideration for publication in another journal"
- Disclosure of any commercial or financial involvement
- Reviewing the statistical design of the research article
- Last control for fluent English

Copyright Transfer Form

Author Contribution Form

ICJME Form for Disclosure of Potential Conflicts of Interest

-Permission of previous published material if used in the present manuscript

-Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of in 2000.

-Statement that informed consent was obtained after the procedure(s) had been fully explained.

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-Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in “Guide for the Care and Use of Laboratory Animals”.

-Title page

-The title of the manuscript both in Turkish and in English

-All authors and their affiliations

-All authors’ e-mail address, full postal address, GSM phone, business telephone and fax numbers

-Abstracts (400-500 words) Both in Turkish and in English

-Keywords: 3 to 10 words (in Turkish and in English)

-Body text

-Acknowledgement

-Reference

-All tables (including title, description, footnotes)

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YAZARLARA BİLGİ

Hakem Değerlendirmesi, Yayın Etiği ve Kötüye Kullanım

Hakem Değerlendirmesi

Makalelerin daha önce yayınlanmamış olması ve aynı anda başka bir yere gönderilmemiş olması koşuluyla başvuru kabul edilir; yazarlar, içeriği okuduğunu, onayladığını, tüm yazarların çıkar çatışmalarını beyan ettiğini, çalışmanın etik onaya uygun olduğunu ve uluslararası kabul görmüş etik standartlarda yürütüldüğünü kabul eder. Etik suistimalden şüphelenilmesi durumunda, Yayın Kurulu ilgili uluslararası yayın etiği kurallarına (COPE yönergelerine) uygun olarak hareket edecektir.

Derginin yayın politikaları, Bilim Konseyi Editörleri tarafından önerilen kurallarda belirtildiği gibi yürütülür ve ICMJE Biyomedikal Dergilere Gönderilen Makaleler için Tekdüzen Gereklilikler: Biyomedikal Yayın için Yazma ve Düzenleme'de yansıtılır. Buna göre yazarlar, gözden geçirenler ve editörlerin bu bildirimde yer alan etik davranışa ilişkin en iyi uygulama kılavuzlarına uymaları beklenmektedir.

Gönderilen yazılar çift-kör hakem değerlendirmesine tabi tutulur. Dergide yayımlanacak yazıların seçimine rehberlik eden bilim kurulu, derginin seçilmiş uzmanlarından ve gerekirse ilgili araştırma alanında ulusal ve uluslararası uzmanlardan seçilmiş uzmanlardan oluşur. Tüm yazılar editör, bölüm yardımcı editörleri ve en az üç dahili ve harici uzman hakem tarafından incelenir. Tüm araştırma makaleleri de bir istatistik editörü tarafından yorumlanır.

İnsan ve Hayvan Araştırmaları

Deneysel, klinik, ilaç ve insan çalışmaları için, etik kurul onayı ve çalışma protokolünün uluslararası anlaşmalara uygunluğuna dair bir beyan (World Medical Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," Ekim 2013) gereklidir. Deneysel hayvan çalışmalarında yazarlar, izlenen prosedürlerin hayvan haklarına uygun olduğunu (Laboratuvar Hayvanlarının Bakım ve Kullanım Kılavuzu) belirtmeli ve hayvan Etik Kurul Onayı almalıdır. Etik Kurul Onayı belgesi, makale ile birlikte Bağcılar Tıp Bülteni'ne gönderilmelidir.

Etik Kurul Onayı ile yukarıda belirtilen uluslararası kılavuzlara uyum ve hastanın aydınlatılmış onamının alındığına dair beyan "Materyal ve Yöntem" bölümünde belirtilmeli ve kullanılan veri/medyanın hastanın kimliğini ortaya çıkarabileceği durumlarda vaka raporları gerekmektedir. Yazarlar, kurumlar arasında çıkar çatışması beyanı, herhangi bir mali veya maddi desteğin kabulünün belirtilmesi makale gönderen yazarlar için zorunludur ve bu açıklama makalenin sonunda yer almalıdır. Hakemler, yazarlar veya kurumlar ile aralarında herhangi bir potansiyel çıkar çatışması varsa, bunu rapor etmelidir.

18 yaşın altındaki kişiler için, her iki ebeveynin veya kişinin yasal vasisi veya velisinin imzasını içeren bir onay formu gönderilmelidir.

İntihal ve Etik Suistimal

Bağcılar Tıp Bülteni, tüm makaleleri yayınlanmadan önce "iThenticate" kullanarak intihal taramasına tabi tutar. Dergi, iThenticate raporlarına göre benzerlik oranı %15'in üzerinde olan makaleleri kabul etmemektedir.

Yazarların aşağıda yazılanlar gibi her türlü intihal ve etik suistimalden kaçınmaları önemlidir:

İntihal: Başka bir yazarın yayınındaki bir içeriğin tamamını veya bir kısmını kaynak göstermeden yeniden yayınlamak.

Fabrikasyon (Uydurma): Var olmayan veri ve bulguları/sonuçları yayınlamak.

Çoğaltma: Bir makalenin farklı dillerde yeniden yayınlanmasını içeren başka bir yayından alınan verileri kullanmak.

Dilimleme (Salamizasyon): Bir çalışmanın sonuçlarını bölerek birden fazla yayın oluşturma.

Veri Manipülasyonu/Yanlışlığı: Yanlış bir izlenim vermek için araştırma verilerini manipüle etmek veya kasıtlı olarak çarpıtmak.

İntihal, fabrikasyon, çoğaltma, veri manipülasyonu ve dilimleme gibi etik olmayan uygulamaları ve yazarlık hediye etme, uygunsuz teşekkür ve COPE akış şemalarına uygun olmayan referanslar gibi uygulamalarla inceleme sürecini etkilemeye yönelik çabaları onaylamıyoruz.

YAZARLARA BİLGİ

Gönderilen yazılar ayrıca otomatik yazılım tarafından intihal ve yayın değerlendirmesine tabi tutulur. Yazarlar, çalışma sonuçlarını tamamen veya kısmen özet şeklinde yayınlayıp yayınlamadıklarını bildirmekle yükümlüdür.

A. YAYINCININ GÖREVLERİ:

Etik Olmayan Yayınlama Davranışının Ele Alınması

Yayıncı, iddia edilen veya kanıtlanmış bilimsel suistimal, hileli yayın veya intihal durumlarında, söz konusu makaleyi editörlerle yakın iş birliği içinde değiştirmek için tüm uygun önlemleri alacaktır. Bu, en ciddi durumda, etkilenen çalışmanın bir yanlışlık sonucu yayınlanmasını, ifşa edilmesini veya geri çekilmesini içerir. Yayıncı, editörlerle birlikte, araştırma suistimalinin meydana geldiği makalelerin yayınlanmasını tespit etmek ve önlemek için makul adımları atacak ve hiçbir koşulda bu tür kötüye kullanımın gerçekleşmesine teşvik etmeyecek veya bilerek izin vermeyecektir.

Editöryal Özerklik

Bağcılar Tıp Bülteni, herhangi birinin veya ticari ortakların etkisi olmaksızın editöryal kararların özerkliğini sağlamayı taahhüt eder.

Fikri Mülkiyet ve Telif Hakkı

Bağcılar Tıp Bülteni, dergide yayınlanan makalelerin mülkiyetini ve telif haklarını korur ve her makalenin yayınlanmış kaydını tutar. Dergi, yayınlanan her makalenin bütünlüğünü ve şeffaflığını sağlar.

Bilimsel Suistimal

Bağcılar Tıp Bülteni'nin yayıncısı, hileli yayın veya intihal ile ilgili gerekli tüm önlemleri almaktadır.

B. EDİTÖRLERİN GÖREVLERİ:

Yayın Kararı ve Sorumluluğu

Dergi editörü, dergideki her şeyi kontrol altında tutar, okuyucuların ve yazarların ihtiyaçlarını karşılamaya çalışır. Editör ayrıca dergiye gönderilen makalelerin hangilerinin yayınlanması gerektiğine karar vermekten ve hakaret, telif hakkı ihlali ve intihal ile ilgili yasal gerekliliklere tabi politikalar tarafından yönlendirilmekten sorumludur. Editör, yayın kararları verirken hakemlerle tartışabilir. Yayının içeriğinden ve genel kalitesinden editör sorumludur. Editör, adil ve uygun bir hakemlik süreci sağlamalıdır.

Nesnellik

Dergiye gönderilen makaleler her zaman önyargısız olarak değerlendirilir.

Gizlilik

Editör, gönderilen bir makaleyle ilgili herhangi bir bilgiyi, editör kadrosu, hakemler ve yayıncı dışında hiç kimseye açıklamamalıdır.

Çıkar Çatışmaları ve İfşa

Bağcılar Tıp Bülteni, yazarlar, hakemler ve editörler gibi taraflar arasında herhangi bir çıkar çatışmasına izin vermez. Gönderilen bir makaledeki yayınlanmamış materyaller, yazarın açık izni olmaksızın hiç kimse tarafından kullanılmamalıdır.

Yayımlanan Eserlerde Temel Hatalar

Yazarlar, yayınlanan çalışmada önemli hatalar veya yanlışlıklar tespit edilirse, derhal dergi editörlerini veya yayıncısını bilgilendirmek ve makaleyi düzeltmek veya geri çekmek üzere onlarla iletişim sağlamakla yükümlüdür. Editörler veya yayıncı, yayınlanan bir çalışmanın önemli bir hata veya yanlışlık içerdiğini üçüncü bir taraftan öğrenirse, yazarlar makaleyi derhal düzeltmeli, geri çekmeli veya dergi editörlerine makalenin doğruluğuna dair kanıt sağlamalıdır.

YAZARLARA BİLGİ

C. HAKEMLERİN GÖREVLERİ:

Değerlendirme

Hakemler, yazarların kökeni, cinsiyeti, cinsel yönelimi veya politik felsefesini gözetmeksizin yazıları değerlendirir. Hakemler ayrıca değerlendirme sırasında gönderilen yazılar için adil bir kör hakem incelemesi sağlar.

Gizlilik

Gönderilen makalelerle ilgili tüm bilgiler gizli tutulur. Hakemler, editör tarafından izin verilmedikçe başkalarıyla tartışılmamalıdır.

Çıkar Çatışmaları ve İfşa

Hakemlerin yazarlar, fon sağlayıcılar, editörler vb. taraflarla ilgili herhangi bir çıkar çatışması yoktur.

Editöre Katkı

Hakemler, editöre karar vermede ve makaleyi geliştirmede yardımcı olabilir.

Nesnellik

Daima objektif bir değerlendirme yapılır. Hakemler görüşlerini uygun destekleyici argümanlarla açıkça ifade eder.

Kaynakların Onaylanması

Hakemler, yazarların atıfta bulunmadığı ilgili yayınlanmış bir çalışmayı tanımlamalıdır. Hakemler ayrıca, makale ile kişisel bilgilerine sahip oldukları diğer yayınlanmış makaleler arasındaki önemli benzerlikleri veya örtüşmeleri editörün dikkatine sunarlar.

D. YAZARLARIN GÖREVLERİ:

Raporlama Standartları

Gönderilen bir makale orijinal olmalı ve yazarlar, makalenin daha önce herhangi bir dergide yayınlanmamış olmasını sağlamalıdır. Araştırmanın verileri makalede tam anlamıyla sunulmalıdır. Bir makale, başkalarının çalışmayı yeniden kopyalamasına izin vermek için gerekli ayrıntı ve referansları içermelidir.

Özgünlük

Çalışmalarını dergiye göndermek isteyen yazarlar, çalışmalarının tamamen özgün olduğundan emin olmalıdır. Literatürden alınan kelime ve cümleler uygun şekilde alıntılanmalıdır.

Çoklu Yayınlar

Yazarlar, aynı çalışmayı başka bir dergide yayınlanmak veya değerlendirilmek üzere göndermemiş olmalıdır. Aynı çalışmanın birden fazla dergiye aynı anda gönderilmesi kabul edilemez ve etik dışı bir davranış olarak nitelendirilir.

Kaynakların Belirtilmesi

Başkalarının çalışmalarının uygun bir şekilde alıntılanması gerekir. Yazarlar, çalışmayı belirlemede etkili olan yayınlara atıfta bulunmalıdır. Çalışmanın sürecini kapsayan tüm kaynaklar belirtilmelidir.

Makale Yazarlığı

Bir makalenin yazarlığı, çalışmaya kayda değer bir katkı yapmış olanlarla sınırlı olmalıdır. Başkaları araştırmaya katılmışsa, katkıda bulunanlar olarak listelenmelidir. Yazarlık aynı zamanda bir derginin editörü ile iletişim halinde olan bir sorumlu yazarı da içerir. Sorumlu yazar, tüm uygun ortak yazarların bir makaleye dahil edilmesini sağlamalıdır.

YAZARLARA BİLGİ

Çıkar Çatışmaları ve İfşa

Tüm finansal destek kaynakları açıklanmalıdır. Tüm yazarlar, çalışmalarını oluşturma sürecinde (varsa) çıkar çatışmasını ifşa etmelidir. Gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali yardımlar veya diğer destekler, Bağcılar Tıp Bülteni Yayın Kurulu'na açıklanmalıdır. ICMJE Potansiyel Çıkar Çatışması Bildirim Formu, olası bir çıkar çatışmasını açıklamak için katkıda bulunan tüm yazarlar tarafından doldurulmalı ve gönderilmelidir. Derginin Yayın Kurulu, editörler, yazarlar veya hakemler arasında olası bir çıkar çatışması durumlarında COPE ve ICMJE yönergeleri kapsamında hareket eder.

Mali veya şahsi fayda sağlayan koşullar, bir çıkar çatışması doğurur. Bu durum, bilimsel sürecin ve yayınlanan makalelerin güvenilirliği, bilimsel çalışmaların planlanması, uygulanması, yazılması, değerlendirilmesi, düzenlenmesi ve yayınlanması sırasında çıkar çatışmalarının objektif olarak ele alınması ile doğrudan ilişkilidir.

Finansal ilişkiler en kolay tespit edilen çıkar çatışmalarıdır ve derginin, yazarların ve bilimin güvenilirliğini zedelemesi kaçınılmazdır. Bu çatışmalara bireysel ilişkiler, akademik rekabet veya entelektüel yaklaşımlar neden olabilir. Yazarlar, çalışmanın tüm verilerine ulaşmalarını veya makalelerini analiz etme, yorumlama, hazırlama ve yayınlama olanaklarını kısıtlayan kâr veya başka bir avantaj elde etme düşüncesiyle sponsorlarla anlaşmalardan mümkün olduğunca kaçınmalıdır. Editörler, çalışmaları değerlendirirken aralarında ilişki olabilecek kişileri bir araya getirmekten kaçınmalıdır. Makaleler hakkında nihai kararı verecek olan editörlerin, karar verecekleri konulardan hiçbiriyle kişisel, mesleki veya mali bağı olmamalıdır. Yazarlar, makalelerinin bağımsız bir değerlendirme süreci ile etik ilkeler çerçevesinde değerlendirilmesini sağlamak için olası çıkar çatışmalarını yayın kuruluna bildirmelidir.

Editörlerden birinin herhangi bir yazıda yazar olması durumunda editör, makale değerlendirme sürecinden çıkarılır. Herhangi bir çıkar çatışmasını önlemek için makale değerlendirme süreci çift kör olarak yapılmaktadır. Çift kör değerlendirme sürecinden dolayı Baş Editör dışında hiçbir yayın kurulu üyesine, uluslararası danışma kurulu üyesine veya hakemlere, makalenin yazarları veya yazarların kurumları hakkında bilgi verilmemektedir.

Yayın ekibimiz tüm bu durumları göz önünde bulundurarak değerlendirme sürecinin tarafsız bir şekilde yürütülmesi için özveriyle çalışmaktadır.

YAZARLARA BİLGİ

Bağcılar Tıp Bülteni (Bagcilar Medical Bulletin), tıbbın her alanında araştırma makalelerini, güncel derleme yazılarını, olgu sunumlarını ve editöre mektupları İngilizce tam metin ve Türkçe özle yayınlayan hakemli bir dergidir. Dergi online olarak yılda 4 sayı yayınlanmaktadır. Tüm makaleler kabul edilir edilmez, online olarak pdf formatında bu web sitesinde, o dönemdeki sayının bir makalesi olarak yer alacaktır. Dergi Galenos Yayınevi tarafından yayımlanmaktadır.

Editoryal Politikalar ve Hakem Süreci

Yayın Politikası

Bağcılar Tıp Bülteni, yayınlanmak üzere gönderilen yazıları aşağıda belirtilen şekillerde kabul eder:

-Orijinal araştırmalar,

-Kısa araştırmalar,

-Olgu sunumları,

-Derlemeler,

-Editöre mektup

Dergi, Türkiye'de yapılan araştırmaların uluslararası bilim arenasına duyurulması, uluslararası bilim çevrelerince paylaşılması ve bu bağlamda Türkiye'nin tanıtılmasına katkıda bulunmayı misyon edindiğinden özellikle orijinal araştırma niteliğindeki yazıları yayınlamaya öncelik vermektedir. Dergide yayınlanacak derleme türündeki yazılar editör tarafından konu ile ilgili çalışan yetkin kişilere hazırlatılmaktadır.

Genel İlkeler

Daha önce yayınlanmamış ya da yayınlanmak üzere başka bir dergide halen değerlendirmede olmayan ve her bir yazar tarafından onaylanan makaleler dergide değerlendirilmek üzere kabul edilir. Yayın kurulu, yazarların iznini alarak yazıda değişiklikler yapabilir. Editör ve dil editörleri dil, imlâ ve kaynakların National Library of Medicine MEDLINE/PubMed Resources'da belirtildiği gibi yazılmasında ve ilgili konularda tam yetkilidir.

Eğer makalede daha önce yayınlanmış alıntı yazı, tablo, resim vs. mevcut ise makale yazarı, yayın hakkı sahibi ve yazarlarından yazılı izin almak ve bunu makalede belirtmek zorundadır. Gerekli izinlerin alınıp alınmadığından yazar(lar) sorumludur.

Bilimsel toplantılarda sunulan özet bildiriler, makalede belirtilmesi koşulu ile kaynak olarak kabul edilir. Editör, dergiye gönderilen makale biçimsel esaslara uygun ise, gelen yazıyı yurtiçinden ve/veya yurtdışından en az iki hakemin değerlendirmesinden geçirtir, hakemler gerek gördüğü takdirde yazıda istenen değişiklikler yazarlar tarafından yapıldıktan sonra yayınlanmasına onay verir. Makale yayınlanmak üzere dergiye gönderildikten sonra yazarlardan hiçbirinin ismi, tüm yazarların yazılı izni olmadan yazar listesinden silinemez ve yeni bir isim yazar olarak eklenemez ve yazar sırası değiştirilemez. Yayına kabul edilmeyen makale, resim ve fotoğraflar yazarlara geri gönderilmez.

Yazar Hakları

Makalelerinin telif haklarını dergiye devreden yazarlar, yayınladıkları yazıdaki yazılarını diğer çalışmalarında kısmen veya tamamen, herhangi bir revizyon veya değişiklik yapmadan kullanma ve uygun gördükleri takdirde kitap haline getirme hakkını saklı tutarlar. Dergideki, CC BY-NC-ND 4.0 Lisansıvnda ve derginin Açık Erişim politikasında belirtildiği gibi açıkça yayınlanmalıdır. Makale, yazar tarafından bir kitap bölümü olarak veya bir koleksiyonda veya derlemede yeniden kullanılacaksa veya ticari amaçlarla bir kitap haline getirilecekse, atama veya feragat etme hakkını saklı tutan Dergi'den izin alınması gerekir. Bu yeniden kullanım için bedel ve dergide asıl yayına açıkça verilmek üzere uygun bir atıf yapılması gerekmektedir.

Yazarların Soru mluluğu

Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır. Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat

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sağlamalıdır. Uygulamadaki telif kanunları ve anlaşmaları gözetilmelidir. Telife bağlı materyaller (örneğin tablolar, şekiller veya büyük alıntılar) gerekli izin ve teşekkürle kullanılmalıdır. Başka yazarların, katkıda bulunanların çalışmaları ya da yararlanılan kaynaklar uygun biçimde kullanılmalı ve referanslarda belirtilmelidir.

Gönderilen makalede tüm yazarların akademik ve bilimsel olarak doğrudan katkısı olmalıdır, bu bağlamda "yazar" yayınlanan bir araştırmanın kavramsallaştırılmasına ve desenine, verilerin elde edilmesine, analizine ya da yorumlanmasına belirgin katkı yapan; yazının yazılması ya da bunun içerik açısından eleştirel biçimde gözden geçirilmesinde görev yapan; yazının yayınlanmak üzere nihai halini onaylayan ve çalışmanın herhangi bir bölümünün doğruluğuna ya da bütünlüğüne ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul eden kişi olarak görülür. Fon sağlanması, ya da araştırma grubunun genel süpervizyonu tek başına yazarlık hakkı kazandırmaz. Yazar olarak gösterilen tüm bireyler sayılan tüm ölçütleri karşılamalıdır ve yukarıdaki ölçütleri karşılayan her birey yazar olarak gösterilebilir. Çok merkezli çalışmalarda grubun tüm üyelerinin yukarıda belirtilen şartları karşılaması gereklidir. Yazarların isim sıralaması ortak verilen bir karar olmalıdır. Tüm yazarlar yazar sıralamasını Telif Hakkı Devir Formunda imzalı olarak belirtmek zorundadırlar. Yazarların tümünün ismi yazının başlığının altındaki bölümde yer almalıdır.

Yazarlık için yeterli ölçütleri karşılamayan ancak çalışmaya katkısı olan tüm bireyler Teşekkür (Acknowledgement) kısmında sıralanmalıdır. Bunlara örnek olarak ise sadece teknik destek sağlayan, yazıma yardımcı olan ya da sadece genel bir destek sağlayan kişiler verilebilir. Finansal ve materyal destekleri de belirtilmelidir.

Yazıya materyal olarak destek veren ancak yazarlık için gerekli ölçütleri karşılamayan kişiler "klinik araştırıcılar" ya da "yardımcı araştırıcılar" gibi başlıklar altında toplanmalı ve bunların işlevleri ya da katılımları "bilimsel danışmanlık yaptı", "çalışma önerisini gözden geçirdi", "veri topladı" ya da "çalışma hastalarının bakımını üstlendi" şeklinde belirtilmelidir. Teşekkür (Acknowledgement) kısmında belirtilen bu ifadeler için bu bireylerden de yazılı izin alınması gerekmektedir.

Bütün yazarlar, araştırmanın sonuçlarını ya da bilimsel değerlendirmeyi etkileyebilme potansiyeli olan finansal ilişkiler, çıkar çatışması ve çıkar rekabetini beyan etmelidirler. Bir yazar kendi yayınlanmış yazısında belirgin bir hata ya da yanlışlık tespit ederse, bu yanlışlıklara ilişkin düzeltme ya da geri çekme için yayın yönetmeni ile hemen temasa geçme ve işbirliği yapma sorumluluğunu taşır. Yazarların katkısını belirten Yazar Katkı Formu ve çıkar çatışması olup olmadığını belirten ICMJE Potansiyel Çıkar Çatışması Beyan Formu makale ile birlikte gönderilmelidir. Yazarların görevleri ve sorumlulukları ICMJE yönergelerine dayandırılmaktadır.

Editör ve Hakem Sorumlulukları ve Değerlendirme Süreci

Editörler, makaleleri, yazarların etnik kökeninden, cinsiyetinden, cinsel yöneliminden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Yayına gönderilen makalelerin adil bir şekilde çift taraflı kör hakem değerlendirmesinden geçmelerini sağlarlar. Gönderilen makalelere ilişkin tüm bilginin, makale yayınlanana kadar gizli kalacağını garanti ederler. Editörler içerik ve yayının toplam kalitesinden sorumludurlar. Gereğinde hata sayfası yayınlamalı ya da düzeltme yapmalıdırlar.

Genel Yayın Yönetmeni; yazarlar, editörler ve hakemler arasında çıkar çatışmasına izin vermez. Hakem atama konusunda tam yetkiye sahiptir ve Bağcılar Tıp Bülteni'nde yayınlanacak makalelerle ilgili nihai kararı vermekle yükümlüdür. Dergide yayın etiği hususunda COPE yönergeleri izlenmektedir.

Hakemler makaleleri, yazarların etnik kökeninden, cinsiyetinden, cinsel yöneliminden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Araştırmayla ilgili, yazarlarla ve/veya araştırmanın finansal destekçileriyle çıkar çatışmaları olmamalıdır. Değerlendirmelerinin sonucunda tarafsız bir yargıya varmalıdırlar. Hakemler yazarların atıfta bulunmadığı konuyla ilgili yayınlanmış çalışmaları tespit etmelidirler. Gönderilmiş yazılara ilişkin tüm bilginin gizli tutulmasını sağlamalı ve yazar tarafında herhangi bir telif hakkı ihlali ve intihal fark ederlerse Genel Yayın Yönetmeni`ne raporlamalıdırlar. Hakem, makale konusu hakkında kendini vasıflı hissetmiyor ya da zamanında geri dönüş sağlaması mümkün görünmüyorsa, Baş Editör`e bu durumu bildirmeli ve hakem sürecine kendisini dahil etmemesini istemelidir.

Editör makalelerle ilgili bilgileri (makalenin alınması, içeriği, gözden geçirme sürecinin durumu, hakemlerin eleştirileri ya da varılan sonuç) yazarlar ya da hakemler dışında kimseyle paylaşmaz.

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Değerlendirme sürecinde editör hakemlere gözden geçirme için gönderilen makalelerin, yazarların özel mülkü olduğunu ve bunun imtiyazlı bir iletişim olduğunu açıkça belirtir. Hakemler ve yayın kurulu üyeleri topluma açık bir şekilde makaleleri tartışamazlar. Hakemlerin kendileri için makalelerin kopyalarını çıkarmalarına izin verilmez ve editörün izni olmadan makaleleri başkasına veremezler. Hakemler gözden geçirmelerini bitirdikten sonra makalenin kopyalarını yok etmeli ya da editöre göndermelidirler. Dergimiz editörü de reddedilen ya da geri verilen makalelerin kopyalarını imha etmelidir.

Yazarın ve editörün izni olmadan hakemlerin gözden geçirmeleri basılamaz ve açıklanamaz. Hakemlerin kimliğinin gizli kalmasına özen gösterilmelidir. Bazı durumlarda editörün kararıyla, ilgili hakemlerin makaleye ait yorumları aynı makaleyi yorumlayan diğer hakemlere gönderilerek hakemlerin bu süreçte aydınlatılması sağlanabilir. Değerlendirme süreciyle ilgili COPE yönergeleri izlenmektedir.

Açık Erişim İlkesi

Açık erişimli bir yayın olan Bağcılar Tıp Bülteni dergisinin tüm içeriği okura ya da okurun dahil olduğu kuruma ücretsiz olarak sunulur. Okurlar, yayıncı ya da yazardan izin almadan dergi makalelerinin tam metnini okuyabilir, indirebilir, kopyalayabilir, dağıtabilir, basabilir, arayabilir ve link sağlayabilir.

Yayın Etiği

İlke ve Standartlar

Bağcılar Tıp Bülteni yayın etiğinde en yüksek standartlara bağlıdır ve Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) ve International Committee of Medical Journals (ICJME) tarafından geliştirilen yayın etiği ilkelerini ve tavsiyelerini gözetir.

Gönderilen tüm makaleler orijinal, yayınlanmamış (konferans bildirilerindeki tam metinler de dahil) ve başka bir dergide değerlendirme sürecinde olmamalıdır. Her bir makale editörlerden biri ve en az iki hakem tarafından çift kör değerlendirmeden geçirilir. Gönderilen makaleleri intihal yazılımı ile denetleme hakkımız haklıdır. İntihal, veride hile ve tahrif (araştırma verisi, tabloları ya da imajlarının manipülasyonu ve asılsız üretimi), insan ve hayvanların araştırmada uygun olmayan kullanımı konuları denetimden geçmektedir. Bu standartlara uygun olmayan tüm makaleler yayından çıkarılır. Buna yayından sonra tespit edilen olası kuraldışı, uygunsuzluklar içeren makaleler de dahildir. Yayın etiği kurallarına bağlı olarak, intihal şüphesini ve duplikasyon durumlarını rapor edeceğimizi belirtiriz. Olası bilimsel hatalı davranışları ve yayın etiği ihlali vakalarını ele alırken COPE Ethics Flowcharts izlenir.

İnsan ve Hayvan Hakları, Bilgilendirilmiş Olur, Çıkar Çatışması

Bağcılar Tıp Bülteni, yayınladığı makalelerin ticarî kaygılardan uzak ve konu ile ilgili en iyi etik ve bilimsel standartlarda olması şartını gözetmektedir. Makalelerin etik kurallara uygunluğu yazarların sorumluluğundadır.

Bağcılar Tıp Bülteni, 2013 yılında revize edilen Helsinki Deklarasyonu “Ethical Principles for Medical Research Involving Human Subjects”e ve 2006 yılında revize edilen WMA Statement on Animal Use in Biomedical Research’e uymayı prensip edinmiştir. Bu yüzden dergide yayınlanmak üzere gönderilen yazılarda, klinik deneylere katılan denekler ile ilgili olarak yukarıda belirtilen etik standartlara uyulduğunun mutlaka belirtilmesi gerekmektedir. Ayrıca deneyin türüne göre gerekli olan yerel veya ulusal etik komitelerden alınan onay yazıları yazı ile birlikte gönderilmelidir. Bununla birlikte deneye katılan kişi/hastalardan, hastalar eğer temyiz kudretine sahip değilse vâsilerinden yazılı bilgilendirilmiş onam alındığını belirten bir yazı ile beraber tüm yazarlar tarafından imzalanmış bir belgenin editöre gönderilmesi gerekmektedir.

Hastalardan izin alınmadan mahremiyet bozulamaz. Hastaların ismi, isimlerinin baş harfleri ya da hastane numaraları gibi tanımlayıcı bilgiler, fotoğraflar ve soy ağacı bilgileri vb. bilimsel amaçlar açısından çok gerekli olmadıkça ve hasta (ya da anne-baba, ya da vâsisi) yazılı bilgilendirilmiş onam vermedikçe basılmazlar. Özellikle olgu bildirimlerinde, çok gerekli olmadıkça hasta ile ilgili tanımlayıcı ayrıntılar çıkarılmalıdır. Örneğin, fotoğraflarda göz bölgesinin maskelenmesi kimliğin gizlenmesi için yeterli değildir. Eğer veriler kimliğin gizlenmesi için değiştirildiyse yazarlar bu değişikliklerin bilimsel anlamı etkilemediği konusunda güvence vermelidirler. Olgu sunumlarında yer verilen hastalardan bilgilendirilmiş onam alınmalıdır. Bilgilendirilmiş onam alındığı da makalede belirtilmelidir.

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Bu tip çalışmaların varlığında yazarlar, makalenin YÖNTEM(LER) bölümünde bu prensiplere uygun olarak çalışmayı yaptıklarını, kurumlarının etik kurullarından ve çalışmaya katılmış insanlardan "bilgilendirilmiş onam" aldıklarını belirtmek zorundadırlar.

Çalışmada "hayvan" kullanılmış ise yazarlar, makalenin YÖNTEM(LER) bölümünde "Guide for the Care and Use of Laboratory Animals" doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadırlar. Hayvan deneyleri rapor edilirken yazarlar, laboratuvar hayvanlarının bakımı ve kullanımı ile ilgili kurumsal ve ulusal rehberlere uyup uymadıklarını yazılı olarak bildirmek zorundadırlar.

Editör ve yayıncı, reklâm amacı ile dergide yayınlanan ticari ürünlerin özellikleri ve açıklamaları konusunda hiçbir garanti vermemekte ve sorumluluk kabul etmemektedir. Eğer makalede doğrudan veya dolaylı ticarî bağlantı veya çalışma için maddî destek veren kurum mevcut ise yazarlar; kaynak sayfasında, kullanılan ticarî ürün, ilaç, ilaç firması vb. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar) bildirmek zorundadır.

Buna göre, yazar, hakem ya da editör sorumluluklarını aşırı düzeyde ve/veya haksızlığa yol açabilecek düzeyde etkileyebilecek ya da etkileyebileceği olası bir çıkar rekabeti içindeyse, çıkar çatışması söz konusudur ve bunun açıklanması gerekir. Açıklanması öngörülen çıkar çatışması tipleri, finansal bağlar, akademik taahhütler, kişisel ilişkiler, politik ya da dini inançlar, kurumsal bağlantılardır. Çıkar çatışması söz konusuysa bu makalede açıklanmalıdır.

Dergiye yayımlanmak üzere gönderilen tüm yazılar editör ve hakemlerin uzmanlığı ile Crossref Similarity Check "iThenticate" programı ve internet üzerinden arama motorlarında taranarak, intihal kontrolünden geçmektedir. İntihal taraması sonucuna göre yazılar reddedilebilir. İntihal tespit edilmesi halinde, ilgili kurumlara yazarlar hakkında ihbar yapılabilir. Bu durumda yazarlar sorumlu kurumlara çalışmalarının ham sonuçlarını teslim etmek zorunda kalabilir.

Dil

Bağcılar Tıp Bülteni`nin yayın dili Amerikan İngilizcesi'dir. Ayrıca makalelerin özleri hem İngilizce, hem Türkçe yayınlanır. Her iki dildeki özler yazarlardan istenir.

Yazıların Hazırlanması

Aksi belirtilmedikçe gönderilen yazılarla ilgili tüm yazışmalar ilk yazarla yapılacaktır. Gönderilen yazılar, yazının yayınlanmak üzere gönderildiğini ve Bağcılar Tıp Bülteni`nin hangi bölümü (Orijinal Araştırma, Kısa Araştırma, Olgu Sunumu, Derleme, Editöre Mektup) için başvurulduğunu belirten bir mektup, yazının elektronik formunu içeren Microsoft Word 2003 ve üzerindeki versiyonları ile yazılmış elektronik dosya ile tüm yazarların imzaladığı 'Telif Hakkı Devir Formu' , Yazar Katkı Formu ve ICMJE Potansiyel Çıkar Çatışması Beyan Formu eklenerek gönderilmelidir. Yazıların alınmasının ardından yazarlara makalenin alındığı, bir makale numarası ile bildirilecektir. Tüm yazışmalarda bu makale numarası kullanılacaktır. Makaleler sayfanın her bir kenarından ,5 cm kenar boşluğu bırakılarak ve çift satır aralıklı yazılmalıdır. Makalelerde aşağıdaki sıra takip edilmelidir ve her bölüm yeni bir sayfa ile başlamalıdır: 1) başlık sayfası, 2) öz, 3) metin, 4) teşekkür / 5) kaynaklar ve 6) tablo ve/veya şekiller. Tüm sayfalar sırayla numaralandırılmalıdır.

Başlık

Başlık sayfasında, yazarların adları, akademik ünvanları ve yazışılacak yazarın tam adres, telefon ve faks numaraları ile e-mail adresi mutlaka bulunmalıdır. Yazıların Türkçe özlerinde mutlaka Türkçe başlık da yer almalıdır.

Öz ve Anahtar Sözcükler

Makalenin İngilizce başlığı İngilizce özde, Türkçe başlığı da Türkçe özde yer almalıdır. Bütün makaleler öz ve anahtar kelime içermelidir. Özler bir makalenin birçok elektronik veri tabanında yer alan en belirgin kısmı olduğundan, yazarlar özün makalenin içeriğini doğru olarak yansıttığından emin olmalıdır. Öz çalışmanın temeliyle ilgili bilgi vermeli ve çalışmanın amacını, temel prosedürleri (olguların ya da laboratuvar hayvanlarının seçimi, gözlemsel ve analitik yöntemler), ana bulguları (mümkünse özgül etki büyüklüklerini ve istatistiksel anlamlılıklarını vererek) ve temel çıkarımları içermelidir. Çalışmanın ya da gözlemlerin yeni ve önemli yönleri belirtilmelidir. Anahtar sözcükler, her türlü yazıda Türkçe ve İngilizce özlerin altındaki sayfada 3-10 adet

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verilmelidir. Anahtar sözcük olarak National Library of Medicine'ın Tıbbi Konu Başlıkları'nda (Medical Subject Headings, MeSH) yer alan terimler kullanılmalıdır. MeSH'de yer alan terimlerin Türkçe karşılıklarına Türkiye Bilim Terimleri'nden erişilebilir.

Makale Türleri

Orijinal Araştırma

Orijinal araştırma makaleleri derginin kapsamına uygun konularda önemli, özgün bilimsel sonuçlar sunan araştırmaları raporlayan yazılardır. Orijinal araştırma makaleleri, Öz, Anahtar Kelimeler, Giriş, Yöntem ve Gereçler, Bulgular, Tartışma, Sonuçlar, Kaynaklar bölümlerinden ve Tablo, Grafik ve Şekillerden oluşur. Öz bölümü araştırma yazılarında aşağıda belirtilen formatta yapılandırılmış olmalıdır.

Öz

Araştırma yazılarında Türkçe ve İngilizce özler en fazla 500 kelime olmalı ve şu şekilde yapılandırılmalıdır: Amaç/Objective: Yazının birincil ve asıl amacı; Yöntem ve Gereçler/Material and Method(s): Veri kaynakları, çalışmanın iskeleti, hastalar ya da çalışmaya katılanlar, görüşme/değerlendirmeler ve temel ölçümler; Bulgular/Results: Ana bulgular; Sonuç(lar)/Conclusion(s):Doğrudan klinik uygulamalar, çıkartılacak sonuçlar belirtilmelidir.

Anahtar Kelimeler

National Library of Medicine'ın Tıbbi Konu Başlıkları'nda (Medical Subject Headings, MeSH) yer alan terimler kullanılmalıdır, en az üç anahtar kelime belirtilmelidir.

Giriş

Giriş/Introduction bölümünde konunun önemi, tarihçe ve bugüne kadar yapılmış çalışmalar, hipotez ve çalışmanın amacından söz edilmelidir. Hem ana hem de ikincil amaçlar açıkça belirtilmelidir. Sadece gerçekten ilişkili kaynaklar gösterilmeli ve çalışmaya ait veri ya da sonuçlardan söz edilmemelidir.

Yöntem ve Gereçler

Yöntem ve Gereçler/Material and Methods bölümünde, veri kaynakları, hastalar ya da çalışmaya katılanlar, ölçekler, görüşme/değerlendirmeler ve temel ölçümler, yapılan işlemler ve istatistiksel yöntemler yer almalıdır. Yöntem bölümü, sadece çalışmanın planı ya da protokolü yazılırken bilinen bilgileri içermelidir; çalışma sırasında elde edilen tüm bilgiler bulgular kısmında verilmelidir. Yöntem ve Gereçler bölümünde olguların seçimi ve tanımlanması hakkında bilgi, teknik bilgi ve istatistik hakkında bilgi yer almalıdır. Araştırmanın Etik Kurul Onayı ve katılımcılardan alınan yazılı Bilgilendirilmiş Onam belirtilmelidir.

Olguların Seçimi ve Tanımlanması

Gözlemsel ya da deneysel çalışmaya katılanların (hastalar, hayvanlar, kontroller) seçimi, kaynak popülasyon, çalışmaya alınma ve çalışmadan dışlanma ölçütleri açıkça tanımlanmalıdır. Yaş ve cinsiyet gibi değişkenlerin çalışmanın amacıyla olan ilişkisi her zaman açık olmadığından yazarlar çalışma raporundaki kullanımlarını açıklamalıdır; örneğin yazarlar niçin sadece belli bir yaş grubunun alındığını ya da neden kadınların çalışma dışında bırakıldığını açıklamalıdır. Çalışmanın niçin ve nasıl belli bir şekilde yapıldığı açık bir şekilde belirtilmelidir. Yazarlar etnisite ya da ırk gibi değişkenler kullandıklarında bu değişkenleri nasıl ölçtüklerini ve geçerliklerini açıklamalıdır.

Teknik Bilgi

Diğer çalışmacıların sonuçları yineleyebilmesi için yöntem ve kullanılan araçlar (üretici firma ve adres paragraf içinde belirtilerek) ayrıntılı bir şekilde belirtilmelidir. Önceden kullanılan bilinen yöntemler için (istatistiksel yöntemler dahildir) kaynak gösterilmeli, basılmış ama iyi bilinmeyen bir yöntem için kaynak verilmeli ve yöntem açıklanmalıdır. Aynı şekilde yeni ya da belirgin olarak modifiye edilmiş yöntemler tanımlanmalı ve kullanılma nedenleri belirtilip kısıtlılıkları değerlendirilmelidir. Kullanılan tüm ilaç ve

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kimyasallar doğru olarak tanımlanıp jenerik isimleri, dozları ve kullanım biçimleri belirtilmelidir. Gözden geçirme yazısı gönderen yazarlar veriyi bulma, seçme, ayırma ve sentezleme yöntemlerini belirtmelidir. Bu yöntemler aynı zamanda özde de yer almalıdır.

İstatistik

İstatistiksel yöntem, orijinal veriye erişebilecek bilgili bir okuyucunun rapor edilen sonuçları onaylayabileceği bir ayrıntıda belirtilmelidir. Mümkünse, bulgular niceliksel hale getirilmeli ve hata ölçümleri (güvenlik aralıkları gibi) sunulmalıdır. Etki büyüklüğünü vermeyen, p değerlerinin kullanımı gibi, salt istatistiksel hipotez sınamasına dayanılmamalıdır. Çalışma deseni ve istatistiksel yönteme dair kaynaklar sayfalar belirtilerek mümkün olduğu sürece standart kaynaklar olmalıdır. İstatistiksel terimler, kısaltmalar ve semboller tanımlanmalıdır. Kullanılan bilgisayar programı belirtilmelidir.

Bulgular

Ana bulgular istatistiksel verilerle desteklenmiş olarak eksiksiz verilmeli ve bu bulgular uygun tablo, grafik ve şekillerle görsel olarak da belirtilmelidir. Bulgular yazıda, tablolarda ve şekillerde mantıklı bir sırayla önce en önemli sonuçlar olacak şekilde verilmelidir. Tablo ve şekillerdeki tüm veriyi yazıda vermemeli, sadece önemli noktaları vurgulanmalıdır. Ekstra materyal ve teknik bilgi ek kısmında verilerek yazının akışının bozulmaması sağlanmalı, alternatif olarak bunlar sadece elektronik versiyonda yer almalıdır.

Tartışma

Tartışma/Discussion bölümünde o çalışmadan elde edilen veriler, kurulan hipotez doğrultusunda hipotezi destekleyen ve desteklemeyen bulgular ve sonuçlar irdelenmeli ve bu bulgu ve sonuçlar literatürde bulunan benzeri çalışmalarla kıyaslanmalı, farklılıklar varsa açıklanmalıdır. Çalışmanın yeni ve önemli yanları ve bunlardan çıkan sonuçları vurgulanmalıdır. Giriş ya da sonuçlar kısmında verilen bilgi ve veriler tekrarlanmamalıdır.

Sonuçlar

Sonuçlar/Conclusions bölümünde çalışmadan çıkarılan sonuçlar sıralanmalıdır. Deneysel çalışmalar için tartışmaya sonuçları kısaca özetleyerek başlamak, daha sonra olası mekanizmaları ya da açıklamaları incelemek ve bulguları önceki çalışmalarla karşılaştırmak, çalışmanın kısıtlılıklarını özetlemek, gelecekteki çalışmalar ve klinik pratik için uygulamalarını belirtmek faydalıdır. Varılan sonuçlar çalışmanın amacıyla karşılaştırılmalı, ancak elde edilen bulgular tarafından yeterince desteklenmeyen çıkarımlardan kaçınılmalıdır. Yazarlar, eğer elde ettikleri veriler ekonomik veri ve analizler içermiyorsa, ekonomik çıkar ya da faydalarla ilgili yorumlardan özellikle kaçınılmalıdır. Gerektiğinde yeni hipotezler ortaya konmalı, ancak bunların yeni hipotezler olduğu belirtilmelidir.

Tablo, Grafik ve Şekiller

Yazı içindeki grafik, şekil ve tablolar Arap sayıları ile numaralandırılmalıdır. Şekillerin metin içindeki yerleri belirtilmelidir. Ayrıntılı bilgi aşağıda ilgili başlık altında yer almaktadır.

Kısa Araştırma

Kısa Araştırma makaleleri tarz ve format açısından Orijinal Araştırma makaleleri gibidir; ancak daha küçük ölçekli araştırmaları ya da geliştirme çalışmasının erken aşamalarında olan araştırmaları ele alır. Basit araştırma tasarımı kullanan ön çalışmalar, sınırlı pilot veri sağlayan küçük örnek kitle ile yapılan çalışmalar, ileri araştırma gereksinimine işaret eden başlangıç bulguları bu tür araştırmalar kapsamında sayılabilir. Kısa Araştırma makaleleri, büyük ölçekli gelişkin araştırma projelerini konu alan Orijinal Araştırma makalelerinden daha kısadır. Ancak Kısa Araştırma, Orijinal Araştırma makalesi olabilecek kalitede bir araştırma makalesinin kısa versiyonu olarak anlaşılmamalıdır; önem derecesi düşük, titizlikle yapılmamış bir araştırma hakkında bir yayın malzemesi hazırlamak için kullanılmamalıdır ya da genişletildiğinde Orijinal Araştırma makalesi ya da araştırma niteliği kazanmayacak bir içeriği değerlendirecek bir makale türü olarak anlaşılmamalıdır.

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Olgu Sunumu

Olgu sunumu makaleleri özgün vakaları rapor eden yazılardır. Derginin kapsamına giren konulara ilişkin bir problemin üstesinden gelen tedaviyle ilgili, yeni araçlar, teknikler ve metotlar göstererek okuyucular için bilgilendirme sağlamalıdır. Olgu sunumu yazıları Öz (özün araştırma makalesinde olduğu gibi belli bir formatta yapılandırılmış olması gerekmiyor), Anahtar Kelimeler, Giriş, Olgu Sunumu, Tartışma, Referanslar, gerekirse Tablo ve açıklayıcı bilgilerden oluşur. Olgu sunumunda yazılı bilgilendirilmiş onam alınmalı ve makalede belirtilmelidir.

Derleme

Derleme makaleleri alanında zengin birikime ve atıf alan çalışmalara sahip uzman kişilerce yazılan yazılardır. Klinik pratiğe ilişkin bir konuda mevcut bilgiyi tanımlayan, değerlendiren ve tartışan; geleceğe ilişkin çalışmalara yol gösteren derleme yazıları yazmaları için dergi belirlediği yazarlara davet gönderir. Derleme makaleleri, Öz (özün, araştırma makalesinde olduğu gibi belli bir formatta yapılandırılmış olması gerekmiyor), Anahtar Kelimeler, Giriş, Sonuç bölümlerinden oluşur. Derleme makale gönderen yazarların, makalede kullandıkları verinin seçimi, alınması, sentezi için kullandıkları yöntemleri tanımlayan bir bölüme de makalede yer vermeleri gerekir. Bu yöntemler Öz bölümünde de belirtilmelidir.

Editöre Mektup

Editöre Mektup, kısa ve net görüş bildiren yazılardır. Dergide daha önce yayınlanmış olan makalelerle ilgili olarak ya da dergide ifade edilmiş görüşlerle ilgili olarak yazılmış olması tercih edilir. Editöre Mektup yazıları, daha sonra yeni bir yazı ile geçerlilik ispatı gerektirebilecek ön görüş bildiren yazılar olmamalıdır.

Tablolar

Tablolar bilgileri etkin bir şekilde gösterir ve ayrıca bilginin istenen tüm ayrıntı seviyelerinde verilmesini sağlar. Bilgileri metin yerine tablolarda vermek genelde metnin uzunluğunu kısaltır.

Her tablo ayrı bir sayfaya çift aralıklı olarak basılmalıdır. Tablolar metindeki sıralarına göre numaralanıp, her birine kısa bir başlık verilmelidir. MS Word 2003 ve üstü versiyonlarında otomatik tablo seçeneğinde “tablo klasik 1” ya da “tablo basit 1” seçeneklerine göre tablolar hazırlanmalıdır. Başlık satırı ve tablo alt üst satırları dışında tablonun içinde başka dikey ve yatay çizgiler kullanılmamalıdır. Her sütuna bir başlık verilmelidir. Yazarlar açıklamaları başlıkta değil, dipnotlarda yapmalıdır. Dipnotlarda standart olmayan tüm kısaltmalar açıklanmalıdır. Dipnotlar için sırasıyla şu semboller kullanılmalıdır: (*,†,‡,§,ǁ,¶,**,††,‡‡).

Varyasyonun standart sapma ya da standart hata gibi istatistiksel ölçümleri belirtilmelidir. Metin içinde her tabloya atıfta bulunulduğuna emin olunmalıdır. Eğer yayınlanmış ya da yayınlanmamış herhangi başka bir kaynaktan veri kullanılıyorsa izin alınmalı ve onlar tam olarak bilgilendirilmelidir. Çok fazla veri içeren tablolar, çok yer tutar ve sadece elektronik yayınlar için uygun olabilir ya da okuyuculara yazarlar tarafından doğrudan sağlanabilir. Böyle bir durumda uygun bir ifade metne eklenmelidir. Bu tip tablolar, hakem değerlendirmesinden geçmesi için makaleyle beraber gönderilmelidir.

Şekiller

Şekiller ya profesyonel olarak çizilmeli ve fotoğraflanmalı ya da fotoğraf kalitesinde dijital olarak gönderilmelidir. Şekillerin basıma uygun versiyonlarının yanı sıra JPEG ya da GIF gibi elektronik versiyonlarda yüksek çözünürlükte görüntü oluşturacak biçimlerde elektronik dosyaları gönderilmeli ve yazarlar göndermeden önce bu dosyaların görüntü kalitelerini bilgisayar ekranında kontrol etmelidir.

Röntgen, CT, MRI filmleri ve diğer tanısal görüntülemeler yüksek kalitede basılmış olarak gönderilmelidir. Bu nedenle şekillerin üzerindeki harfler, sayılar ve semboller açık ve tüm makalede eşit ve yayın için küçültüldüklerinde bile okunabilecek boyutlarda olmalıdır. Şekiller mümkün olduğunca tek başlarına anlaşılabilir olmalıdır. Fotomikrografik patoloji preparatları iç ölçekler içermelidir. Semboller, oklar ya da harfler fonla kontrast oluşturmalıdır. Eğer insan fotoğrafı kullanılacaksa, ya bu kişiler fotoğraftan tanınmamalıdır ya da yazılı izin alınmalıdır (Etik bölümüne bakınız).

Şekiller metinde geçiş sıralarına göre numaralandırılmalıdır. Eğer önceden yayınlanmış bir şekil kullanılacaksa, yayın hakkını elinde bulunduran bireyden izin alınmalıdır. Toplum alanındaki belgeler hariç yazarlığa ve yayıncıya bakılmadan bu izin gereklidir.

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Basılacak bölgeyi gösteren ek çizimler editörün işini kolaylaştırır. Renkli şekiller editör gerekli gördüğünde ya da sadece yazar ek masrafı karşılarsa basılır.

Şekillerin Dipnotları

Ayrı bir sayfadan başlayarak şekiller için tablo başlıkları ve dipnotları tek aralıklı olarak ve Arap sayıları ile hangi şekle karşı geldikleri belirtilerek yazılmalıdır. Semboller, oklar, sayılar ya da harfler şeklin parçalarını belirtmek için kullanıldığında, dipnotlarda her biri açıkça tanımlanmalıdır. Fotomikrografik patoloji preparatlarında iç ölçek ve boyama tekniği açıklanmalıdır.

Ölçüm Birimleri

Uzunluk, ağırlık ve hacim birimleri metrik (metre, kilogram, litre) sistemde ve bunların onlu katları şeklinde rapor edilmelidir. Sıcaklıklar Celsius derecesi, kan basıncı milimetre civa cinsinden olmalıdır. Ölçü birimlerinde hem lokal hem de Uluslararası Birim Sistemleri (International System of Units, SI) kullanılmalıdır. İlaç konsantrasyonları ya SI ya da kütle birimi olarak verilir, alternatif olarak parantez içinde de verilebilir.

Kısaltmalar ve Semboller Sadece standart kısaltmaları kullanın, standart olmayan kısaltmalar okuyucu için çok kafa karıştırıcı olabilir. Başlıkta kısaltmadan kaçınılmalıdır. Standart bir ölçüm birimi olmadıkça kısaltmaların uzun hali ilk kullanılışlarında açık, kısaltılmış hali parantez içinde verilmelidir.

Teşekkür(ler)

Yazının sonunda kaynaklardan önce yer verilir. Bu bölümde kişisel, teknik ve materyal yardımı gibi nedenlerle yapılacak teşekkür ifadeleri yer alır.

Kelime Sayısı Sınırlandırması

Türkçe ve İngilizce özler en fazla 500 kelime olmalıdır. Orijinal makaleler ve derleme yazılarında özel bir kelime sayısı sınırlandırması yoktur. Olgu sunumları öz /abstract hariç 1000 kelime ile sınırlandırılmalı ve en az sayıda şekil, tablo ve kaynak içermelidir. Editöre mektuplar (en fazla 1000 kelime, tablosuz ve şekilsiz) olmalı ve mektup, tüm yazarlar tarafından imzalanmış olmalıdır. Bağcılar Tıp Bülteni`nde yayınlanmış olan bir yazı ile ilgili eleştiri ya da değerlendirme niteliğindeki mektuplar sözü edilen yazının yayınlanmasından sonraki 12 hafta içinde alınmış olmalıdır.

Makale Hazırlığı

"Bağcılar Tıp Bülteni", Tıp Dergilerinde Bilimsel Çalışmaların Yürütülmesi, Raporlanması, Düzenlenmesi ve Yayınlanmasına İlişkin Yönergeleri takip eder "(Uluslararası Tıp Dergisi Editörleri Komitesi ICMJE). Makalenin sunulması üzerine, yazarlar deneme/araştırma türünü belirtmeli ve uygun olduğunda aşağıdaki kuralların kontrol listesini sağlamalıdır:

Randomize çalışmalar için CONSORT beyanı (CONSORT Grubu için Moher D, Schultz KF, Altman D. CONSORT beyanı paralel grup randomize çalışmaların raporlarının kalitesini iyileştirmek için önerileri gözden geçirdi. JAMA 2001; 285: 1987-91),

Sistematik gözden geçirmeler ve meta-analizler için tercih edilen raporlama maddeleri için PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Grubu. Sistematik İncelemeler ve Meta-Analizler için Tercih Edilen Raporlama Maddeleri: PRISMA Beyanı. PLoS Med 2009; 6 (7): e1000097.),

Tanısal doğruluk çalışmalarının raporlanması için STARD kontrol listesi (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, vd, STARD Grubu için. Teşhis doğruluğu çalışmalarının eksiksiz ve doğru raporlanmasına yönelik: STARD girişimi, Ann Intern Med 2003; 138: 40-4.),

STROBE gözlemsel çalışma raporlarında yer alması gereken maddelerin kontrol listesi,

Gözlemsel çalışmaların meta-analizi ve sistemik incelemeleri için MOOSE yönergeleri (Stroup DF, Berlin JA, Morton SC, vd.) Epidemiyolojideki gözlemsel çalışmaların meta-analizi: Epidemiyoloji (MOOSE) grubundaki gözlemsel çalışmaların Meta-analizini bildirme önerisi JAMA 2000; 283: 2008-12),

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CARE kuralları, vaka raporlarının doğruluğunu, şeffaflığını ve kullanışlılığını artırmak için tasarlanmıştır. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Grubu. CARE Yönergeleri: Konsensüs Tabanlı Klinik Vaka Raporlama Rehberinin Geliştirilmesi).

Kaynaklar

Kaynaklarla İlgili Genel Konular

Gözden geçirme yazıları okuyucular için bir konudaki kaynaklara ulaşmayı kolaylaştıran bir araç olsa da, her zaman orijinal çalışmayı doğru olarak yansıtmaz. Bu yüzden mümkün olduğunca yazarlar orijinal çalışmaları kaynak göstermelidir. Öte yandan, bir konuda çok fazla sayıda orijinal çalışmanın kaynak gösterilmesi yer israfına neden olabilir. Birkaç anahtar orijinal çalışmanın kaynak gösterilmesi genelde uzun listelerle aynı işi görür. Ayrıca günümüzde kaynaklar elektronik versiyonlara eklenebilmekte ve okuyucular elektronik literatür taramalarıyla yayınlara kolaylıkla ulaşabilmektedir.

Özler kaynak olarak gösterilmemelidir. Kabul edilmiş ancak yayınlanmamış makalelere atıflar "basımda" ya da "çıkacak" şeklinde verilmelidir; yazarlar bu makaleleri kaynak gösterebilmek için yazılı izin almalıdır ve makalelerin basımda olduğunu ispat edebilmelidir. Gönderilmiş ancak yayına kabul edilmemiş makaleler, "yayınlanmamış gözlemler" olarak gösterilmeli ve kaynak yazılı izinle kullanılmalıdır. Genel bir kaynaktan elde edilemeyecek temel bir konu olmadıkça "kişisel iletişimlere" atıfta bulunulmamalıdır. Eğer atıfta bulunulursa parantez içinde iletişim kurulan kişinin adı ve iletişimin tarihi belirtilmelidir. Bilimsel makaleler için yazarlar bu kaynaktan yazılı izin ve iletişimin doğruluğunu gösterir belge almalıdır.

Referans Stili ve Formatı

Tek tip kurallar esas olarak National Library of Medicine, tarafından uyarlanmış olan bir ANSI standart stilini kabul etmiştir. Kaynak atıfta bulunma örnekleri için yazarlar NIH Samples of Formatted References for Authors of Journal Articles sitesine başvurabilirler. Dergi isimleri National Library of Medicine kaynağında yer alan şekilleriyle kısaltılmalıdır. Kaynaklar yazının sonunda (Kaynaklar/References) başlığı altında metindeki geçiş sırasına göre numaralandırılıp dizilmelidir. Metin içinde ise parantez içinde belirtilmelidir. Kaynakların listesiyle metin içinde yer alış sırası arasında bir uyumsuzluk bulunmamalıdır.

Kaynaklar yazının sonunda (Kaynaklar/References) başlığı altında metindeki geçiş sırasına göre numaralandırılıp dizilmelidir. Metin içinde ise () şeklinde parantez içinde referans numarası belirtilmelidir. Kaynakların listesiyle metin içinde yer alış sırası arasında bir uyumsuzluk bulunmamalıdır.

Kaynakların doğruluğundan yazar(lar) sorumludur. Tüm kaynaklar metinde belirtilmelidir. Kaynaklar aşağıdaki örneklerdeki gibi gösterilmelidir. Altı yazardan fazla yazarı olan çalışmalarda ilk altı yazar belirtilmeli, sonrasında "ve ark." ya da "et al." ibaresi kullanılmalıdır. Kaynak dergi adlarının kısaltılması National Library of Medicine'de belirtilen kısaltmalara uygun olmalıdır. National Library of Medicine'da indekslenmeyen bir dergi kısaltılmadan yazılmalıdır.

Kaynaklar için örnekler aşağıda belirtilmiştir:

1. Dergilerdeki makaleler için örnekler: MEDLINE'da yer alan ve kısaltması MEDLINE'a göre yapılan dergi makalesi için: Crow SJ, Peterson CB, Swanson SA, Raymond NC, Specker S, Eckert ED, et al. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009;166(12):1342-1346.

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Association Between Left Sided Inguinal Hernia and Varicocele

Sol Taraflı İnguinal Herninin Varikosel ile İlişkisi

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Abstract

Objective: The aim of this study was to investigate the relationship between left sided inguinal hernia and varicocele.

Method: Between July and October 2022, 60 patients with left inguinal hernia (group 1) and 60 patients without hernia (group 2, control group) were included in our prospective study. Those with a history of right inguinal hernia, left epididymoorchitis, scrotal surgery or inguinal hernia surgery were not included in the study. The patients were evaluated for the presence of left varicocele. Grade of the varicocele, the diameters of the pampiniform plexus veins, and the neck diameter of the hernia were measured.

Results: There were 120 male patients in our study (group 1 n=60, group 2 n=60). While the age range of the patients with hernia was 23-60 years (mean age: 36±8.4 years), the age range of the patients without hernia was 20-58 years (mean age: 33±9.5 years). There was no statistically significant difference between the groups in terms of age distribution (p=0.89). While the incidence of varicocele was 58.3% (35/60) in group 1, it was 23.3% (14/60) in group 2 [relative risk 2.5 (95% confidence interval (CI) (1.507, 4.147)] and odds ratio of 4.6 [95% CI (2.091, 10.118)]. While the median grade of varicocele was 1 in group 1, it was 0 in group 2, and a statistically significant difference was found (p<0.001). Diameters of pampiniform plexus veins were found to be significantly larger in group 1 [2.402, standard deviation (SD)=0.586 vs 1.867, SD=0.375, p<0.001].

Conclusion: The risk of varicocele increases in patients with left sided inguinal hernia.

Keywords: Infertility, inguinal hernia, hernia, ultrasound, varicocele

Öz

Amaç: Bu çalışmanın amacı sol taraflı kasık fıtığı ile varikosel arasındaki ilişkiyi araştırmaktır.

Yöntem: Temmuz-Ekim 2022 tarih aralığında, sol inguinal herni saptadığımız 60 hasta (grup 1) ve herni saptamadığımız 60 hasta (grup 2, kontrol grubu) prospektif çalışmamıza dahil edildi. Sağ inguinal hernisi, sol epididimoorşit öyküsü, skrotal cerrahi veya inguinal herni cerrahisi öyküsü olanlar çalışma kapsamına alınmadı. Olgular sol varikosel varlığı açısından değerlendirildi. Varikosel derecesi, pampiniform pleksus ven çapı ve herni kesesinin boyun çapı ölçüldü.

Bulgular: Çalışmamızda toplam 120 erkek hasta mevcuttu (grup 1 n=60, grup 2 n=60). Hernisi olan hastaların yaş aralığı 23-60 yıl iken (ortalama yaş: 36±8,4 yıl), hernisi olmayan hastaların yaş aralığı 20-58 yıl (ortalama yaş: 33±9,5 yıl) idi. Yaş dağılımı açısından gruplar arasında istatistiksel anlamlı farklılık saptanmadı (p=0,89). Grup 1'de varikosel sıklığı %58,3 (35/60) görülürken, grup 2'de %23,3 (14/60) saptandı [rölatif risk 2,5 (%95 güven aralığı (GA) (1,507, 4,147)] ve olasılık oranı 4,6 [%95 GA (2,091, 10,118)]. Grup 1'de ortanca varikosel derecesi 1 iken, grup 2'de ise 0 saptanmış olup istatistiksel anlamlı farklılık saptandı (p<0,001). Pampiniform pleksus ven çapları grup 1'de anlamlı olarak daha geniş bulunmuştur [2,402, standart sapma (SS)=0,586 vs. 1,867, SS=0,375, p<0,001)].

Sonuç: Sol inguinal hernisi olan hastalarda varikosel riski artmaktadır.

Anahtar kelimeler: İnfertilite, inguinal herni, herni, ultrason, varikosel

Introduction

Inguinal hernia (IH) is the most common abdominal wall hernia (80%). There is male predominance with a male: female ratio of 7:1. The most common symptom is swelling and pain in the groin, and testicular pain can be seen in male patients. Risk factors include obesity, pregnancy, collagen vascular diseases, smoking and chronic obstructive pulmonary disease (1). Varicocele is a condition found in 15% of all males, 35% of males with primary infertility and

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approximately 80% of males with secondary infertility (2). Varicocele is mostly seen on the left side (80-90%) and it has been reported that the opening of the left testicular vein at right angles to the left renal vein and the consequent turbulent flow and increase in back pressure towards the testicular vein play a role in the etiology (3). There are studies reporting that varicocele is associated with IH (4) and connective tissue diseases (5). It has been reported that IH is also associated with collagen vascular diseases and there may be a connection with connective tissue diseases in its etiology (6). In the current study, the frequency and grade of varicocele were determined to be increased in cases with IH.

The purpose of this study was to evaluate the presence of varicocele in patients with left-sided IH. The study hypothesis was that the risk and degree of varicocele would be increased in patients with left-sided IH due to its association with collagen vascular diseases and the compression effect.

Materials and Methods

This prospective study included 60 patients (group 1) who were referred to our ultrasound unit with the suspicion of IH and possible scrotal extension, and were diagnosed with left IH for the first time between July 2022 and October 2022. In addition, 60 patients in the same age range who were referred to the ultrasound unit with same clinical findings and hernia was not detected were included in the study as the control group (group 2).

Patients with right-sided IH were excluded from the study because of other possible underlying retroperitoneal pathologies in terms of varicocele. Patients with comorbidities that may be associated with varicocele such as hyperlipidemia, diabetes mellitus and hyperlipidemia were also excluded from the study, as were those with a history of left epididymoorchitis, scrotal surgery or IH surgery. Both groups were evaluated for the presence of a left-sided varicocele. During ultrasound examination, the grade of varicocele, diameter of pampiniform plexus veins and neck diameter of the hernia were measured. The groups were compared in respect of statistically significant differences.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee (University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, reference number: 2022-14-10, 18/07/2022) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All individuals were fully informed and gave their written informed consent.

Imaging Technique

The patient was asked to undress and lie on his back with his legs together. A towel was placed between the legs and under the scrotum to support the testicles. The penis was placed on the abdomen and only the scrotum was exposed. A linear array 7-15 MHz transducer (Samsung RS85) was used. Transverse and longitudinal views of each testis were obtained. The inguinal canal was included in the examination. Color Doppler and spectral Doppler were used for varicocele. At least one image showing both testicles was acquired on the same image to compare overall testicular echogenicity.

Evaluation of IH

The presence of adipose tissue or intestinal loop herniation into the left inguinal canal at rest or during the valsalva maneuver was examined. The neck diameter of the hernia was measured.

Evaluation of Varicocele

Presence of varicocele was examined in both the supine and standing positions. Diameter of pampiniform plexus vein was measured. Largest vein diameter, irrespective of location, being more than 2 mm is considered abnormal. The presence of reflux was examined during the valsalva maneuver. Varicocele was classified into five grades according to the Sarteschi classification (7).

Statistical Analysis

All statistical analyses were performed using a commercially available SPSS release 20.0 software package (SPSS Inc., Chicago, IL, USA). In statistical analysis, Pearson chi-squared test (x^2), Mann-Whitney U test where appropriate was used to compare the distribution of categorical data relative to each other. One-Way ANOVA test was used in terms of age distribution of the groups. A p-value <0.05 was considered to show a statistically significant result.

Results

Evaluation was made of a total of 120 male patients, as 60 in group 1, and 60 in group 2. The mean age was 36±8.4 years (range, 23-60 years) in group 1, and 33±9.5 years (range, 20-58 years) in group 2. There was no statistically significant difference between the groups in terms of age distribution (p=0.89).

The incidence of varicocele was determined as 58.3% (35/60) in group 1, and 23.3% (14/60) in group 2 (Table 1). The relative risk was calculated as 2.5 [95% confidence interval (CI) (1.507, 4.147)] and the odds ratio as 4.6 [95% CI (2.091, 10.118)] (Figure 1).

The median grade of varicocele was 1 in group 1, and 0 in group 2, and the difference was determined to be statistically significant (p<0.001) (Figure 2).

The Mann-Whitney U test was used to compare the diameter of the pampiniform plexus vein, which was found to be significantly larger in the hernia group [2.402, standard deviation (SD)=0.586 vs. 1.867, SD=0.375, p<0.001] (Table 2).

No significant correlation was determined between the diameter of the hernia neck and the diameter of the pampiniform plexus vein in the hernia group (r=-0.06, p=0.66).

In the hernia group, no significant difference was determined between patients with and without varicocele in terms of diameter of the neck (mean diameter was 13.5 mm in those with varicocele and 14.9 mm in those without varicocele, p=0.27) (Table 3).

Table 1. Distribution of hernia and varicocele

	Varicocele (+) n=49	Varicocele (-) n=71
Hernia (+) n=60	35 (58.3%)	25 (41.7%)
Hernia (-) n=60	14 (23.3%)	46 (76.7%)

Discussion

The principal findings of this study demonstrate that the risk of varicocele increases in patients with left sided IH. An increased prevalence of varicocele was seen in patients with IH (58.3%) compared to the prevalence of varicocele in patients without IH (23.3%) and the prevalence in the general population (15%) reported in the literature (8-10). Some studies in the literature have investigated diseases that may be associated with varicocele. El-Tatawy et al. (11) reported an increased risk of varicocele over time in adolescent patients with a history of epididymoorchitis. Wang et al. (12) investigated the relationship between varicocele and vascular diseases and stated that the risk of heart disease, diabetes and hyperlipidemia was increased in patients with varicocele, especially in symptomatic individuals. It was suggested that the decrease in testosterone level, hypogonadism and oxidative stress developing in the background of varicocele may increase the risk of metabolic and vascular diseases. In a study by Tsukanov et al. (13), a high rate (87.2%) of connective tissue dysplasia findings such as asthenic body type, arrhythmia, arterial hypotension and disturbed tooth growth were found in cases with varicocele, and it was stated that varicocele may be a manifestation of connective tissue dysplasia. Similarly, Serra et al. (5) stated that the detection of varicocele at a young age may be an early marker for the progression of a connective tissue-related disease such as IH and chronic venous disease at older ages.

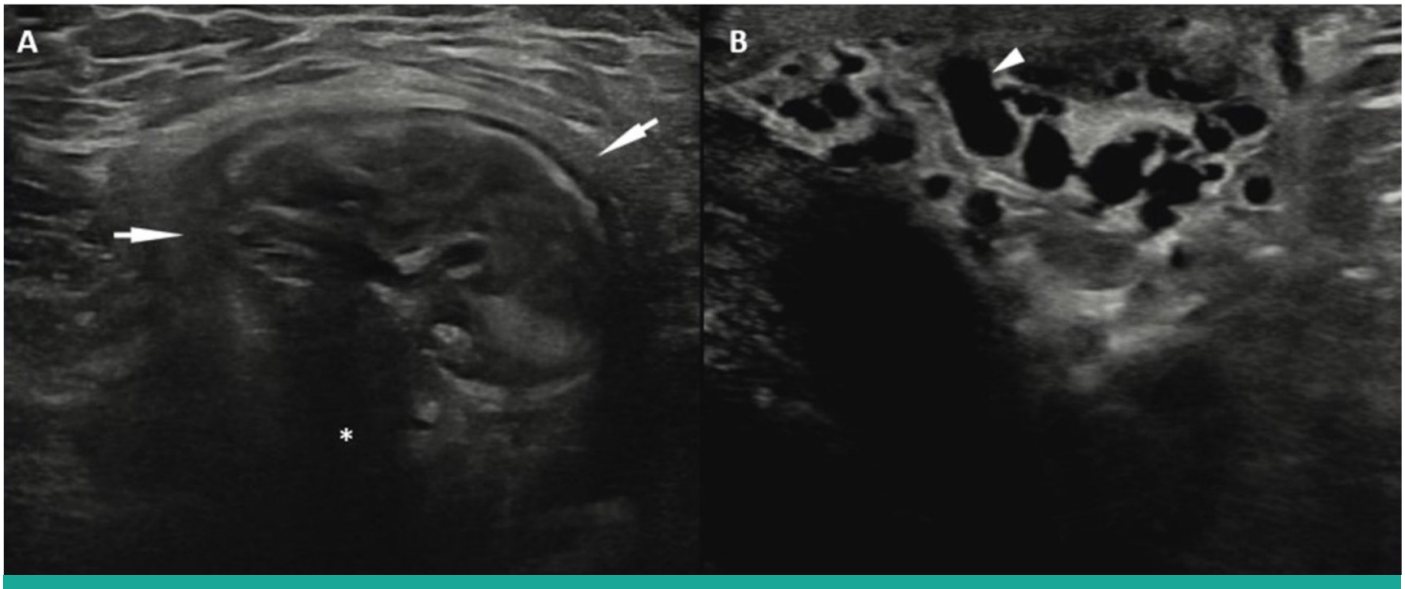

Figure 1. Ultrasound examination shows marked inguinal hernia (A, arrows) with neck of hernia (A, star) and accompanying enlarged pampiniform plexus veins consistent with varicocele (B, arrowhead)

The only study in the literature [Albuz et al. (4)], conducted with a similar method to the current study, investigated the role of IH in the development of varicocele in the young age group and found that the risk of varicocele was increased in hernia cases. It was stated that the development of varicocele may be secondary to compression of the testicular vein, or in some cases, to some enzymatic or biochemical disorders that may play a role in the development of both hernia and varicocele. However, that study (4) was retrospective, right hemiscrotum was included in the study (due to possible non-hernial pathologies that may cause secondary varicocele), and its surgical history was not known were disadvantages. Therefore, the current study can be considered more specific research. In addition, the neck diameter of the hernia, the diameter of pampiniform plexus veins and grade of varicocele were examined in the current study, and vein diameter and mean grade of varicocele were found to be higher in cases of IH.

When evaluated together with the literature (4,5,13), we thought that the increased risk of varicocele in cases of hernia may be secondary to the high risk of connective tissue-related disease in these cases or compression of testicular vein due to IH or both. Physiopathology is remain unclear. Although the treatment of varicocele has not been standardised, it is usually determined according to the fertility status of the patient. In the current study, since the grade of varicocele was higher in patients with IH, it was assumed that the risk of infertility may be higher in these patients. Therefore, hernia can be a guiding finding in terms of varicocele treatment. There is a need for further studies in this direction supported by clinical and laboratory findings.

Study Limitations

Our study has some limitations. The first is the limited number of patients, and second is the lack of clinical and laboratory characteristics.

Conclusion

The risk of varicocele increases in patients with left-sided IH. As the higher grade of varicocele in these patients poses a risk for infertility, hernia may be a guide for treatment of varicocele which does not have a standard treatment. More comprehensive studies supported by clinical findings are needed.

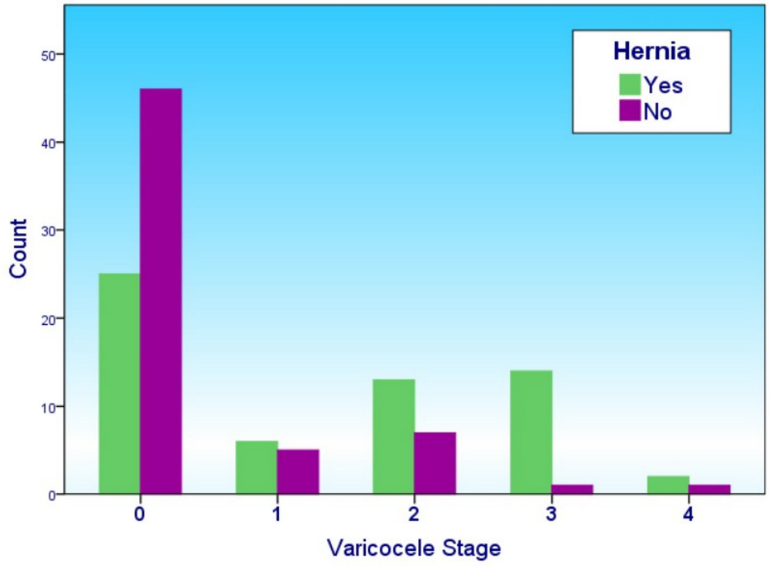

Figure 2. The present graphic shows grades of varicocele in patients with and without inguinal hernia

Table 2. Mean diameter of pampiniform plexus vein (DPPV) with standard deviation (SD) in patients with and without hernia

	DPPV	SD
Hernia (+) n=60	2.402 mm	0.586
Hernia (-) n=60	1.867 mm	0.375
p-value	p<0.001	

Table 3. Mean diameter of the neck of hernia (DNH) in patients with and without varicocele in the hernia group

	Varicocele (+) n=14	Varicocele (-) n=46
DNH	13.5 mm	14.9 mm
p-value	p=0.27	

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee (University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, reference number: 2022-14-10, 18/07/2022) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: All individuals were fully informed and gave their written informed consent.

Peer-review: Internally and externally peer-reviewed.

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ORIGINAL RESEARCH

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Evaluation of Preoperative Hematological Parameters in Patients with Endometrial Adenocarcinoma

Endometrium Adenokanserli Hastalarda Preoperatif Hematolojik Parametrelerin Değerlendirilmesi

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Abstract

Objective: The aim of the study was to compare mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), eosinophil-lymphocyte ratio (ELR), platelet/lymphocyte ratio (PLR) between the patients diagnosed as low-risk or intermediate-advanced risk endometrial cancer and those with benign endometrial pathology.

Method: The study included patients who underwent hysteroscopy, dilatation curettage, or endometrial biopsy with endometrial sampling due to abnormal uterine bleeding between March 2014 and April 2022. The groups were formed according to the pathology report of endometrial sampling. In addition, subgroup analysis was made based on intraoperative frozen evaluation and final pathology results. Group 1 included benign endometrial pathology; group 2 included low-risk endometrial adeno cancer cases; and group 3 were those with endometrial adeno cancer other than low-risk endometrial cancer.

Results: No statistically significant difference was found between the groups in terms of neutrophil count, lymphocyte count, platelet count, eosinophil count, MPV, PDW, NLR, MLR, ELR, PLR (p>0.05). Endometrial thickness, body mass index, advanced age were found to be statistically significant in the endometrial adeno cancer groups.

Conclusion: MPV, NLR, ELR, MLR, and PLR values did not show any difference between groups may be because systemic inflammation was not triggered in low-risk or medium-high-risk endometrial cancer.

Keywords: ELR, endometrium adeno ca, MLR, MPV, NLR, PLR

Öz

Amaç: Çalışmamızın amacı düşük riskli ve orta ileri riskli endometrium kanseri tanısı konan hastalar ile benign endometriyal patoloji tanısı konan hastaların ortalama trombosit hacmi (MPV), platelet dağılım genişliği (PDW), nötrofil/lenfosit oranı (NLO), monosit lenfosit oranı (MLO), eozinofil lenfosit oranı (ELO), trombosit/lenfosit oranı (PLO) değerlerini karşılaştırmaktır.

Yöntem: Çalışmamıza Mart 2014-Nisan 2022 tarihlerinde hastanemizde anormal uterin kanama ön tanısıyla histeroskopi, dilatasyon küretaj ya da endometriyal biyopsi ile endometriyal örnekleme yapılan hastalar dahil edilmiştir. Endometriyal örnekleme sonuçlarına göre gruplar; benign grup, malign grup olarak isimlendirildi. Ek olarak; malign grup kendi arasında intraoperatif frozen değerlendirme ve postoperatif kesin patoloji sonucuna göre iki gruba ayrılarak alt grup analizi yapıldı. Endometriyal patolojisi olmayanla grup 1, düşük riskli endomeriyal adenokanserli olgular grup 2, düşük riskili endometrun Ca dışındaki endometrum adenokanserli (orta ve daha ileri riskli endometrum adenokanserli) olgular grup 3 olarak tanımlandı.

Bulgular: Gruplar arasında nötrofil sayısı, lenfosit sayısı, trombosit sayısı, eozinofil sayısı, MPV, PDW, NLO, MLO, ELO, PLO (p>0,05) açısından istatistiksel olarak anlamlı fark bulunmadı. Endometriyal kalınlık değeri, vücut kitle indeksi, ileri yaş endometriyal kanser grubunda anlamlı bulundu.

Sonuç: Gruplar arasında MPV, NLO, ELO, MLO ve PLO değerleri istatistiksel açısından farklılık izlenmedi. Bunun sebebi düşük riskli ve de orta-yüksek riskli endometrium adenokanserinin sistemik enflamasyonu tetiklemediğinden kaynaklanmış olabilir.

Anahtar kelimeler: Endometrium adenokanser, ELO, MNO, MPV, NLO, PLO

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Introduction

The inflammation process has a critical role in tumor development and progression (1). Neutrophils, lymphocytes, and platelets are thought to have a major role in tumor inflammation and immunology (2). Platelets, neutrophils, lymphocytes, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), eosinophil-lymphocyte ratio (ELR) monocyte/lymphocyte ratio (MLR) and mean platelet volume (MPV), and platelet distribution width (PDW) were evaluated for prediction of systemic inflammatory response in various solid tumors (3). Studies have shown that hematopoietic cytokines secreted by tumor cells cause an increase in neutrophil count (4). Nitric oxide secreted from increased circulating neutrophils, and reactive oxygen radicals suppress the T-cell response and reduce lymphocytes (5). Relative lymphopenia accompanies neutrophilia and NLR increases (6). Lymphocytes have an important role in tumor defense by preventing tumor cell proliferation and migration leading to inducing cytotoxic cell death (7). Lymphopenia has been found to associated with poor prognosis in some cancers (8). An excess of neutrophils contributes to tumor growth by affecting the cytolytic activity of lymphocytes or NK cells (9). Since the physiological reaction of leukocytes to stress causes an increase in the number of neutrophils and a decrease in the number of lymphocytes, practically the ratio of neutrophil to lymphocytes has been used as an inflammation marker (10). NLR seems to be a cost-effective inflammatory marker with prognostic and predictive value in cancer and inflammatory diseases. NLR has now been shown to be a prognostic factor for lung cancer, colorectal and ovarian cancer (11,12). On the other hand, platelets have a role in cancer progression. For example, platelets can increase angiogenesis and stimulate tumor growth with cytokines and vascular endothelial growth factor (13). In conclusion, NLR and PLR in preoperative peripheral blood are increased in many cancers including colon, esophagus, stomach, ovarian and breast cancers and are thought to be associated with poor prognosis (14-17).

Endometrial cancer is the most common cancer among gynecological malignancy in developing countries, and the most common type is endometrioid endometrial cancer (18).

Patients with early diagnosis and low-risk factors have good survival rates (95%) (19). However, adjuvant therapy (radiotherapy and/or chemotherapy) is needed in the high-risk patients. The management of the disease is carried out by determining risk groups as a result of surgical staging and evaluation of risk factors (19). Low-risk, medium, medium-high and high-risk groups are defined (19). The risk group of the patient is decided by evaluating age, stage, grade of tumor, histopathological type, degree of myometrial invasion (MI), and lymphovascular space invasion (LVSI) (19). But it is thought that the above-mentioned parameters do not determine survival with sufficient accuracy (20). Therefore, new prognostic factors are needed to predict survival in patients who have endometrial cancer.

Inflammation is the most important cause in the pathophysiology of carcinogenesis. Endometrial tumor cells first develop the ability to spread locally, and then spread to the lymphatic and vascular area from the inter-endothelial cell connections. Then they metastasize to other sites. There are no well-defined risk factors and markers to predict intermediate/advanced risk for endometrial cancer preoperatively. Tumor cells cause inflammation in the uterus. Low-cost markers that can be useful in predicting this inflammation can be useful in guiding patients' treatment. NLR, NLR, PLR, ELR, MLR, MPV in blood are simple markers of systemic inflammatory response that can be easily obtained by complete blood count. The aim of this study is to determine whether the inflammation in uterus stimulates the systemic generalized inflammatory response which can be detected by the markers of the immune response.

In a study conducted on precancerous and cancerous lesions of the endometrium, white blood cell (WBC) count has been suggested in the differentiation of endometrial hyperplasia/carcinoma. Additionally, it was emphasized that patients with abnormal uterine bleeding (AUB) without pathological findings could be identified with the help of many inflammatory parameters (21).

In this study we aim to explore the values of WBC, NLR, MLR, ELR, PLR, MPV, PDW in discrimination of the benign endometrial findings and endometrioid endometrial adeno cancer also in diffentiation of the low-risk and high-risk endometrial cancer. To the best of knowledge, this is the first study evaluating the effect of WBC, NLR, MLR, ELR, PLR, MPV, PDW among low-risk and high-risk endometrial cancer patients and benign endometrial findings individually.

Materials and Methods

Ethical approval for this retrospective study was obtained from the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee and the study was approved

on 03.04.2018 with the decision number 08/03. Patients over the age of 40 who admitted to outpatient clinics suffering from AUB or post menapousal bleeding (PMB) in the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Obstetrics and Gynecology between March 2014 and April 2022, and underwent endometrial sampling for histopathological evaluation with three basic diagnostic methods such as hysteroscopy, dilatation and curettage or endometrial biopsy, were included in the study. Histopathologicaly confirmed 115 cases with endometrial cancer and 75 cases with benign findings were included in the study. The data of the cases were evaluated retrospectively. The cases were divided into 3 groups according to the pathological results. The first group is consisted of 75 cases that were found to have benign endometrial findings. In cases with endometrial cancer, operation and pathological staging were performed in accordance with the 2009 recommendations of International Federation of Gynecology and Obstetrics (22). The patients with pathologic diagnose of endometrial cancer were divided into two groups by risk stratification according to preoperative histological type, intraoperative frozen, and postoperative final pathological results. Seventy-three patients with histological type of endometrial adenocancer grade 1-2, MI less than 50%, and those with negative LVSI were considered as low-risk patients consisting group 2 (stage 1a grade 1-2, lymphovascular area invasion negative). Fourty-two cases with intermediate and high-risk endometrial adenocancer greater than stage 1a grade 1-2 were evaluated in group 3 (Figure 1).

Patients with AUB, PMB, endometrial cells in cervical cytology, and postmenopausal endometrial thickness greater than 4 mm in routine gynecologycal examination were included in the study. Exclusion criteria were as follows: Having endometrial polyp(s), endometritis, acute infection, diabetes mellitus, hypertension, autoimmune diseases, chronic inflammatory disease, liver disease, malignancy hematological disease, using some medications (recombinant granulocyte colony stimulating factor, corticosteroid, tamoxifen, anticoagulant therapy and chemotherapeutic agents, hormonal therapy in the last 12 months), history of pelvic radiation and history of blood product administration in the last 12 months. In addition, patients who underwent operations such as endometrial ablation, bilateral oophorectomy, and hysterectomy were also excluded from the study.

Demographic data such as gravida, parity, age, height, weight, endometrial sampling results, transvaginal ultrasonography findings (endometrial thickness), hematological parameters were obtained from medical records retrospectively and compared. Body mass index (BMI) was calculated by dividing the weight to the square of height. A sample of 5-7 cc peripheral venous blood taken

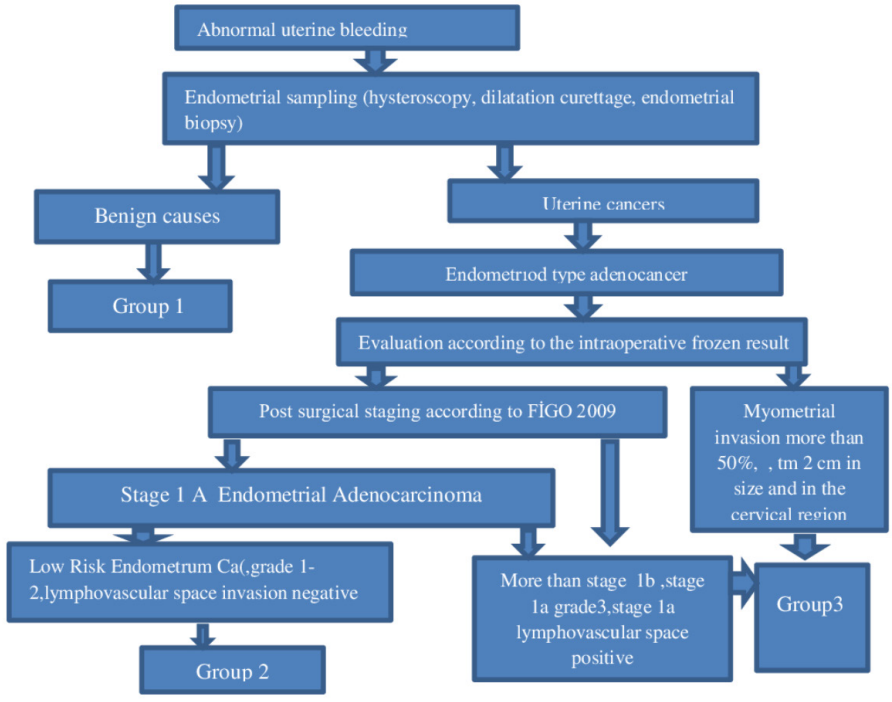

Figure 1. Shows the patients' selection flow chart

from antecybital vein and placed in a sterile EDTA tube to prevent coagulation. Hematological parameters were calculated automatically with Abbott cell dyn 3,700 blood count device within thirty minutes. MPV, PDW, eosinophil (10^3/uL), neutrophil (10^3/uL), monocyte, lymphocyte (10^3/uL) and thrombocyte (10^3/uL) counts were recorded. The ratio of ELR, MLR, NLR and PLR was calculated using these parameters. The values of MPW, PDW, NLR, PLR, MLR, ELR which are considered systemic inflammatory markers in patients diagnosed with low-risk endometrial ca, moderate-high-risk endometrial ca, and patients with benign endometrial findings were compared with each other.

Statistical Analysis

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis. Shapiro-Wilk normality tests were used to check whether the variables follow a normal distribution. In addition to descriptive statistical methods (mean, standard deviation, frequency), One-Way ANOVA test was used for the comparison of the normally distributed quantitative variables, and the Tamhane's T2 test was used to determine the group that show difference. The Kruskal-Wallis test was used for the comparison of the parameters that did not show normal distribution, and the Dunn's test was used to determine the group showing difference. Statistical significance was evaluated at the level of $p<0.05$.

Results

The study was conducted with 190 patients. Seventy-five patients with benign endometrial biopsy results, 73 cases diagnosed aslow-risk endometrium cancer, and 42 cases diagnosed as medium-high-risk endometrium cancer were named as group 1, group 2, and group 3 respectively. The mean age, endometrial thickness, and BMI were significantly lower in group 1 compared to group 2 and group 3 ($p<0.05$). Parity was similar among groups ($p>0.05$). When groups 2 and group 3 were compared within themselves, there was no significant difference in demographic characteristics ($p>0.05$). Comparison of demographic data and endometrial thicknesses between 3 groups is given in Table 1.

When the groups were evaluated in terms of hematological parameters before treatment, it was determined that there was no statistically important difference among the groups in terms of any inflammatory parameters measured ($p>0.05$) (Table 2).

Discussion

Transvaginal sonography and endometrial biopsy are suggested to diagnose any endometrial pathology in patients with perimenopausal and postmenopausal bleeding at high-risk for endometrial cancer. Dilatation and curettage is the most common gynecological procedure for sampling endometrial tissue for histopathological evaluation (23). The use of tumor markers in the diagnosis of endometrial cancer is limited. Although there are conventional prognostic parameters used to predict the survival or to plan treatment modality for patients with endometrial cancer, these parameters seem to be insufficient especially for predicting survival. Therefore, new prognostic factors are needed (20). Many recent studies have tried to reveal the relationship between inflammation and cancer pathogenesis. Currently, there is no clear consensus on the specificity of hematological parameters in the diagnosis of endometrial cancer (24).

In a study investigating the relationship between endometrial pathologies and NLR, Mete Ural et al. (25) found NLR obviously higher in patients who have endometrial cancer than in patients who have not. Haruma et al.'s (26) study conducted with 320 endometrial cancer patients revealed that patients with high NLR had a shorter disease-free and overall survival rate than patients with low NLR. Yayla Abide et al. (27) found no significant relationship

Table 1. Comparison of demographic data between groups

	Group 1: Benign endometrial pathology (n=75)	Group 2: Low-risk endometrial adeno cancer cases (n=73)	Group 3: Medium-high-risk endometrial cancer cases (n=42)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	48.67±6.78	60.36±10.8	63.6±8.36	[1]**0.000***
Parity	3.31±1.28	3.25±0.78	3.07±1.7	[2]**0.428**
BMI	26.29±5.46	30.78±4.35	31.14±3.65	[1]**0.000***
Endometrial thickness (mm)$_{(median)}$	7.73±3.85	15.45±7.2	17.81±8.39	[2]**0.000***

[1]One-Way ANOVA test, [2]Kruskal-Wallis test,*p<0.05, SD: Standard deviation, BMI: Body mass index

between endometrial hyperplasia, endometrial cancer and control groups in terms of NLR and PLR. Likewise with Yayla Abide et al. (27), in our study, no significant relationship was found among groups in terms of NLR.

The presence of thrombocytosis in patients with malignant tumors was shown in some previous studies (28). Gücer et al. (29) showed that thrombocytosis negatively affects the prognosis in endometrial cancer and significantly reduces the 5-year survival rat. Conversely, Oge et al. (30) reported that hemoglobin value and platelet count did not change between endometrial cancer patients and healthy women in their study. In another study, Acmaz et al. (21) showed that PLR was lower in patients with benign endometrial findings and suggested that this ratio could be used to differentiate these patients from endometrial cancer and hyperplasia. On the other hand, Mete Ural et al. (25) suggested that unlike NLR, PLR was not useful in distinguishing these three groups from each other in a study of 472 cases including benign endometrial findings, endometrial hyperplasia, and endometrial cancer cases. In our study, no significant relationship was found between groups in terms of PLR.

There are many studies showing that MPV is increased in gastrointestinal and urinary system malignancies independent of the number of platelets (31,32). In the study by Oge et al. (30), conducted with 310 patients diagnosed with endometrial cancer, MPV values were statistically significantly higher in patients diagnosed with advanced endometrial cancer compared to control group (30). In a study by Karateke et al. (33), the highest MPV and N/L rates were found in endometrial cancer group compared to hyperplasia, and benign pathologies. There are also studies that have opposing results. Temur et al. (34) reported that MPV values were not associated with prognostic factors or survival rate in endometrial cancer. They found no difference between the benign group and cancer group regarding endometrium in terms of the MPV value (35). In our study, no significant relationship was found between groups in terms of MPV.

Monocytes/macrophages also have a very important role in tumor progression. There is increasing proof that tumor-associated macrophages originating from circulating monocytes depress the host immune system and induce tumor angiogenesis, proliferation, migration, and metastasis (36,37). In the study of Cummings et al. (38), no relationship was found between MLR and survival, and it was emphasized that NLR and PLR are superior markers than MLR in endometrial cancer. There was no evidence of an effect of absolute lymphocyte count, MLR, NLR on overall, cancer-specific or recurrence-free survival (39). In our study, no important relationship was found among groups in terms of MLR value.

There is only one study in the literature addressing the prognostic potential of ELR in endometrial cancer (40). Increased ELR portend worse overall survival in endometrial cancer, especially in patients characterized as a high-risk group (40). In this study, no important relationship was found between groups in terms of ELR.

Table 2. Comparison of hematological parameters among the three groups

	Group 1: Benign endometrial pathology (n=75)	Group 2: Low-risk endometrial adeno cancer cases (n=73)	Group 3: Medium-high-risk endometrial cancer cases (n=42)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
$NLR_{(median)}$	2.21±0.88 (2)	2.31±0.88 (2.1)	2.47±0.95 (2.5)	[1]**0.309**
$MLR_{(median)}$	0.2±0.07 (0.2)	0.23±0.1 (0.2)	0.22±0.11 (0.2)	[1]**0.263**
$ELR_{(median)}$	0.07±0.05 (0.1)	0.08±0.1 (0.1)	0.11±0.15 (0.1)	[1]**0.303**
$PLR_{(median)}$	132.17±46.09 (129.9)	145.8±59.05 (136.6)	139.71±48.76 (134.5)	[1]**0.592**
$Neutrophil_{(median)}$	4.76±1.53 (4.8)	4.64±1.72 (4.5)	5.05±1.38 (4.9)	[1]**0.222**
$Lymphocyte_{(median)}$	2.36±0.93 (2.1)	2.13±0.82 (2)	2.24±0.82 (2.3)	[1]**0.256**
Monocyte	0.45±0.13	0.45±0.14	0.46±0.16	[1]**0.912**
Platelet	281.67±61.71	280.63±74.06	292.17±76.96	[1]**0.666**
$Eisonophile_{(median)}$	0.17±0.1 (0.2)	0.15±0.11 (0.1)	0.19±0.15 (0.2)	[1]**0.196**
$MPV_{(median)}$	8.87±1.22 (9.1)	9.09±0.91 (9.1)	9.11±0.88 (9)	[1]**0.653**
$PDW_{(median)}$	16.20±1.310 (16.1)	15.67±2.45 (15.9)	15.59±1.94 (15.8)	[1]**0.062**

[1]Kruskal-Wallis test, *p<0.05, SD: Standard deviation, NLR: Neutrophil/lymphocyte ratio, PDW: Platelet distribution width, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MPV: Mean platelet volume

Karateke et al. (33) found a significant relationship between endometrial hyperplasia, endometrial cancer and control groups in terms of PDW in their study. Conversely, Temur et al. (35) found no difference in PDW value between benign endometrial pathology and endometrial cancer. In this study, no meaningful relationship was found among the 3 groups in terms of PDW.

Conclusion

In cancer patients, prognostic parameters provide information about the possible clinical course of the disease and allow patients to be divided into different risk groups. Presence of reliable and valid prognostic markers is very important in planning the treatment modality. It has been indicated in certain studies that MPV, NLR and PLR values are elevated in advanced endometrial malignancies and may be used as a prognostic factor. However, the results of our study revealed that the use of inflammatory parameters before treatment in endometrial cancer does not give an idea about the course of the disease. There is still no clear consensus on the specificity of these hematological parameters in the diagnosis of endometrial cancer.

In our study, we see that MPV, NLR, PLR, ELR, and MLR values did not change regardless of the etiology (benign or endometrial cancer) for AUB or PMB. This may be because the inflammation occurring in endometrium due to cancer did not trigger the release of some cytochemicals known to stimulate a systemic generalized inflammatory response.

Ethics

Ethics Committee Approval: Ethical approval required for this retrospective study was obtained from the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee and was approved on 03.04.2018 with the decision number 08/03.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., F.K.G., Concept: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Design: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Data Collection or Processing: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Analysis or Interpretation: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Literature Search: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C., Writing: S.K., D.K., Ö.K., F.K.G., H.Y.N., E.N.D., N.B.C.

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ORIGINAL RESEARCH

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The Effect of Coronary Artery Disease and Related Drugs on Sexual Activity in Turkish Society

Türk Toplumunda Koroner Arter Hastalığı ve İlişkili İlaçların Cinsel Aktiviteye Etkisi

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Abstract

Objective: Sexual dysfunction after acute coronary syndrome (ACS), is a frequently encountered problem in clinical practice. The aim of our study is to determine the time it takes for patients to switch to a healthy sexual life, which is one of the basic elements of a healthy social life, after a cardiovascular event in Turkish society and investigation of the effect of drugs related to ACS on sexual activity.

Method: In our study, volunteer women and men who had a cardiovascular event at least 3 months before and were sexually active before the ACS between January 2017-December 2019 were evaluated using a closed questionnaire. The demographic characteristics of the patients, their comorbidities and medications, and their sexual activity levels before and after the ACS were compared.

Results: After ACS, sexual dysfunction developed in 36% (n=117) of the patients. In the group with sexual dysfunction, heart failure [21% (n=25) - 9% (n=18) - p=0.001], chronic renal failure [9% (n=11) - 0% (n=0) p<0.001], and BPH presence [34% (n=40)- (11% (n=23) p<0.001] were higher. Similarly, beta-blocker use [95% (n=111) - 84% (n=172) p=0.001] and ACE-I/ARB use [62% (n=73) - 54% (n=111) p=0.05] were also higher in participants with sexual dysfunction.

Conclusion: In our study, an increase in the prevalence of sexual dysfunction was observed in patients with multiple comorbidities, especially heart failure. Sexual dysfunction was found to be higher in patients using beta-blockers.

Keywords: Acute coronary syndrome, beta-blocker, sexual dysfunction, Turkish society

Öz

Amaç: Akut koroner sendrom (AKS) sonrasında cinsel fonksiyon bozuklukları klinik pratikte sıklıkla karşılaşılan problemlerdir. Çalışmamızın amacı Türk toplumunda AKS sonrası sosyal hayatlarına dönen hastaların sağlıklı bir sosyal hayatın temel unsurlarından olan sağlıklı bir cinsel yaşama geçebilme zamanının belirlenmesi ve AKS ile ilgili ilaçların cinsel aktiviteye etkisinin araştırılmasıdır.

Yöntem: Çalışmamızda, Ocak 2017-Aralık 2019 yılları arasında en az 3 ay önce AKS geçiren ve polikliniğe başvuran AKS öncesinde cinsel olarak aktif olan gönüllü kadın ve erkekler kapalı anket usulü ile değerlendirildi. Hastaların demografik özellikleri, ek hastalıkları ve kullandığı ilaçlar ile birlikte AKS öncesi ve sonrasındaki cinsel aktivite düzeyleri karşılaştırıldı.

Bulgular: AKS sonrasında hastaların %36'sında (n=117) cinsel disfonksiyon gelişmiştir. Cinsel disfonksiyonu olan grupta kalp yetmezliği [%21 (n=25) - %9 (n=18) - p=0,001], kronik böbrek yetmezliği [%9 (n=11) - %0 (n=0) p<0,001], BPH varlığı [%34 (n=40)- (%11 (n=23) p<0,001] yüksek saptanmıştır. Ayrıca beta-bloker kullanımı [%95 (n=111) - %84 (n=172) p=0,001] ve ACE-İ/ARB kullanımı [%62 (n=73) - %54 (n=111) p=0,05] cinsel disfonksiyonu olan grupta daha yüksek saptanmıştır.

Sonuç: Çalışmamızda başta kalp yetmezliği olmak üzere multipl komorbiditesi olan hastalarda cinsel isteksizlik prevelansında artış izlenmiştir. Beta-bloker kullanan hastalarda cinsel isteksizlik fazla bulunmuştur.

Anahtar kelimeler: Akut koroner sendrom, beta-blocker, cinsel disfonksiyon, Türk toplumu

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Introduction

Cardiovascular disease (CVD), are among the most important causes of mortality and morbidity all over the world. Approximately one-third of all deaths in the world are caused by CVD, mainly due to ischemic heart disease (1). CVD, especially acute coronary syndrome (ACS) affects the quality of life in terms of physical activity, psychosocial state as well as sexual life (2). Sexual dysfunction, mainly erectile dysfunction (ED) and decreased libido, especially in male gender are common in patients with CVD. Psychologic factors, side effects of medications such as beta-blockers and lipid-lowering agents, the number of the medications, the accompanying risk factors, such as hyperlipidemia, diabetes mellitus, cigarette smoking, and metabolic syndrome are related to an increased prevalence of sexual dysfunction after CVE (2,3). Although, it takes a long time to regain the normal physical and psychosocial functions after cardiovascular events, this process can be facilitated by regular multidisciplinary rehabilitation (2,3).

The effect of ACS and related factors on sexual dysfunction in the Turkish population has not yet been clearly clarified. The aim of this study was to determine the time of transition to a healthy sexual life and the effects of the medication or other factors on sexual activity in Turkish men and females with ACS who return to their social lives.

The aim of our study is to determine the time of transition to a healthy sexual life, which is one of the basic elements of a healthy social life, and the factors affecting sexual life in patients who return to their social lives after ACS in Turkish society. In addition, it we defined the effects of the use of beta-blockers on sexual functions.

Materials and Methods

A total of 321 (female =100, male =221) Caucasian (Turkish) patients between January-2017 and December-2019, from 6 centers were included in the study. The present study was planned as a closed-envelope questionnaire survey study, taking into account social factors. This study was conducted in ACS patients. Patients with any form of ACS (STEMI, NSTEMI and USAP) and have >50% coronary artery stenosis diagnosed with conventional angiography and have active sexual life were included in the study. Patients without active sexual life were excluded from the study. Patients with previous coronary artery disease and major psychological disorders were not included in the study.

Sexual dysfunction includes sexual reluctance (lack of sexual desire), ED, impaired arousal, inability to achieve orgasm, diminished libido, and ejaculatory disorders (4). In this article in general we examined sexual dysfunction. Active sex position was defined as; to be more active and/or on top during sexual intercourse, and passive sexual position was defined as; to be on the bottom or more passive in contrast to the partner (5).

Due to the cultural and religious traditions of Turkish society, instead of asking such a subject openly in the form of a mutual conversation, it was asked in closed envelopes containing a few questions. Furthermore, female sexual function index (6) and international erectile function index (7) are scales that can be used for this purpose. However, since it is not possible to use these scales simultaneously in men and women, they were not used in our study.

Participants were asked whether they have diabetes mellitus (DM), hypertension, hyperlipidemia, chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), cerebrovascular accident, peripheral artery disease, malignancy and benign prostatic hypertrophy (BPH).

A glomerular filtration rate calculated by the Cockroft-Gault formula and glomerular filtration rate below 30 was defined as severe chronic renal failure. An ejection fraction (EF) below 40% was defined as heart failure. GFR and EF were considered during data collection but were not reported quantitatively. The New York Heart Association (NYHA) Classification was used defining the functional capacity of the patients. Frequency of the sexual intercourse before and after the cardiovascular event, and the time of the first intercourse after the cardiovascular event were evaluated. Since there is no accepted classification for the evaluation of sexual activity according to the frequency of sexual activity, the patients were asked about their weekly frequency of sexual activity. This study was conducted in accordance to the guidelines proposed in the Declaration of Helsinki and has been approved by a Local Clinical Research Ethics Committee of Dokuz Eylül University (date: 03.03.2016, no: 2016/06-39). Written informed consent was obtained from the all participants included in the present study.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Two-tailed $p<0.05$ indicated statistical significance. A histogram with a bell curve and one-sample Kolmogorov-Smirnov and Shapiro-Wilk tests were used in assessing the distribution of age; the only continues variable of the sample. The normally distributed age was described as the mean and standard deviation, while the remaining categorical variables were expressed as frequencies and percentages. Differences between age

of the groups were analyzed by Independent-Samples t-test. On the other hand, chi-square and Fisher's Exact tests were performed to determine whether there was a difference between the groups in terms of categorical variables. Logistic regression analysis was used to assess the role of related variables for the likelihood of the sexual dysfunction.

Results

This study included a total of 321 patients [100 (31.2%) female and 221 (68.2%) male]. The mean age of the population was 58±8.94. HT, DM, HL, cigarette smoking, HF, history of CVA, CRF, COPD, PAH, malignancy and BPH were found to have the frequencies of [150 (46.7%), 76 (23.7%), 219 (68.2%), 121 (37.7%), 43 (13.4%), 3 (0.9%), 11 (3.4%), 19 (5.9%), 2 (0.6%), 1 (0.3%), 63 (19.6%)] respectively. RASI, beta-blocker, statin, PDE5-I and sexual performance enhancing drug usage were as 186 (57.9%), 283 (88.2%), 250 (77.9%), 18 5.6 (%) and 66 (20.6%) respectively. 117 of 321 patient reported to have sexual dysfunction after ACS. Individuals with sexual dysfunction were significantly older and have a significant high rate of HT, DM, HF, CRF, BB treatment, performance enhancing drug usage and passive sex position in contrast to the without sexual dysfunction group. On the other hand, cigarette smoking, being informed about sexual dysfunction before the ACS and active sex position were significantly higher in patients without sexual dysfunction. There was no statistically significant difference between the groups in terms of gender, HL, CVA, COPD, PAH, malignancy, RASI, statin and PDE5-I usage and outpatient policlinic information (Table 1) (note: Calculations regarding BPH and performance enhancing drug are done within the male gender only).

General characteristics of the study population was shown in Table 2. 37 (31.6%) of patients with sexual dysfunction were in NYHA class I, while 80 (68.3%) were in a NYHA class II functional state. In contrast, patients without sexual dysfunction have a 152 (74.5%) and 52 (25.5%) of NYHA class I and II respectively. While the number of patients who underwent coronary stent procedure without myocardial infarction (MI) was 83 (71%) in the group with sexual dysfunction, it was found 161 (79%) in the group without sexual dysfunction. In the group with sexual dysfunction, the time after MI was 3-6 months in 4 (3%) patients, 6-12 months in 6 (5%) patients, 12-36 months in 7 (6%) patients, and >36 months in 17 (14%) patients. In the group without sexual dysfunction, the time after MI was 3-6 months in 7 (3%) patients, 6-12 months in 2 (1%) patients, 12-36 months in 16 (8%) patients, and >36 months in 18 (9%) patients. No hospitalization after ACS was reported in 52 (89.7%) and 96 (89.7%) of with and without sexual dysfunction groups respectively. Once and twice hospitalization were 5 (8.6%) and 1 (1.7%) in sexual dysfunction group and 10 (9.3%) and 1 (0.9%) in without sexual dysfunction group respectively. Two persons in sexual dysfunction group were illiterate, 100 (85%) were primary educated, 9 (8%) were high school educated and 6 (5%) were a university educated, where these rates were 2 (1%), 142 (70%), 32 (16%) and 28 (14%) in without sexual dysfunction group respectively.

Beta-blockers receiving group encountered 88.1% (n=283) of the sample. Information about the medical history and sexual functions of patients using beta-blockers are shown in Table 3. While the mean age of the group using beta-blockers was 58.69±8.89, the mean age was found to be 55.37±8.88 in the group not using beta-blockers (p=0.031). There was no significantly difference related to gender, DM, HT, HL, smoking, HF, CVA, CRF, COPD, PAH, malignancy, BPH, MI and RAS-I and statin usage in both groups.

However, values of age (p=0.031), PDE5-I usage (p=0.012), and sexual dysfunction [111 (39.2%) vs. 6 (15.8%), p=0.005] were higher in patients who are on beta-blocker treatment than in patients are not on beta-blocker treatment (note: Calculations regarding BPH were done only for males).

81.6% of the patients stated that they did not receive counseling from any health personnel about sexual intercourse before discharge and 78.8% of them stated that they did not receive any counseling about sexual intercourse during their follow-up outpatient clinic controls. A significant decrease was observed in the frequency of intercourse compared to pre-ACS period. Before the ACS, 71 (22.1%) individuals have sexual intercourse once a week, 143 (44.5%) twice a week, 40 (12.5%) three times or more per week, 43 (13.4%) biweekly and 24 (7.5%) once in a month. In post ACS period the rates of sexual intercourse were changed to 81 (25.2%) once a week, 78 (24.3%) twice a week, 28 (8.7%) three times or more per week, 78 (24.3%) biweekly and 56 (17.4%) once in a month. In pre and post ACS periods rate the of sexual intercourse was higher in beta-blocker user group. Furthermore, in post ACS period the rate of sexual intercourse was significantly lower in contrast to the pre-ACS period (p<0.001). Sexual intercourse after ACS was initiated at first week by 23 (7.2%) individuals, 15 days later by 145 (45.2%), one month later by 99 (30.8%), two months later by 30 (9.3%), three months later by 18 (5.6%) and four months later by 4 (1.2%). Two (0.6%) persons had never sexual intercourse after ACS (Table 4).

Binary multivariate logistic regression analysis was done to investigate the role of age, gender, BB treatment, statin treatment, functional capacity, information before discharge and sexual intercourse position for the likelihood of the sexual dysfunction. The model as a whole that included all eight predictors was statistically significant [X^2 (8, n=321)=7.678, p<0.001], determining that the model can discriminate presence/absence of sexual dysfunction. The full model clarified between 29.2% (Cox & Snell R square) and 39.9% (Nagelkerke R square) of the variance in sexual dysfunction and correctly classified 77.3% of the cases. Age showed an odds ratio (OR) of 1.064; this indicates that each one-year increase in age, increases the probability of sexual dysfunction by 1.064 times. Similarly, functional capacity was among independent explanatory variables related to sexual dysfunction. Moreover, sexual intercourse position was also a significant predictor of the sexual dysfunction (OR: 6.299 p<0.001). However, gender, beta-blocker treatment, statin treatment and having information before discharge did not contributed significantly to this model (Table 5).

Discussion

Many physical and psychosocial pathologies are observed in patients after cardiovascular events, especially after MI. It may take a long time for individuals to regain their functions before the cardiovascular event. In our study, a decrease was found in the frequency of sexual intercourse after a cardiovascular event. This process may be associated with regression in cardiac functions and psychosocial factors in the post-MI period. In a study on the subject, a decrease in sexual activity of 22-75% was found as a result of physiological and psychosocial effects in the period after MI (8). In a review study by Drory et al. (9), male patients who were sexually active before CVE were evaluated with information obtained from one-to-one

Table 1. Clinical characteristics of the entire sample and by sexual reluctance

Variables	Entire study sample n=321	With sexual dysfunction n=117	Without sexual dysfunction n=204	p
Age (year)	58.3±8.94	62.01±7.56	56.16±9	<0.001
Gender				
Female n (%)	100 (31.2%)	39 (33.3%)	61 (29.9%)	0.523
Male n (%)	221 (68.8%)	78 (66.7%)	143 (70.1%)	
Hypertension, n (%)	150 (46.7%)	66 (56.4%)	84 (41.2%)	0.008
Diabetes mellitus, n (%)	76 (23.7%)	35 (29.9%)	41 (20.1%)	0.046
Hyperlipidemia n (%)	219 (68.2%)	81 (69.2%)	138 (67.6%)	0.769
Smoking, n (%)	121 (37.7%)	27 (23.1%)	94 (46.1%)	<0.001
Heart failure n (%)	43 (13.4%)	25 (21.4%)	18 (8.8%)	0.001
CVA n (%)	3 (0.9%)	2 (1.7%)	1 (0.5%)	0.275
Severe CRF n (%)	11 (3.4%)	11 (9.4%)	0 (0%)	<0.001
COPD, n (%)	19 (5.9%)	9 (7.7%)	10 (4.9%)	0.308
PAH n (%)	2 (0.6%)	1 (0.9%)	1 (0.5%)	0.692
Malignancy n (%)	1 (0.3%)	1 (0.9%)	0 (0%)	0.186
BPH n (%)*	63 (19.6%)	40 (34.2%)	23 (11.3%)	<0.001
RAS inhibitors n (%)	186 (57.9%)	73 (62%)	111 (54%)	0.050
Beta-blocker n (%)	283 (88.2%)	111 (95%)	172 (84%)	0.005
Statin n (%)	250 (77.9%)	86 (73%)	164 (80%)	0.152
PDE-5 inhibitors n (%)	18 5.6 (%)	4 (3.4%)	14 (6.9%)	0.197
Performance enhancing drug*	66 (20.6%)	32 (27.4%)	34 (16.7%)	0.023
Pre-event information n (%)	59 (18.4%)	8 (0.8%)	51 (25%)	<0.001
Outpatient clinic inform. n (%)	68 (21.2%)	24 (20.5%)	44 (21.6%)	0.824
Active sex position n (%)	271 (84.4%)	80 (68.4%)	191 (93.6%)	<0.001
Passive sex position n (%)	50 (15.6%)	37 (31.6%)	13 (6.4%)	<0.001

* Calculations regarding BPH and performance-enhancing drugs were done only for males. CVA: Cerebrovascular accident, CRF: Chronic renal failure, COPD: Chronic obstructive pulmonary disease, PAH: Pulmonary arterial hypertension, BPH: Benign prostatic hypertrophy

Table 2. General characteristics of the study population

Variables	With sexual dysfunction n=117	Without sexual dysfunction n=204	p
Functional capacity			
NYHA-I n (%)	37 (31.6%)	152 (74.5%)	<0.001
NYHA-II n (%)	80 (68.3%)	52 (25.5%)	
MI time			
None n (%)	83 (71%)	161 (79%)	0.026
3-6 months n (%)	4 (3%)	7 (3%)	
6-12 months n (%)	6 (5%)	2 (1%)	
12-36 months n (%)	7 (6%)	16 (8%)	
>36 months n (%)	17 (14%)	18 (9%)	
Post-ACS hospitalization			
None n (%)	52 (89.7%)	96 (89.7%)	0.898
Once n (%)	5 (8.6%)	10 (9.3%)	
Two times n (%)	1 (1.7%)	1 (0.9%)	
Level of education			
Illiterate n (%)	2 (2%)	2 (1%)	0.008
Primary education n (%)	100 (85%)	142 (70%)	
High school n (%)	9 (8%)	32 (16%)	
University n (%)	6 (5%)	28 (14%)	

ACS: Acute coronary syndrome, MI: Myocardial infarction

Table 3. Clinical characteristics of the study population in regard to beta-blocker treatment

Variables	Total n=321	Taking BB n=283	Do not taking BB n=38	p
Age (year)	58.3±8.94	58.69±8.89	55.37±8.88	0.031
Gender (female)	100 (31%)	87 (30.7%)	13 (34.2%)	0.665
DM n (%)	76 (23.7)	67 (23.7%)	9 (23.7%)	0.999
HT n (%)	150 (46.7%)	135 (39.5%)	15 (47.7%)	0.340
HL n (%)	219 (68.2%)	193 (68.2%)	26 (68.4%)	0.978
Smoking n (%)	121 (37.7%)	105 (37.1%)	16 (42.1%)	0.550
HF n (%)	43 (13.4%)	40 (14.1%)	3 (7.9%)	0.289
CVA n (%)	3 (0.9%)	3 (1.1%)	0 (0%)	0.684
CRF n (%)	11 (3.4%)	11 (3.9%)	0 (0%)	0.244
COPD n (%)	19 (5.9%)	16 (5.7%)	3 (7.9%)	0.396
PAH n (%)	2 (0.6%)	2 (0.7%)	0 (0%)	0.776
Malignancy n (%)	1 (0.3%)	1 (0.4%)	0 (0%)	0.882
BPH n (%)*	63 (19.6%)	58 (20.5%)	5 (13.2%)	0.285
MI n (%)	321 (100%)	283 (100%)	38 (100%)	0.395
ACEI/ARB n (%)	186 (57.9%)	168 (59.4%)	18 (47.4%)	0.160
Statin n (%)	250 (77.9%)	219 (77.4%)	31 (81.6%)	0.559
PDE5-I n (%)	18 (5.6%)	12 (4.2%)	6 (15.8%)	0.012
Sexual dysfunction n (%)	117 (36.4%)	111 (39.2%)	6 (15.8%)	0.005

* Calculations regarding BPH were done only for males. DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, HF: Heart failure, CRF: Chronic renal failure, COPD: Chronic obstructive pulmonary disease, PAH: Pulmonary arterial hypertension, BPH: Benign prostatic hypertrophy, MI: Myocardial infarction, CVA: Cerebrovascular accident

interview records and treatment cards. In the study, it was concluded that the most important factor determining the frequency of sexual activity before MI was the frequency of intercourse before MI (9). While the major factors affecting the frequency of sexual intercourse and pleasure were determined as education status and age; medical and physiological variables (diabetes, depression, medication) were determined as minor factors. In our study group, we see that the frequency of sexual intercourse decreased in each group compared to the pre-MI, and this decrease was associated with the previous frequency, as in the study by Drory et al. (9). In a study published in ESC in 2015, in which sexual activity in women and men 1 year before and after MI was evaluated on 128 patients, it was found that the frequency of sexual activity, desire and pleasure from sexual activity decreased in the male population after MI, and erection problems developed in patients. However, it was determined that there was no significant change in women. In addition, it was stated that the results of the study did not reach statistical significance and that larger study groups were needed (10). In our study, there was no significant difference between male and female patients in terms of sexual dysfunction. The frequency of ED was found to be higher in the group using beta-blockers. There is no consensus on the effects of beta-blockers in the development of erectile dysfunction, which

Table 4. Sexual activity related data of the study population in regard to beta-blocker treatment

Variables	Total n=321	Taking BB n=283	Do not taking BB n=38	p
Frequency of intercourse before CV event				
1/week	71 (22.1%)	65 (23%)	6 (15.8%)	0.001
2/week	143 (44.5%)	126 (44.5%)	17 (44.7%)	
≥3/week	40 (12.5%)	28 (9.9%)	12 (31.6%)	
Biweekly	43 (13.4%)	40 (14.1%)	3 (7.9%)	
Once in a month	24 (7.5%)	24 (8.5%)	0 (0%)	
Frequency of intercourse after CV event				
1/week	81 (25.2%)	76 (26.9%)	5 (13.2%)	0.002
2/week	78 (24.3%)	62 (21.9%)	16 (42.1%)	
≥3/week	28 (8.7%)	21 (7.4%)	7 (18.4%)	
Biweekly	78 (24.3%)	70 (24.7%)	8 (1.1%)	
Once in a month	56 (17.4%)	54 (19.1%)	2 (5.3%)	
First intercourse time after the CV event				
First week	23 (7.2%)	16 (5.7%)	7 (18.4%)	0.089
15 days later	145 (45.2%)	128 (45.2%)	17 (44.7%)	
After 1 month	99 (30.8%)	88 (31.1%)	11 (28.9%)	
After 2 months	30 (9.3%)	27 (9.5%)	3 (7.9%)	
After 3 months	18 (5.6%)	18 (6.4%)	0 (0%)	
After 4 months	4 (1.2%)	4 (1.4%)	0 (0%)	
Never	2 (0.6%)	2 (0,7%)	0 (0%)	

Table 5. Binary multivariate logistic regression analysis for the likelihood of the sexual reluctant

Variables	B	SE	Wald	df	p	Odds	95% CI for p
Age	0.062	0.019	10.908	1	0.001	1.064	1.025-1.103
Gender (male)	0.245	0.347	0.499	1	0.480	1.278	0.647-2.524
Betablocker taking	-0.755	0.532	2.010	1	0.156	0.470	0.166-1.334
Statin taking	0.122	0.342	0.128	1	0.721	1.130	0.578-2.211
NYHA (I)	-1.536	0.297	26.787	1	<0.001	0.215	0.120-0.385
Being informed before discharge	0.861	0.442	3.788	1	0.052	2.365	0.994-5.626
Sexual intercourse position (active)	1.840	0.407	20.441	1	<0.001	6.299	2.836-13.987
Constant	-4.472	1.208	13.714	1	<0.001	0.011	-

SE: Standard error, CI: Confidence interval

is a multifactorial process. The physical and psychosocial transformations of patients after MI and the use of multiple drugs contribute to this process. In a study evaluating the relationship between cardiac drug use and the frequency of erectile dysfunction, a relationship was shown between cardiac drug use and erectile dysfunction. Especially in patients using calcium channel blockers [RR=1.6, confidence interval (CI) 95% 1.0-2.4], ARB users (RR=2.2, 95% CI 1.0-4.7), non-selective beta-blockers (RR=1.7, 95% CI 0.9-3.2) and diuretic users (RR=1.3, CI 0.7-2.4) ED was found to be high. However, no correlation could be found between organic nitrates, ACE inhibitors and selective beta-blockers and ED (11). In our study, age was found to be significantly higher in the group using beta-blockers. Although the frequency of heart failure and BPH were found to be higher in the group using beta-blockers, this did not create a statistically significant difference. However, the frequency of PDE5 inhibitor use was found to be higher in the group that did not use beta-blockers. This may have had an effect on the lesser development of sexual dysfunction in the group that did not use beta-blockers. Age, functional capacity and sexual intercourse position contributed significantly when binary multivariate logistic regression analysis was performed in our study.

There are also opinions that the negative effects of beta-blockers on sexual functions are related to psychogenic factors. In individuals with newly diagnosed cardiovascular disease, the frequency of ED was found to be higher in the group that was informed about the relationship between beta-blockers and erectile dysfunction, compared to the group that was not informed. This situation has been primarily related to anxiety related to drug side effects (12).

All these data show that the psychological component is also effective in the effects of beta-blockers on erectile dysfunction. It is of great importance to provide sexual counseling during the cardiac rehabilitation process and to inform patients in detail about cardiac drugs, especially beta-blockers, and their side effects. In our study, the rate of patients who received sexual counseling after discharge and at the outpatient clinic controls was 21.2%. In a way, it should be considered that this may be one of the factors in the decrease in sexual activity disorder and the frequency of intercourse in the study population. In support of our hypothesis, in a study published in the Journal of Cardiovascular Nurse in 2014, it was investigated how much counseling the patients received regarding their return to their sexual life during the cardiac rehabilitation process after MI in Sweden and how effective it was on their sexual life. It was determined that only 41% of the patients and 31% of the partners of the patients received sexual intercourse counseling after MI. In the sexual satisfaction scoring questionnaire of the study population after sexual counseling, it was concluded that there was a significant improvement in these patients after the training (13).

Study Limitations

As a result of cardiovascular events and also predisposition factors of sexual dysfunction, the psychological components, such as anxiety and/or depression are not reported in our analyzes. In addition, the lack of data on the various classes of beta-blockers with different effects on sexual activity is another shortcoming of this study. Furthermore, no validated questionnaire was used to determine sexual activity in both sexes.

Conclusion

After acute coronary syndrome, sexual life is affected by organic and psychosocial reasons. However, in this process, it is not considered reasonable to stay away from beta-blockers due to their side effects. Implementing cardiac rehabilitation, including sexual counseling, and preferring selective beta-blockers, if possible, should be adopted as an appropriate process.

Ethics

Ethics Committee Approval: This study was conducted in accordance to the guidelines proposed in the Declaration of Helsinki and has been approved by a Local Clinical Research Ethics Committee of Dokuz Eylül University (date: 03.03.2016, no: 2016/06-39).

Informed Consent: Written informed consent was obtained from the all participants included in the present study.

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Authorship Contributions

Surgical and Medical Practices: A.A., G.A., Concept: B.D., Ö.Ş., O.Ç., A.O.E., Design: B.D., Ö.Ş., O.Ç., A.O.E., Data Collection or Processing: T.Y., G.A., L.B., A.A., Analysis or Interpretation: D.E.A., A.N., Drafting Manuscript: D.E.A., A.N., T.Y., O.Ç., Critical Revision of Manuscript: L.B., A.A., G.A., A.O.E., Ö.Ş., B.D., Final Approval and Accountability: Ö.Ş., D.E.A., A.N., Supervision: B.D., A.O.E., T.Y., Ö.Ş., L.B., Writing: Ö.Ş., D.E.A., A.N.

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ORIGINAL RESEARCH

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Mediolateral Episiotomy in Nulliparous Women Increases the Risk of Sexual Dysfunction

Mediolateral Epizyotomi Yapılan Nullipar Kadınlarda Seksüel Disfonksiyon Riski Artabilir

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Abstract

Objective: Postpartum sexual functions may be affected in women who have had a vaginal delivery by performing an episiotomy. The aim of this study is to compare the frequency of sexual dysfunction between women who were delivered with a mediolateral episiotomy and those who were delivered without an episiotomy.

Method: A total of 179 women who gave birth in a tertiary center were included in the prospective study. The patients were divided into two groups as women with and without mediolateral episiotomy. The groups were compared in terms of age, body mass index, educational status, duration of active phase of labor and Arizona sexual experiences scale (ASEX). Mediolateral episiotomy increases the risk of sexual dysfunction.

Results: Labor and duration of active phase of labor are associated with sexual dysfunction in patients undergoing mediolateral episiotomy (p<0.001 and p=0.01, respectively). But the duration of delivery is not an independent factor. However, performing an episiotomy increases the risk of sexual dysfunction 2.5 times (odds ratio: 2.35, confidence interval: 1.45-3.83, p=0.001). In evalutaion of ASEX subscores according to the presence of episitomy; patients with episiotomy had significantly higher scores in sex drive, ability to reach orgasm and satisfaction from the orgasm (p<0.001 for all). Besides arousal and lubrication was not affected by presence of episiotomy.

Conclusion: According to the results of our study, performing mediolateral episiotomy during vaginal delivery increases the frequency of sexual dysfunction in postpartum women.

Keywords: Arizona sexual experiences scale, episiotomy, mediolateral episiotomy, sexual dysfunction

Öz

Amaç: Bu çalışmanın amacı, mediolateral epizyotomi ile doğum yapan kadınlar ile epizyotomi yapılmadan doğum yapan kadınlar arasındaki cinsel işlev bozukluğu sıklığını karşılaştırmaktır.

Yöntem: Bu prospektif çalışmaya üçüncü basamak bir merkezde doğum yapan toplam 179 kadın dahil edildi. Hastalar mediolateral epizyotomi yapılan ve yapılmadan vajinal doğum yapan kadınlar olarak iki gruba ayrıldı. Gruplar yaş, vücut kitle indeksi, eğitim durumu, doğum için hastanede kalış süresi ve Arizona cinsel deneyimler ölçeği (ASEX) açısından karşılaştırıldı.

Bulgular: Mediolateral epizyotomi uygulanan hastalarda doğum eylemi ve doğum süresi cinsel işlev bozukluğu ile ilişkili bulundu (sırasıyla p<0,001 ve p=0,01). Ancak doğum için geçen süre seksüel disfonksiyon açısından bağımsız bir faktör değildir. Ancak epizyotomi yapılması cinsel işlev bozukluğu riskini 2,5 kat artırmaktadır. (olasılık oranı: 2.35, güven aralığı: 1,45-3,83, p=0,001). ASEX subskorlarının epizitomi varlığına göre değerlendirilmesinde; epizyotomili hastaların cinsel dürtü, orgazma ulaşma ve orgazmdan tatmin olma puanları anlamlı olarak daha yüksekti (tümü için p<0,001). Ayrıca epizyotomi yapılanlarda cinsel uyarılma ve lubrikasyon etkilenmedi.

Sonuç: Çalışmamızın sonuçlarına göre vajinal doğum sırasında mediolateral epizyotomi yapılması, doğum sonrası kadınlarda cinsel işlev bozukluğu sıklığını artırmaktadır.

Anahtar kelimeler: Arizona cinsel deneyimler ölçeği, cinsel işlev bozukluğu, epizyotomi, mediolateral epizyotomi

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Introduction

The concept of sexual dysfunction in women means lack of sexual desire, arousal disorder, inability to reach orgasm, sexual activity and pain, or a combination of these problems. All these problems can develop due to cultural, physical, mental, psychological and hormonal changes. Studies have shown that 30-60% of women experience sexual dysfunction at least once in their lives (1,2).

Pregnancy and childbirth can cause pelvic floor dysfunction and sexual dysfunction. Sexual dysfunction in women is most common in the first postpartum year (3). In the literature, the frequency of postpartum sexual dysfunction is approximately 70-80% in the first 3 months and 30-60% in the 6th month. In more than one third of women (38%), postpartum sexual life does not reach pre-pregnancy levels (4,5).

In the postpartum period, the frequency of sexual dysfunction may increase due to loss of desire, dyspareunia, lack of lubrication, pain and decreased orgasmic capacity. Among these, loss of desire and dyspareunia are the most important factors (6).

Episiotomy can be done routinely or optionally in vaginal delivery. The literature on the effect of routine episiotomy on sexual functions is contradictory. In some publications, it is said that it has no benefit and even worse effects (7), while in others it is suggested that it reduces pain (8).

Although median episiotomy is most preferred in America, mediolateral episiotomy is mostly performed in Europe and Turkey. Despite the recommendation in the recent literature not to perform routine episiotomy, episiotomy is still routinely performed in primiparous and multiparous patients in many countries. The episiotomy rate of primiparous and multiparous women is 9.7-100% worldwide, while the episiotomy rate of primiparous women is 63-100% (9). The effect of episiotomy on female sexual life is not clear. It has not been clarified yet in evidence-based medicine how long and how intense the perineal injury and healing process caused by median, mediolateral episiotomy are effective on sexual life. The benefits of performing routine episiotomy are currently being questioned.

The Arizona sexual satisfaction scale (ASEX) is a test used for the diagnosis of sexual dysfunction, which takes a short time to perform and is easy to comply with.

Although there are publications in the literature investigating the effect of mode of delivery on female sexual life, publications investigating the effect of epistotomy are contradictory and limited. In this study, we prospectively evaluated patients in active phase of labor using ASEX and wanted to investigate the effect of mediolateral episiotomy on female sexual life.

Materials and Methods

This prospective study was performed in a tertiary hospital in accordance with principles of Helsinki Decleration. We started the study with the permission of the Ethics Committee of Batman State Hospital numbered 249, dated 20/07/2020. Study included 179 primiparous patients who applied to the clinic in labor and gave a vaginal delivery spontaneously between 2020 August to 2021 September. All patients were called up for a control in 6th month after delivery and sexual function was evaluated according to ASEX.

In our study, we used the ASEX test, age, education level, body mass index (BMI) and time spent in hospital for delivery to investigate sexual dysfunction in healthy women who had a vaginal delivery with or without mediolateral episiotomy. The ASEX test is a 5-question survey. In the questionnaire, women were questioned for sexual drive, arousal, vaginal lubrication, ability to reach orgasm, satisfaction from the orgasm. Women gave points from 1 to 6 and their results were recorded. A total score of more than 19 in the ASEX test, or a score of more than 5 in any section, or a score of >4 in 3 sections is considered sexual dysfunction (10,11).

The Turkish validity and reliability study of ASEX was performed by Soykan (12). In Soykan's study, the Cronbach's α values of the scale were determined as 0.89-0.90.

The labor (active phase of labor) was defined as cervical dilatation of at least 2 cm with at least 80% of effacement with regular contractions or 4 centimeter dilatation with any effacement with regular contractions or the flow of amniotic fluid. The active phase of labor lasts for 12 hours in nulliparous pregnant women (13).

We performed mediolateral episiotomy in cases where labor was prevented by perineal tissue or when the fetal head circumference was >90. Episiotomy was not performed on the woman who did not need it. We registered the patients according to the criteria, we recorded their birth notes and types from their files without interfering with the flow of birth, and then we applied asex 6 months after the birth.

Mediolateral episitomy was used in all patients when

required and repaired with the same surgical technique. After cutting the midline of the posterior fourchette 3 mm, the incision is advanced laterally to the ischiotuberal process at an angle of 60 degrees (14).

Exclusion criteria were need of labor induction, history of any pregnancy complication (gestational diabetes, hypertension, oligohydramnios, any suspicion of infection or chorioamnionitis…etc.), history of multiparity, women who had problems in their sexual life before pregnancy, women who have experienced the postpartum blues or depression (pregnant women with postpartum mood disorder using Edinburgh scale and postpartum depression scale were not included in the study). Moreover, women who are separated from their baby due to postpartum maternal or infant-related problems, women who do not have enough time and space for postpartum sex, history of vaginal surgery and frequent vaginal infection.

The duration of active phase of labor was defined as the time between hospitalization to delivery (hours). BMI and duration of active phase of labor were analysed according to the median values. Educational status was evaluated according to primary and university graduation.

Statistical Analysis

Data were analyzed using SPSS for Windows v.15.0 (SPSS,Inc., Chicago, IL, USA). Descriptive and frequency analyses were performed. Categorical variables were compared using the chi-square test or Fisher's Exact test, as appropriate. Binary logistic regression analysis was used to evaluate independent samples (BMI, age, duration of active phase of labor) sexual function. Independent samples t-test was used to evaluate the affect of episiotomy on parts of ARISONA score. The level of statistical significance was set at $p<0.05$.

Results

Study included 179 patients. The median age of the patients was 24 (18-48) years old. Mean duration of active phase of labor was 14.2 hours. Episiotomy was perfomed in 66 (36.9%) patients. We asked all women who participated in the study when they first had sexual intercourse after giving birth. 90% of the women said they had intercourse in the 1st month postpartum, and 10% in the 2nd month. Sexual dysfunction was detected in 121 (67.6%) patients (Table 1). While 88% (58 patients) of women who underwent episiotomy had standard deviation, this rate was significantly lower in women who did not undergo episiotomy (56%) (Table 2).

Twenty three out of 179 patients had never been to school. 80% of the women who went to school had completed primary education, 10% had graduated from high school and 10% had graduated from university (Table 2).

In univariate analysis the presence of episiotomy and the duration of active phase of labor more than 12 hours were associated with the presence of sexual dysfunction ($p<0.001$ and $p=0.010$, respectively). Age, BMI and educational status did not affect sexual function. (Table 2). In multivariate analysis the presence of episiotomy was the only factor which was independently and significantly associated with sexual dysfunction [odds ratio (OR): 2.35, confidence interval (CI): 1.45-3.83, $p=0.001$]. Table 3 shows the multivariate analyses. In the multivariate analysis, we found that the duration of active phase of labor was not significant as an independent factor.

In evalutaion of ASEX subscores according to the presence of episiotomy; patients with episiotomy had significantly higher scores in sex drive, Ability to reach orgasm and satisfaction from the orgasm ($p<0.001$ for all). Besides arousal and lubrication was not affected by presence of episiotomy.

Table 1. General characteristics of the patients

	Mean ± SD
Age (years)	24.8±4.6
BMI (kg/m²)	15.8±4.2
Duration of labor (hours)	14.2±4.7
Total ASEX score	
Sex drive	2.4±0.9
Arousal	2.4±0.5
Vaginal lubrication	3.5±1.0
Ability to reach orgasm	3.4±1.1
Satisfaction from orgasm	3.5±1.8
	n (%)
Educational status	
Present	156 (87.2)
Absent	23 (12.8)
Episiotomy	
Present	66 (36.9)
Absent	113 (63.1)
Sexual dysfunction	
Present	121 (67.6)
Absent	58 (32.4)

BMI: Body mass index, ASEX: Arizona sexual experience scale, SD: Standard deviation

Discussion

We investigated the factors related to sexual dysfunction in the postpartum period and found that only episiotomy and delivery time were effective. We found that the rate use of episiotomy is not recommended. A systematic sexual dysfunction in women who delivered vaginally with review showed that routine episiotomy does not improve mediolateral episiotomy was approximately 2.5 times higher self-reported sexual function outcomes. According to the than those who did not undergo episiotomy (OR: 2.35, CI: 1.45-3.83, p<0.001) (Table 3). We could not find a relationship between age, education, BMI, duration of delivery and sexual functions in our study patients (Tables 2, 3).

Sexual life is a different phenomenon in the postpartum period than before pregnancy and childbirth. Age, education, BMI, marital status, whether the pregnancy is a desired pregnancy, whether she has given birth before, the weight of the baby born, whether it is intervened (vacuum or forceps delivery), vaginal or abdominal delivery and breastfeeding can cause female sexual dysfunction (15-18).

In the past, episiotomy was frequently used to protect the pelvic floor and for better and aesthetic wound healing. With many publications published today, it has been seen that these benefits are not as many as thought and the rates of episiotomy have decreased. Today, the decision to perform an episiotomy is a clinical decision and routine use of episiotomy is not recommended. A systematic review showed that routine episiotomy does not improve self-reported sexual function outcomes. According to the results of this review, patients who underwent routine episiotomy were more likely to experience pain during sexual intercourse, and it was recommended to limit the use of episiotomy (7).

In fact, there is no evidence to suggest that episiotomy prevents sexual dysfunction, according to a meta-analysis that scanned 54 years of published data published in JAMA in 2005. In fact, pain during sexual intercourse is more common in women with episiotomy. In the same meta-analysis, the evidence does not support traditionally routine episiotomy benefits for the mother. In fact, the results obtained with episiotomy can be considered worse because it is stated that a perineal tear that may occur during delivery will be less of an injury than an episiotomy (7).

Table 2. Factors affecting sexual dysfunction-univariate analyses

	Sexual dysfunction (+)	Sexual dysfunction (-)	p
Age (years)			
<35	70 (63.1)	41 (36.9)	0.098
>35	51 (75.0)	17 (25.0)	
Educational status			
Present	104 (66.7)	52 (33.2)	0.488
Absent	17 (73.9)	6 (26.1)	
Episiotomy			
Present	58 (87.9)	8 (12.1)	<0.001
Absent	63 (55.8)	50 (44.2)	
BMI (kg/m²)			
<22	61 (64.9)	33 (35.1)	0.416
≥22	60 (70.6)	25 (29.4)	
Duration of labor (hours)			
<12	61 (59.8)	41 (40.2)	0.010
≥12	60 (77.9)	17 (22.1)	

BMI: Body mass index, ASEX: Arizona sexual experience scale

Table 3. Factors affecting sexual dysfunction-multivariate analyses

	Odds ratio	Confidence interval	p
Age (years)	1.05	0.72-1.52	0.801
Educational status	1.09	0.64-1.85	0.749
Episiotomy	2.35	1.45-3.83	0.001
BMI (kg/m²)	1.06	0.75-1.49	0.740
Duration of labor (hours)	0.993	0.65-1.50	0.974

BMI: Body mass index, ASEX: Arizona sexual experience scale

In some publications, it has been stated that performing episiotomy has a positive effect on sexual life. When the data of 774 nulliparous women who underwent restrictive and routine episiotomy at the 4th year after delivery were compared, a lower rate of dyspareunia was observed in the group that underwent limited episiotomy, although it was not statistically significant (8).

WHO reported the episiotomy rate to be approximately 10% in 1996 (19). Following this, the rates of vaginal delivery with episiotomy started to decrease all over the world. It is difficult to determine a routine or liberal rate of episiotomy for individuals with spontaneous vaginal delivery. In a community-based study involving nulliparous and multiparous pregnant women in Canada, the rate of episiotomy in spontaneous vaginal deliveries decreased from 13.5% to 6.5% between 2004 and 2017. Likewise, in a study comparing previous periods in the USA, the rate of episiotomy was 2.5-34% (20,21). We included only nulliparous patients in our study and we found the rate of episiotomy to be 37%.

In our study, we found a significantly higher rate of sexual dysfunction in women who underwent episiotomy. Of 179 patients, 121 (68%) had sexual dysfunction. In 2015, Khajehei et al. (22) in their study with the female sexual function ındex, similar to our results, they reported the rate of sexual dysfunction in the first year postpartum as 64.3%. However, in another study, other sexual problems such as postpartum dyspareunia and loss of sex drive were reported at a rate of 30-60% in the 3rd month and 17-31% in the 6th month (23).

According to the results of our study, the main problem was found in sexual drive, ability to reach orgasm and satisfaction from the orgasm steps. Perineal trauma and episiotomy are associated with sexual dysfunction (3). Episiotomy may cause a decrease in vaginal lubrication, alteration of the vaginal epithelium, and the development of vaginal atrophy and may cause painful sexual intercourse. However, in our study, it was not demonstrated that episiotomy has an effect on vaginal lubrication (Table 4).

In these participant women, who were called and questioned in the 3rd month after giving birth, sexual drive may have been affected due to reasons such as baby care, insomnia, change in body image, social teachings.

In a study conducted with 282 healthy, non-pregnant Turkish women, it was reported that approximately half of the women had sexual dysfunction (24).

We asked whether the postpartum perineal pain in women who had episiotomy prevented them from having sex, and we learned that they did not have any local pain during intercourse at the episiotomy site. Therefore, in fact, the episiotomy site is healed and psychological concerns such as discharge and bleeding that will affect the sexual life psychologically are reduced. Sexual dysfunction seen in the 3rd month postpartum in women may not be due to a physical problem.

Study Limitations

The most important limitation of our study is that we did not apply a valid test for sexual dysfunction to the patients before pregnancy, but it is not possible to predict which patient would be suitable for the study in the prospective design, and the data on the evaluation of the relationship between the ASEX score and biological parameters are limited. ASEX is an objective test that is reliable, easy to perform, easily interpretable, and the results are not dependent on the researcher. The strongest aspect of our study is its prospective design and well-planned study with a homogeneous group. Nullipar has been studied with young, healthy puerperal patients. Each patient and the same doctor were interviewed one-on-one, and their answers were recorded.

Conclusion

According to the results of our study, vaginal delivery with mediolateral episiotomy has a negative effect on sexual function in women. Therefore, we do not support routine episiotomy, although the results are controversial.

Table 4. Effect of episiotomy on parts of the ASEX score

	Episiotomy (-)	Episiotomy (+)	p
Sex drive	2.2±0.9	2.7±0.8	<0.001
Arousal	2.4±0.5	2.4±0.5	0.860
Vaginal lubrication	3.4±1.2	3.7±0.8	0.168
Ability to reach orgasm	3.0±1.0	4.0±0.9	<0.001
Satisfaction from orgasm	3.1±1.7	4.2±1.7	<0.001

ASEX: Arizona sexual experience scale

Ethics

Ethics Committee Approval: This prospective study was performed in a tertiary hospital in accordance with principles of Helsinki Decleration. This study protocol was reviewed and approved by Batman State Hospital Ethical Board, approval number 249, date 20/07/2020.

Informed Consent: Written informed consent form was obtained from the women participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.O., Ö.K.A., E.G., Design: E.O., Ö.K.A., E.G., Data Collection or Processing: E.O., L.T., Analysis or Interpretation: Ö.K.A., E.G., Drafting Manuscript: E.O., Ö.K.A., L.T., Critical Revisation of Manuscript: Ö.K.A., E.G., Final Approval and Accountability: E.O., Ö.K.A., Technical or Material Support: E.G., L.T., E.O., Supervision: E.O., L.T., Ö.K.A., Writing: E.O., Ö.K.A.

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ORIGINAL RESEARCH

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Effects of "Longitudinal Gastrojejunostomy" on Malabsorption in a Rat Model of Short Bowel Syndrome

Kısa Bağırsak Oluşturulan Ratlarda "Longitudinal Gastrojejunostomi" Ameliyatının Malabsorbsiyon Üzerine Olan Etkilerinin Karşılaştırılması

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Abstract

Objective: Short bowel syndrome (SBS) is a serious and chronic disorder of inadequate absorption of nutrients and fluid from the intestines. The most significant symptom of SBS is malnutrition. Weight loss due to malnutrition raised the morbidity and mortality rates of patients to a disappointing level. The use of making longitudinal gastrojejunostomy is a technique to grow neomucosa or intestinal metaplasia in the gastric mucosal surface and increase the intestinal transit time.

Method: Three groups (Sham, SBS, longitudinal gastrojejunostomy) were created for 24 Wistar-Hannover rats. The 1st group was determined as the Sham group. SBS was induced in animals in group 2 with appropriate intestinal resection. Longitudinal gastrojejunostomy was additionally performed in rats with SBS in group 3. At the end of the 14th day all rats were weighted, euthanized, and blood sample was collected and anastomotic parts were resected for histopathological examination.

Results: Weight loss was significantly less in group 3 and vitamin B12 and GLP-2 levels were significantly higher in group 3 compared to group 2. Longitudinal antiperistaltic gastrojejunostomy promotes intestinal metaplasia in the gastric mucosa and increased the absorption surface.

Conclusion: This surgical procedure can be used to increase the absorption surface area in SBS. However, this needs to be supported by sufficiently robust clinical trials.

Keywords: Intestinal metaplasia, longitudinal gastrojejunostomy, short bowel syndrome

Öz

Amaç: Kısa bağırsak sendromu (KBS), bağırsaklardan besin ve sıvının yetersiz emiliminin şiddetli, kronik bir durumudur. Longitudinal gastrojejunostomi, mide mukoza yüzeyinde yeni bağırsak mukozası veya intestinal metaplazisi oluşturmak ve bağırsak geçiş süresini artırmak için düşünülmüş bir tekniktir.

Yöntem: Yirmi dört adet Wistar-Hannover rat 3 gruba ayrıldı. Birinci grup Sham grubu olarak belirlendi, 2. gruptaki hayvanlarda uygun bağırsak rezeksiyonu ile birlikte KBS oluşturuldu, 3. grupta KBS oluşturulan ratlara longitudinal gastrojejunostomi uygulandı. On dört gün sonra tüm sıçanlar tartıldı, ötenazi yapıldı ve kan örnekleri alındı. Histopatolojik inceleme için anastomoz kısımları rezeke edildi.

Bulgular: Grup 3'te kilo kaybı anlamlı olarak daha azdır ve grup 3'te grup 2'ye kıyasla vitamin B12 ve GLP-2 seviyeleri anlamlı olarak daha yüksektir. Longitudinal antiperistaltik gastrojejunostomi mide mukozasında intestinal metaplaziyi teşvik ettiği ve emilim yüzeyini artırdığı gözlenmiştir.

Sonuç: Bu cerrahi işlem kısa bağırsak sendromunda absorpsiyon yüzey alanını artırmak için kullanılabilir. Ancak bunun yeterince güçlü klinik deneylerle belirlenmesi gerekmektedir.

Anahtar kelimeler: İntestinal metaplazi, kısa bağırsak sendromu, longitudinal gastrojejunostomy

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Introduction

Short bowel syndrome (SBS) is a severe, life threatening condition of inadequate absorption of aliments and liquids from the intestines, which can be acquired or congenital. It is characterized by a reduction in the length of the intestines. After the procedure of intestinal resection, SBS is one of the major causes leading to intestinal failure (IF) (1,2). Small bowel atresia, volvulus, necrotizing enterocolitis, and invagination are the main clinical conditions of SBS in children. Strangulated bowel resection, inflammatory bowel diseases, trauma and ischemia are the most common causes leading to SBS in adults.

Important symptoms in these patients are; malnutrition, dehydration, diarrhea and steatorrhea. The severity of these symptoms are correlated to the length of the remnant small bowel (3). The leading clinical symptoms of SBS are malnutrition and loss of weight. A variety of clinical and surgical procedures, as well as parenteral nutrition (PN), have been used in the treatment of patients with SBS and in animal experiments. However, only minimal clinical progress could be acquired so far. Despite all the developments and studies, the morbidity and mortality rates in patients with SBS are disappointingly high. Patients with SBS are somewhat difficult to follow-up and patient survival is closely related to the adaptive capacity of the remaining intestines. However, proper absorption of the intestines may be possible with surgical treatments consisting of reconstructive procedures of the remaining intestine and intestinal transplantation (4). The purpose of reconstructive procedures is to prolong the intestinal transit time and accelerate the development of new intestinal mucosa (neomucosa). All these studies are still experimental (5). These studies for non-transplant procedures for the treatment of SBS can be divided into four categories: (1) Maximizing the remaining segments of the bowel (closure of stomas, minimizing nutritional loss due to enterocutaneous fistulas, and removing obstructions and blind loops) (2) improving peristalsis of dilated and/or dysmotile bowel by tapering or inversion plication (3) delaying the rapid passage of intestinal contents by reversing intestinal segments, forming semi-obstructive valves, or interpositioning the colon between a divided proximal jejunum; and (4) autologous reconstruction with intestinal lengthening, i.e., Longitudinal Intestinal Lengthening and Tailoring (LILT) (Bianchi) and Serial Transverse Enteroplasty (STEP), or sequential combinations of the two.

Published studies have been demonstrated the function of absorption in intestinal metaplasia of the stomach (6). The use of making longitudinal gastrojejunostomy is an intestinal mucosal/intestinal metaplasia augmentation technique in gastric mucosal surface and increase the intestinal transit time. Growing neomucosa/intestinal metaplasia is used for enlargement of absorbtive surface of the intestines.

In our experimental study we aim to investigate the effects of antiperistaltic, longitudinal gastrojejunostomy on malnutrition and weight loss.

Materials and Methods

Experimental design: Twenty-four male Wistar-Hannover rats (350-450 g), obtained from University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Animal Center (BADABEM), were fed with standard pellet, ad libitum. Ethic approval gained from the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Animal Care and Use Committee (2015-39).

Animal groups and surgical procedure: Rats were randomly and equally divided into 3 groups. Rats were anesthetized by an isoflurane (5% for induction and 2% for maintenance, Isoflurane® Baxter, Puerto Rico, USA). Each rat was weighed and recorded preoperatively. 3 cm midline abdominal incision was done. In group 1 (sham) stomach and jejunum were manipulated and revealed. Incisions closed without intervention. In groups 2 and group 3; the jejunum and ileum segments between 10 cm proximal to the ileocecal area and 10 cm distal from the Treitz ligament were resected, and anastomosis was performed with 7/0 polyproplen (Doğsan®, Trabzon, Turkey) suture. Additionally, in group 3; 50% of glandular part of the stomach was separated in longitudinal axis with 3/0 silk suture (Doğsan®, Trabzon, Turkey). The separated stomach was opened with a 1 cm incision in the longitudinal plane at the level of the large curvature and a 1 cm jejunotomy performed to the proximal jejunum and longitudinal, anti-peristaltic anastomosis was performed between these two tissues. This anastomosis was made proximal of the entero-enteral anastomosis (Figure 1). After these procedures, the abdomen was closed anatomically. After 14 days, all subjects were euthanized under anesthesia and blood was drawn by cardiac puncture and centrifuged for the measurement of biochemical parameters. (ALT, AST, magnesium, calcium, iron, glucagon like peptide-2, albumin and vitamin B12). En bloc resection of gastrojejunostomy was performed and 10% formaldehyde solution is used for tissue fixation for histopathological examination.

Histological analysis: The anastomotic parts were processed for paraffin embedding. Four micron paraffin sections were obtained and stained with hematoxylin-eosin. The tissue blocks that have minimum artifacts were gathered for immunohistochemical evaluation with MUC 1 (CellMarque 290M-14) and MUC2 (CellMarque 291-14) anticores. Alcian Blue (pH: 2.5) staining was performed for the intestinal type mucin examination.

Biochemical analysis: Blood samples were centrifuged for 10 minutes in 4000 rpm at +4 °C. Serum samples were stored at -80 °C. Glucagon like peptide-2 assay was carried out using "Micro Elisa" method. Sunred® Biological Technology Co. (Shangai, China) Micro Elisa kits were used in this process. All micro elisa measurements were performed on DAR800 micro elisa reader at 450 nm wavelength.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program was used for the statistical analysis. Descriptive statistical methods (standard deviation, mean), Mann-Whitney U test (group comparison) and chi-square test (comparison of qualitative data) were used. A p-value of <0.05 was considered statistically significant.

Results

No differences were observed between groups in food intake and no complications were observed in animals.

Body weight monitoring: Rats were weighed and recorded separately at the beginning and end of the surgical procedure. The mean weight losses of the groups (1-3) at the end of the experiment were determined as +2.79 gr, -38.88 gr and -34.61 gr, respectively. Weight loss was significantly low in group 3 compared to group 2 ($p<0.05$) (Table 1).

Histological evaluation: Intestinal metaplasia was determined in all rats of group 3 (Figure 1). Stratified epithelium was observed in the gastric mucosa in one specimen in group 3 (Figure 2).

Biochemical evaluation: No significant differences observed between group 1, 2 and 3 in terms of albumin, ALT, AST, Ca, Iron and Mg levels, but there was statistically difference between groups 2 and 3 in terms of vitamin B12 and GLP-2 levels (Table 2).

Discussion

Inability of the gastrointestinal tract to maintain sufficient and proper absorption and digestion without PN defined as IF. The clinical management of SBS is quite difficult and complicated. In cases which PN is not sufficient, a multidisciplinary approach that also requires surgical intervention should be used. Unfortunately, despite advances, these complicated and difficult treatment options are still associated with high morbidity and mortality rates (7,8). In addition to the benefits of PN, especially in its prolonged clinical use; it brings many major complications such as resistant hospital infections, thromboembolism, catheter problems, metabolic complications (renal or liver diseases) and ultimately organ failure (9). Several surgical procedures have been described for the management of SBS, such as construction of reversed intestinal segments, interposition of colon, and lengthening procedures. However, a clear gold standard procedure has not yet to be determined. Intestinal transplantation and autologous

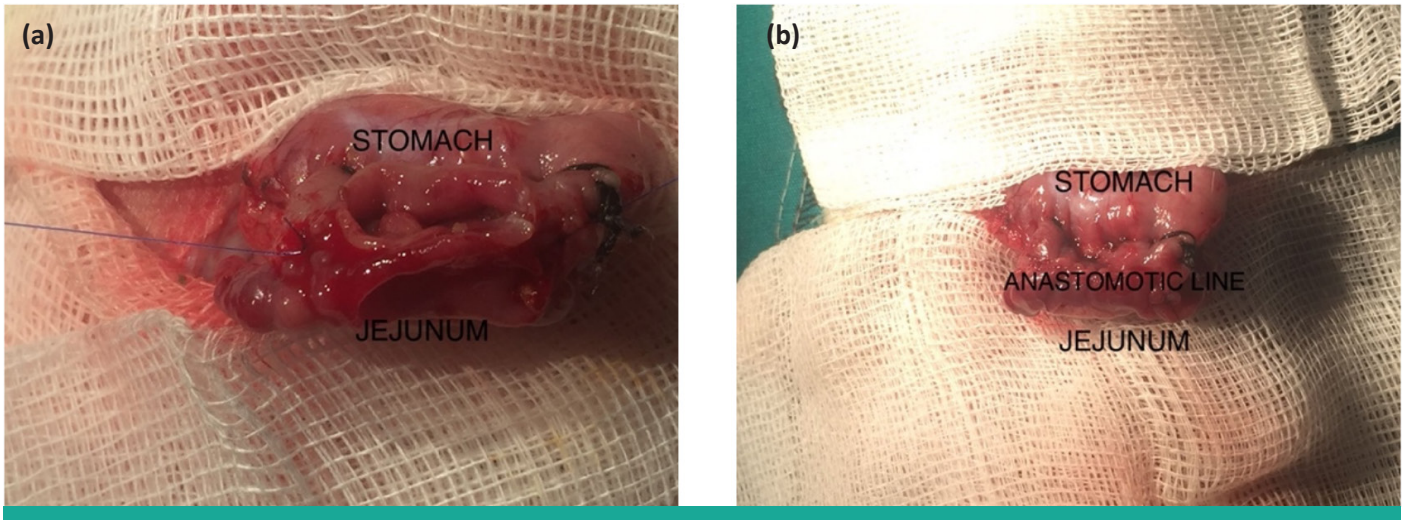

Figure 1. Surgical procedure. (a) and (b) Anastomotic line is shown between the separated gastric partition and ileum

reconstruction procedures consisting of an enlarged mucosal surface area and elongated bowel are the most recommended surgical interventions (7). Accepted autologous intestinal reconstruction procedures for the elimination of PN dependence are Bianchi procedure (LILT) and the STEP. These surgical approaches have major complications such as leakage of the stapler line, bleeding and stricture of the intestinal lumen. Intestinal transplantation is a very complex surgical intervention with high morbidity and mortality rates all over the world. It should be performed by experienced surgeons in specialized centers. For these reasons, it should be considered as the last treatment option (10,11).

Intestinal metaplasia of the stomach has an absorptive function which has been described previously in the literature (6). Growing intestinal metaplasia in gastric mucosa is a technique for expanding the absorptive surface volume of the intestinal mucosa. The use of gastric mucosa to grow intestinal metaplasia in SBS has not been described before and this study is the first experimental model in the literature as we know.

Weight loss is a significant clinical condition in patients with SBS and therefore weight monitoring is an important elimination of PN dependence are Bianci procedure follow-up criteria and it is a frequently used method in SBS studies. Weight gain or reduction in weight loss are a major complications such as a leakage of the stapler line, good indicator for progression in patients with SBS. Studies have reported various percentages of weight loss. Swartz-Basile et al. (12) reported a 10-20% weight loss in their study, Washizawa et al. (13) established a 10.8% weight loss, Koruda et al. (14) reported a 5.7% weight loss over a 1 week follow-up period. In the present study, we observed a 17.56% (38.88 gr) and 15.67% (34.61 gr) (group 2 and 3 respectively) over a 14 days follow-up period. A statistically significant difference was found between group 2 and 3 ($p<0.05$).

Electrolyte disturbances are important reason for morbidity in patients with SBS due to insufficient absorption.

Table 1. Body weight monitoring and the differences before and after the procedure

	Group 1	Group 2	Group 3
Before the procedure	217.81±21.1	221.33±25	220.75±24.5
After the procedure	220.6±24.1	182.45±11	186.14±11.7
Difference	2.79	-38.88*	-34.61*

*(p<0.05)

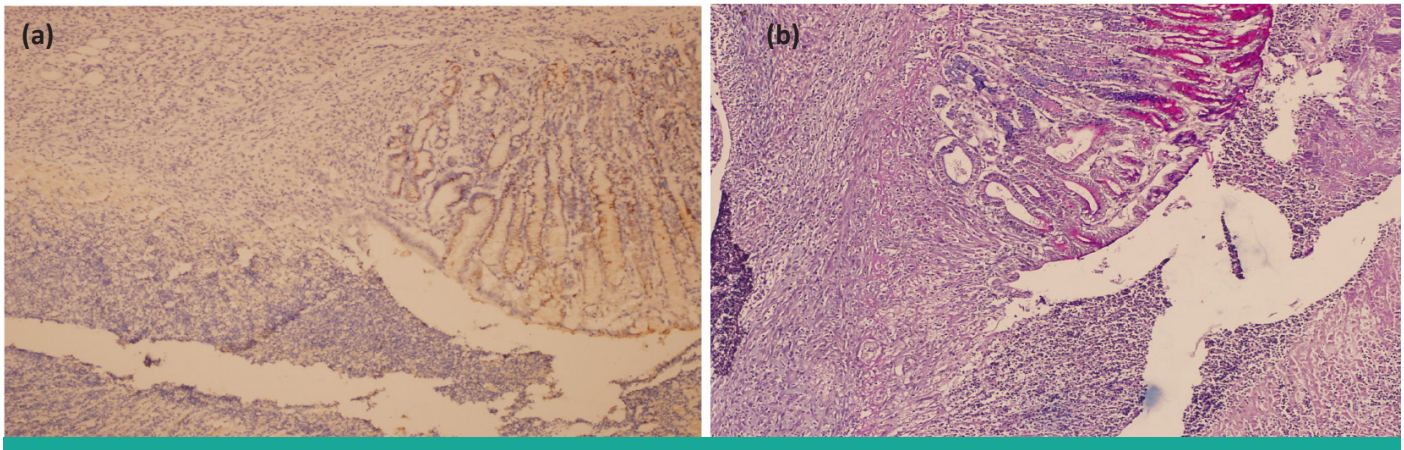

Figure 2. Intestinal metaplasia in the anastomotic line. (a): Hematoxylin and eosin (HE) x220, (b): Alcian blue (AB) x220

Table 2. Mean and standard deviations of biochemical values of the groups

	Albumin (g/dL)	ALT (U/L)	AST (U/L)	Ca (mg/dL)	Iron (mg/dL)	Mg (mg/dL)	Vit B12 (pg/mL)	GLP-2 (ng/mL)
Group 1	4.3±0.72	54.6±4.59	101.6±19.2	9.8±0.37	196.6±89	2.77±0.5	464±80.9	2.012±0.54
Group 2	3.22±0.71	41.51±5.42	118.43±41.9	9.695±0.84	108.31±41	2.52±0.2	374.83±82*	0.412±0.11*
Group 3	3.71±0.5	42.01±4.9	127.22±35.1	9.668±0.73	148.16±119	3.24±0.8	787.01±511*	1.845±1.08*

*(p<0.05), ALT: Aspartate aminotransferase, AST: Alanine aminotransferase, CA: Calcium, GLP-2: Glucagon-like peptide-2, Mg: Magnesium

Albumin, iron, magnesium, vitamin B12, calcium, AST and ALT levels are the significant indicators of nutritional status and liver function of the patient (15-18). Biochemical evaluation revealed that there were no statistically significant differences between the groups in levels of albumin, AST, ALT, Ca, iron and Mg, but group 3 had higher levels of vitamin B12 which is statistically significant ($p<0.05$).

Intestinal L-cells secrete Glucagon-like peptide-2 (GLP-2) after food intake. GLP-2 has effects on the intestines such as stimulating growth, increasing absorption, promoting regeneration and regulating integrity of the intestinal epithelium (19). Drucker et al. (20) reported that, GLP-2 was found to only stimulate the development of colon and small intestine tissues in mice, but had no effect on other gastrointestinal tissues. In SBS, GLP-2 performs its intestinal absorption-enhancing effect by increasing the development of intestinal tissues and slowing gastric emptying and gastro-intestinal transit time (20,21). In present study GLP-2 values of group 3 were significantly higher than group 2 ($p<0.05$).

Conclusion

In the evaluations 2 weeks after the formation of SBS in rat; it has been observed that "antiperistaltic, longitudinal gastrojejunostomy" has a reducing effect on weight loss due to massive resection of small bowel and promotes serum levels of vitamin B12 and GLP-2 which are essentials in the treatment of the patients with SBS. This surgical procedure may be beneficial in the treatment of SBS for expanding the total surface of intestinal absorption. Nevertheless, despite the positive results, this study was limited by the small amount of rats and short experimental follow-up period. Due to the limited number of rats used in the experiment and the short follow-up period, our study needs to be developed with other studies. More studies are needed before firm conclusions can be drawn about the safety and advantages of this surgical procedure. In the potential use of this surgical technique in patients with SBS, some possible side effects such as gastric ulcer or malignancy due to intestinal metaplasia should also be taken into account. Therefore, this experimental study has been an incentive for further studies.

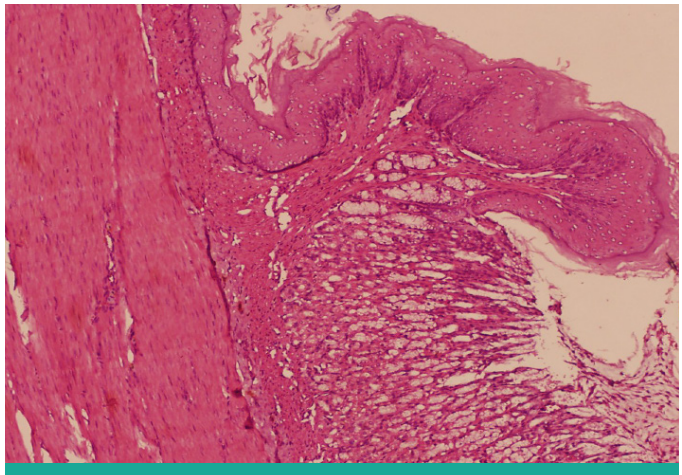

Figure 3. Stratified epithelium in the gastric mucosa (x220)

Ethics

Ethics Committee Approval: All experimental procedures were approved by the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Animal Care and Use Committee (2015-39).

Informed Consent: It is not necessary as it is an animal test.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., A.K.A., C.E., Concept: S.A., O.B.G., A.Ç., Design: S.A., O.B.G., A.Ç., Data Collection or Processing: S.A., A.B., A.K.A., C.E., Analysis or Interpretation: O.B.G., A.Ç., H.Y., A.K.A., Literature Search: C.E., A.Ç., H.Y., A.B., Drafting Manuscript: S.A., A.Ç., E.Y., H.Y., Critical Revision of Manuscript: C.E., A.Ç., H.Y., A.B., Supervision: A.Ç., O.B.G., E.Y., Writing: S.A., O.B.Ç., A.Ç., E.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH

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Evaluation of Demographic and Laboratory Parameters of Acute Coronary Syndrome Cases During and Before the COVID-19 Pandemic

Akut Koroner Sendrom Olgularının COVID-19 Pandemisi Sırasında ve Öncesinde Demografik ve Laboratuvar Parametrelerinin Değerlendirilmesi

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Abstract

Objective: Both ischemic heart diseases and Coronavirus disease-2019 (COVID-19) are the two main patient groups who frequently apply to emergency clinics recently. We aimed to evaluate the impact of the COVID-19 pandemic on the demographic and clinical processes in acute coronary syndrome (ACS) cases.

Method: This retrospective, single-center study was conducted on ACS patients who applied to the emergency department between March 10, 2019 and March 11, 2021. While the patients were divided into two as pandemic and prepandemic, the pandemic period was also grouped as COVID (+) and (-). ACS classification, clinical and laboratory results of the patients were evaluated.

Results: The mean age of 1.067 patients included in the study was 58.0±19.2 years and 785 (73.5%) were male. Two hundred and sixty-two (48.3%) of 542 cases in the pre-pandemic period were non-ST myocardial infarction (NSTEMI) and 202 (37.3%) were ST elevated myocardial infarction (STEMI). Among the COVID (+) cases in the pandemic group, 194 (76.9%) of 252 patients were NSTEMI and 34 (13.6%) were STEMI (p=0.001, p=0.013). During the pandemic period, STEMI was responsible for 7 (87.5%) of the 8 deaths in the COVID (-) group. In contrast, 20 (77%) of 26 COVID (+) deaths occurred in the NSTEMI group. NSTEMI mortality was considerably greater in the COVID (+) group (p=0.001).

Conclusion: Rapid care of instances of ACS in the emergency department has an effect on patient outcomes. Determining the severity, risk factors, laboratory findings, and outcomes of COVID-19 disease is crucial for a complete understanding of the mechanisms that can induce

Öz

Amaç: Hem iskemik kalp hastalıkları hem de Koronavirüs hastalığı-2019 (COVID-19) son dönemlerde acil servislere sıklıkla başvuran iki ana hasta grubunu oluşturmaktadır. Akut koroner sendrom (AKS) olgularında COVID-19 pandemisinin demografik ve klinik süreçlere etkisini değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif, tek merkezli çalışma, 10 Mart 2019-11 Mart 2021 tarihleri arasında acil servise başvuran AKS hastaları üzerinde yapılmıştır. Hastalar pandemi ve prepandemi dönemi olarak ikiye ayrılırken, pandemi dönemi de COVID (+) ve (-) olarak gruplandırıldı. Hastaların AKS sınıflaması, klinik ve laboratuvar sonuçları değerlendirildi.

Bulgular: Çalışmaya alınan 1,067 hastanın yaş ortalaması 58,0±19,2 yıl ve 785'i (%73,5) erkekti. Pandemi öncesi dönemdeki 542 olgunun 262'si (%48,3) non-ST elevasyonlu miyokard enfarktüsü (NSTEMI) ve 202'si (%37,3) ST elevesyonlu miyokard enfarktüsü (STEMI) idi. Pandemi grubundaki COVID (+) olgularından 252 hastanın 194'ü (%76,9) NSTEMI ve 34'ü (%13,6) STEMI idi (p=0,001, p=0,013). Pandemi döneminde COVID (-) grubundaki 8 ölümün 7'si (%87,5) STEMI kaynaklıydı. Buna karşılık 26 COVID (+) ölümün 20'si (%77) NSTEMI grubunda izlendi. NSTEMI mortalitesi COVID (+) grubunda önemli ölçüde daha yüksekti (p=0,001).

Sonuç: Acil serviste AKS olgularının hızlı değerlendirilmesi hasta hasta prognozu üzerinde oldukça etkilidir. COVID-19 hastalığının ciddiyetinin, risk faktörlerinin, laboratuvar bulgularının ve sonuçlarının doğru değerlendirilmesi, şiddetli akut solunum sendromu-koronavirüs-2 enfeksiyonunda AKS indükleyebilecek mekanizmaların tam olarak

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Abstract

ACS in severe acute respiratory syndrome-coronavirus-2 infection and for the development of strategies to facilitate the diagnosis and transfer of treatment in these patients.

Keywords: Acute coronary syndrome, COVID-19, emergency department, mortality

Öz

anlaşılması, tanı ve tedaviyi kolaylaştıracak stratejilerin geliştirilmesi açısından oldukça önemlidir.

Anahtar kelimeler: Acil servis, akut koroner sendrom, COVID-19, mortalite

Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity among adults despite modern medical facilities (1). In acute coronary syndromes (ACS), cardiovascular pathologies require rapid evaluation due to the importance of early diagnosis and treatment (2). In ACS cases, diagnosis and initiation of treatment in the emergency department is a critical dynamic process (3). Not promptly initiating appropriate treatments (cardiovascular and metabolic stability, emergency thrombolysis, oral antiaggregant, anticoagulant treatments or percutaneous interventions) for patients presenting to the emergency department with ACS results in a poor prognosis, and seriously affects morbidity and mortality (4). Negligence and disruptions in this process cause negativities in the health system and high cost rates in economic terms (5).

The emergence of the Coronavirus disease-2019 (COVID-19) pandemic has affected rates of ACS cases and changed the use of healthcare resources worldwide (6). At the onset of the pandemic, invasive cardiac procedures were primarily performed only in cases of ST-segment elevation myocardial infarction (STEMI) and critically non-ST-segment myocardial infarction (NSTEMI) to minimize personnel exposure (7). Considering the change in the application rates made with ACS during the pandemic period, different results were obtained according to the countries (8-10). NSTEMI cases were found to have a higher incidence of MI (45%) with non-obstructive coronary arteries compared to pre-pandemic cases, and this was suggested to be due to the inflammatory role of COVID-19 on acute coronary arteries (11). In a study conducted in Italy, one of the countries most affected during the pandemic, a decrease in STEMI rates was found (12). It has become important to determine patient response during the COVID-19 pandemic and its impact on acute medical conditions such as acute myocardial infarction.

During the COVID-19 pandemic, a sudden decrease in hospitalizations and an increase in out-of-hospital deaths were observed with ACS (13,14). The increase in mortality rates in ACS patients with concomitant COVID-19 was considered to be associated with acute myocardial injury secondary to novel Coronavirus 2019 severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (11). Rapid adaptation of the existing emergency health operation was necessary for overloaded healthcare systems to manage both a new transmission and an existing disease (15). Well-designed prognostic studies in the light of retrospective studies are required to better define the complex interaction of COVID-19 infection and cardiovascular disease caused by SARS-CoV-2.

Thus, it was aimed to contribute to the literature by showing the effect of COVID-19 disease on ischemic heart diseases.

Materials and Methods

Study Design and Population

Our retrospective, single-center study was conducted on patients who applied to our tertiary education and research hospital emergency department between March 10, 2019 and March 11, 2021. The study date range was planned according to the period declared as a pandemic in our country. The groups were divided into pre-pandemic (10.03.2019-10.03.2020) and pandemic (11.03.2020-11.03.2021). Comparisons made during the study were made between the pre-pandemic and the pandemic period. In total, 1.795 patients associated with cardiovascular diseases were studied. Patients diagnosed with STEMI, NSTEMI and unstable angina pectoris (USAP), which are the ACS groups, were selected. A total of 1.067 patients over the age of 18 (mean age 58.6±12.4 years, range 19-96 years) who met the definition of ACS were included in the study. For the definition of ACS, the codes specified in the International Classification of Diseases-10 (ICD-10) international disease coding system [ICD-10 codes for (USAP) (I20.0), STEMI (I21.0, I21.1, I21.2, and I21.3), NSTEMI (I21.4 and I22.2)] were used. Patients over the age of 18, who had complete demographic and laboratory data in the hospital data recording system, gave consent in accordance with the law on personal data protection,

and did not have additional pathologies specified in the exclusion criteria, were included. Among the data obtained from the hospital registry system, patients diagnosed other than ACS, who had recurrent records due to transfer within the cardiology clinic, and whose file information could not be accessed were excluded from the study. Patients diagnosed in the hospital registry system but with erroneous or insufficient test results, patients whose laboratory tests were requested in the hospital registry system but left the hospital without permission, additional disease (non-COVID infection, chronic systemic inflammatory disease, cerebrovascular disease, chronic liver failure). Patients with a history of anemia and haematological diseases, transfusion administration in the last 6 months) were excluded from the study.

Pandemic patients were divided into two groups as COVID (+) and COVID (-). Real-time polymerase chain reaction positivity was used to determine the diagnosis of COVID-19 infection. Age, gender, history, white blood cell (WBC), neutrophil, lymphocyte, thrombocyte, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) values and mortality status of the patients were analyzed. Hemogram blood was measured using Sysmex DI-60 CBC Analyzer (İstanbul, Turkey). Hemogram results were studied in 30-45 minutes.

The study was conducted after the Declaration of Helsinki for Human Research and was approved by the local ethical review board. Ethics committee approval was obtained from the Local Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (E-10840098-772.02-1405, 21.03.2021).

Statistical Analysis

IBM SPSS Statistics 18© (Copyright SPSS Inc. 1989, 2010) software was used for statistical analysis in our study. Frequencies were determined by performing descriptive statistical analyzes on all of the data. Categorical variables were expressed as frequency (n) and percentage (%), and continuous variables as mean ± standard deviation (SD). Comparative statistical analyzes were determined using Independent Student's t-test and chi-square test, depending on the type of variable. Results statistical analyzes were performed based on $p<0.05$ significance level and 95% confidence interval.

Results

The mean age of 1.067 patients included in the study was 58.0±19.2 years and 785 (73.5%) were male. Of the 542 patients in the pre-pandemic period, 405 (74.7%) were male and 137 (25.3%) were female. In the pandemic group, 201 (73.6%) of the COVID (-) cases and 179 (71%) of the COVID (+) cases were male. The mean ages of the groups were 56.3±21.1, 56.5±20.2, and 63.3±15.1 years, respectively, in the prepandemic, pandemic COVID (-), and pandemic COVID (+) periods (Table 1).

While 262 (48.3%) of 542 cases in the pre-pandemic period were NSTEMI and 202 (37.3%) were STEMI; among the COVID (+) cases in the pandemic group, 194 (76.9%) of 252 patients were NSTEMI and 34 (13.6%) were STEMI (p=0.001, p=0.013). USAP cases constituted 78 (14.4%) cases in the pre-pandemic period and 76 (14.5%) of 525 cases in the pandemic period. It was observed that USAP did not differ significantly between the groups (Table 2).

ACS diagnoses and Hb, WBC averages of the patients were compared. PD Hb values were 13.52±1.7 WBC values were 9.8±2.7, in PD Hb values were 14.01±1.9, WBC values, were 9.9±3.1. No significant difference was observed between the groups (p=0.843, p=0.921). ACS diagnoses and Hb, WBC averages of patients diagnosed with COVID-19 were compared. The Hb values of patients without a diagnosis of COVID-19 are 13.66±1.9. WBC values 9.48±2.8. In patients diagnosed with COVID-19, Hb values were measured as 13.68±2.1 and WBC values as 10.49±3.4. No significant difference was observed between the groups (p=0.961, p=0.991). The levels of C-reactive protein (CRP), troponin, and D-dimer were evaluated and found to have substantial SDs and variances. Variations may have come from variations in patients' arrival times at the hospital.

NLR and PRL values of the patients were 2.91±2.5 and 116.5±70.4, respectively, in the prepandemic group, 2.47±1.8 and 110.1±48.4 in NSTEMI, 3.49±2.5 and 125.8±76.4 in STEMI patients, respectively. While these values were similar in COVID (-) cases during the pandemic period, they were determined as 3.2±2.7 and 125.9±82.7 in NSTEMI, 4.1±3.2 and 159.8±80.7 in STEMI in cases with COVID-19 (+). NLR and PLR rates in COVID-19 (+) cases showed statistically significant differences in NSTEMI and STEMI types (p=0.027, p=0.039, Table 3).

Considering the comorbidity rates in COVID-19 (+) patients, 144 (63.7%) of 226 COVID (+) patients had a history of coronary artery disease (CAD) (p=0.001).

Three of the 4 cases (75%) that resulted in mortality in the pre-pandemic period were in the STEMI group. During the pandemic period, 7 (87.5%) of 8 cases in the COVID (-) group with mortality were STEMI. On the other hand,

20 (77%) of 26 patients in COVID (+) deaths were in the NSTEMI group. Mortality with NSTEMI was significantly higher in the COVID (+) group (p=0.001, Table 4).

Discussion

Despite all possibilities of modern medicine, today ischemic heart diseases are one of the leading causes of morbidity and mortality in adults (16,17). In countries where there are more cardiologist and percutaneous coronary intervention centers than the population, the fact that factors such as diabetes mellitus, smoking and obesity increase the mortality in ischemic heart diseases (18). It has been shown that in addition to social factors such as age, gender and lifestyle as the main risk factors in ischemic heart diseases, infectious diseases such as pneumonia lead to an increase in ischemic disease rates (19,20).

The relationship between the increase in mortality rates in the COVID-19 disease pandemic process, which was announced after the pneumonia cases that started in China in December 2019, and later spread to the whole world, with other diseases has been the subject of many studies (21-23). It has become important to reveal the relationship between COVID-19 and cardiovascular pathology, since the mortality rates of COVID-19 are higher in patients with cardiovascular pathology and the severity of COVID-19 is associated with cardiovascular symptoms (24). Making updates for the early diagnosis and intervention of patients with ACS during the COVID-19 process has also been the subject of international cardiology societies (25). Reduction or delay in hospital admissions of patients with ACS during the pandemic, differential diagnosis of acute myocardial injury, hospital isolation and protection of healthcare workers constituted the main difficulties experienced during the pandemic process (26). Considering gender predisposition, it was observed that male rates were higher in COVID-19 patients in previous studies (27). Susceptibility to COVID-19 infection was observed more in European countries in women before 50 years of age (28). On the other hand, it has been determined that in all age groups, men are hospitalized 20% more due to COVID-19 disease, need intensive care, and mortality is 1.74 times higher than women (27). It is suggested that the reason for the high mortality and morbidity rates observed in men is that they have more risk factors due to high smoking, stress and susceptibility to infection (29,30). In all patients examined in our study, the rate of ACS was observed approximately twice as high in men as in women. It was observed that

Table 1. Female and male application rates and mean ages prior to and during the influenza pandemic

	Pre-pandemic	Pandemic		Total
Gender	**n (%)**	**COVID-19 (-) n (%)**	**COVID-19 (+) n (%)**	
Male	405 (74.7)	201 (73.6)	179 (71)	785 (73.5)
Female	137 (25.3)	72 (26.4)	73 (29)	282 (26.5)
Total	542 (100)	273 (100)	252 (100)	1067 (100)
Mean age	**Mean ± SD**	**COVID-19 (-) Mean ± SD**	**COVID-19 (+) Mean ± SD**	
Male	56.6±21.2	55.4±20.5	61.6±14.9	57.4±16.5
Female	57.5±20.8	59.5±19.2	67.6±15.4	60.6±18.8
Total	56.3±21.1	56.5±20.2	63.3±15.1	58.0±19.2

COVID-19: Coronavirus disease-2019, SD: Standard deviation

Table 2. Distribution of patients associated with acute coronary syndrome before and during the pandemic period

	Pre-pandemic	Pandemic		
ACS classification	**n (%)**	**COVID-19 (–) n (%)**	**COVID-19 (+) n (%)**	**p-value**
NSTEMI	262 (48.3)	108 (39.5)	194 (76.9)	**0.001**[a]
STEMI	202 (37.3)	113 (41.4)	34 (13.6)	**0.013**[b]
USAP	78 (14.4)	52 (19.1)	24 (9.5)	0.873
Total	542 (100)	273 (100)	252 (100)	

COVID-19: Coronavirus disease-2019, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris ACS: Acute coronary syndrome

Pearson chi-square tests was used to compare the groups. [a]: Compared with pre-pandemic time, [b]: Compared with pre-pandemic time

NSTEMI rates increased in both genders, while STEMI rates decreased in patients presenting with ACS clinic before and during the pandemic. Similarly, NSTEMI rates were observed to be higher in both genders in patients with a diagnosis of COVID-19. In our study, when we looked at the distribution of diseases according to age ranges in patients diagnosed with cardiovascular disease, it was observed that the prevalence was higher in men between the ages of 40-69, and in women between the ages of 50-70. Although the risk increases in women after menopause, it continues to be lower than in men of the same age (29,31). In our study, when the age distribution of those with COVID-19 disease during the pandemic period was examined, an increase in the number of diseases after the age of 40 in men was observed after the age of 50 in women.

COVID-19 may have direct and indirect effects on the cardiovascular system (8-11). Patients with additional risk factors such as comorbidity associated with COVID-19, inflammatory process, cytokine storm and lung damage due to underlying comorbidity, increasing age, male gender, obesity and intensive care unit admission are at higher risk for ACS (22,23,32). It has been reported that a "cytokine storm", which is stimulated by an unbalanced response in defense cells due to infection and can cause respiratory dysfunction, hypoxemia, shock or hypotension in COVID-19 patients, causes damage to many organs, especially myocardium (33). Hypoxemia, respiratory failure, shock, and hypotension caused by pulmonary infections typically result in insufficient oxygen supply to the myocardium (34). In our study, an increase in NSTEMI rates and a decrease in STEMI rates were observed during the pandemic period. Higher rates of NSTEMI were observed in patients with COVID-19. In a study conducted in the United States, Italy and Spain, it was shown that STEMI rates decreased during the pandemic (12,35,36). Although the reasons for the decrease are unknown, a potential real decrease in acute cardiovascular events due to low stress factors during quarantine and a sedentary life are shown as the main reasons, but the thought that patients apply late for fear of catching a virus when they feel chest pain or while staying in the hospital outweighs (37). Although it is expected that the restrictions experienced in line with the measures taken during the pandemic period in our country may cause a decrease in hospital admissions, no significant difference was observed between the admission rates in our hospital. Considering the increased environmental and psychosocial stressors as a result of the effect of the pandemic, an increase in STEMI activations is expected (13). Possible etiologies for the reduction in STEMI rates include avoidance of medical care due to social distancing or concerns of contracting COVID-19 in the hospital, as well

Table 3. Comparison of laboratory results in acute coronary syndrome types

ACS	Pre-pandemic		Pandemic				
			COVID-19 (-)		COVID-19 (+)		
	Mean ± SD						
	NLR	PLR	NLR	PLR	NLR	PLR	p-value
NSTEMI	2.47±1.8	110.1±48.4	2.9±2.1	109.6±64.4	3.2±2.7	125.9±82.7	**0.027**[a]
STEMI	3.49±2.5	125.8±76.4	3.4±2.5	127.7±55.6	4.1±3.2	159.8±80.7	**0.039**[b]
USAP	2.23±1.6	103.6±54.2	1.5±0.6	86.5±34.4	2.1±1.5	107.7±91.3	0.142
Total	2.91±2.5	116.5±70.4	2.7±1.6	113.3±87.1	3.8±2.4	146.4±45.3	

COVID-19: Coronavirus disease-2019, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris, ACS: Acute coronary syndrome, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, Pearson chi-square tests was used to compare the groups [a]: compared with pre-pandemic time, [b]: compared with pre-pandemic time

Table 4. Mortality assessment before and during the pandemic

ACS cassification	Pre-pandemic	Pandemic		p-value
	n (%)	COVID-19 (-) n (%)	COVID-19 (+) n (%)	
NSTEMI	1 (25)	1 (16.6)	20 (77)	**0.001**[a]
STEMI	3 (75)	7 (87.5)	3 (11.5)	0.981
USAP	-	-	3 (11.5)	
Total	4	8	26	

COVID-19: Coronavirus disease-2019, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris ACS: Acute coronary syndrome, Student's t-test and, Fisher's Exact tests were used to compare the groups [a]: Compared with pre-pandemic time

as delays in transfer times and response in emergency health services that may occur during the COVID-19 pandemic (37). It has been suggested that acute complications are facilitated as a result of the increase in NSTEMI rates in the pandemic period and in COVID-19 patients, the increase in coronary artery disease (CAD) rates due to increased systemic inflammation, acceleration of atherogenesis, and social stress (38,39). The inflammatory response with infectious agents such as COVID-19 may contribute to the acceleration of atherogenesis (39). In our results, an increase was observed in the diagnosis of CAD history when the comorbidity rates were compared before and during the pandemic. In our study, it was observed that CAD history of NSTEMI patients was higher during the pandemic and among COVID-19 patients compared to other forms. Mortality rates were higher in NSTEMI patients.

Inflammatory responses mediated by COVID-19 infection begin with adaptive immunity and neutralization of antibodies and can induce acute organ damage (40). It has been reported that myocardial damage is worsened after acute infection in patients with increased inflammatory activity, platelet activation, increased thromboxane synthesis, and impaired fibrinolytic function (32-34). Levels of biomarkers of myocardial injury are affected by many factors, including infection, hypoxia, and kidney function, so the potential for "false positives" for myocardial injury in patients with COVID-19 should be considered (41,42). More specifically, the presence or absence of myocardial injury or myocarditis should not be based solely on biomarkers of myocardial damage, but rather should be evaluated together with the results of ancillary procedures and tests after careful evaluation of all clinical parameters of the patient (43). In this context, it was found that inflammatory parameters such as CRP, NLR, PLR play a role in the monitoring of COVID-19 infection, and especially lymphocytes and platelet counts are correlated with the severity of COVID-19 disease (44). It has been stated that activation of neutrophils and changes in other leukocyte ratios during the inflammatory response in COVID-19 can be used as a prognostic indicator together with other inflammatory markers (45). Likewise, the increase in NLR observed in the early period of ACS was correlated with the mortality of acute myocardial infarction (46). CRP elevation in 80% of patients with severe COVID-19 disease who died; lympopenia was detected in 74% of them and an elevated neutrophil count was shown in 60% of them together with other inflammatory markers (47). In our study, the PLR rates of the patients were found to be higher in the pandemic period and in COVID-19 patients.

Evaluation of the study as a single-center and retrospective analysis covering a certain time period, the inability to determine the comorbidity rates of the patients clearly due to the deficiencies in the patient information system, the incompleteness of mortality information in the patients referred to an external center, the inability to follow-up the laboratory values in all patients due to the referral of some patients to an external center, can be counted among the limitations. However, our study is a strong study with a strong patient population evaluating changes in patients with ACS in one of Europe's most populous cities, where no healthcare system containment strategy against the COVID-19 pandemic has been included.

Conclusion

Cardiac complications seem to come to the fore among the acute and chronic complications of COVID-19 disease. The rapid management of ACS cases in the emergency department affects patient outcomes. Determining the severity, risk factors, laboratory findings, and outcomes of COVID-19 disease is essential to properly understand all the mechanisms that can induce ACS in SARS-CoV-2 infection, and to develop strategies to facilitate diagnosis and transfer of treatment in these patients. Thanks to the demographic characteristics, laboratory findings and patient outcomes we obtained from our study, guiding predictions can be provided in the diagnosis and treatment of critically ill patients.

The importance of the contribution of retrospective studies and case reports to the literature in the pandemic process has been seen once again. In order to guide the diagnosis and treatment guidelines, retrospective studies should continue, as well as prospective studies that will present the findings related to the relationship between coronary syndromes and COVID-19 to the literature, focused on comprehensive targets, and are suitable for clinical operation.

Ethics

Ethics Committee Approval: The study was conducted after the Declaration of Helsinki for Human Research and was approved by the local ethical review board. Ethics committee approval was obtained from the Local Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (E-10840098-772.02-1405, 21.03.2021).

Informed Consent: All subjects gave their informed consent for inclusion before they participated in the study.

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Authorship Contributions

Surgical and Medical Practices: B.Ç., A.C., B.D., H.K., B.A., Concept: B.Ç., A.C., B.D., B.A., Design: B.Ç., A.C., B.D., B.A., Data Collection or Processing: B.Ç., A.C., B.D., H.K., Analysis or Interpretation: B.Ç., A.C., B.A., Drafting Manuscript: B.Ç., A.C., B.D., H.K., B.A., Critical Revision of Manuscript: B.Ç., A.C., B.D., Final Approval and Accountability: B.Ç., A.C., B.D., H.K., B.A., Supervision: B.Ç., A.C., Writing: B.Ç., A.C., B.D., H.K., B.A.

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ORIGINAL RESEARCH

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Management of Reconstruction of the Columella in Open Rhinoplasty Procedure: Using b-Shaped Columellar Strut Graft

Açık Rinoplasti Prosedüründe Kolumella Rekonstrüksiyonunda b-Şeklinde Dizayn Kolumella Strut Kullanımı

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Abstract

Objective: The columellar strut graft (CSG) can help to correct nasal tip (NT) deformities in rhinoplasty. The value of using the CSG technique as a routine procedure in rhinoplasty is still being debated. The reason for this ambivalence is the increased rotation effect of a CSG on the NT. In this article, "b" (small letter "B") shaped CSG was prepared differently from the traditional CSG, and two different designs of CSGs were compared in terms of nasolabial angles.

Method: A total of 99 patients who were operated on using CSG between September 2018 and March 2020 were included in this study. We analyzed preoperative and postoperative lateral views of photographs and case histories of 99 patients. Traditional shape and b-shaped CSGs were used for 33 (33.3%) and 66 (66.6%) of the total patients, respectively. The groups of traditional shaped and b-shaped CSGs were compared with statistical analysis.

Results: When postoperative nasolabial angles were evaluated, it was found that 36.4% and 7.6% of the nasolabial angles were above the optimal range in the traditional strut graft group and b-shaped CSG group, respectively. Wide-nasolabialangles were observed to be more common in cases with traditional strut grafts than in cases with b-Shaped CSG. The b-shaped CSG provided gain optimal projection without extended rotation. The difference between the two groups was statistically significant (p=0.00).

Conclusion: The overall conclusion derived from this research is that an optimally shaped columella can be obtained using a b-shaped CSG without overrotation of the NT.

Keywords: Columella reconstruction, columellar strut graft, open rhinoplasty

Öz

Amaç: Kolumellar strut greft (KSG), rinoplastide nazal tip (NT) deformitelerinin düzeltilmesine yardımcı olabilir. Rinoplastide rutin bir prosedür olarak KSG tekniğinin kullanılmasının değeri halen tartışılmaktadır. Bu kararsızlığın nedeni, KSG'nin NT üzerindeki artan rotasyon etkisidir. Bu makalede geleneksel KSG'den farklı olarak "b" (küçük harf "B") şeklinde KSG hazırlanmış ve iki farklı KSG tasarımı nazolabial açılar açısından karşılaştırılmıştır.

Yöntem: Bu çalışmaya Eylül 2018-Mart 2020 tarihleri arasında rinoplasti operasyonu geçiren ve KSG kullanılan toplam 99 hasta dahil edildi. Tüm hastaların ameliyat öncesi ve sonrası lateral fotoğrafları incelendi, hasta bilgileri toplandı. Toplam hastaların sırasıyla 33'ünde (%33,3) ve 66'sında (%66,6) geleneksel şekil ve b-şekilli KSG'ler kullanıldı. Geleneksel şekil ve b-şekilli KSG grupları arasındaki NLA açılar arasındaki farklar istatistiksel analiz ile karşılaştırıldı.

Bulgular: Ameliyat sonrası nazolabial açılar değerlendirildiğinde geleneksel strut greft grubunda ve b-şekilli KSG grubunda nazolabial açıların sırasıyla %36,4 ve %7,6'sının optimal aralığın üzerinde olduğu bulundu. Geniş nazolabial açılar, geleneksel strut greftli olgularda b-şekilli KSG'li olgulara göre daha sık gözlendi. b-şekilli KSG, aşırı rotasyon olmaksızın optimum projeksiyon elde edilmesini sağladı. İki grup arasındaki fark istatistiksel olarak anlamlıydı (p=0,00).

Sonuç: Bu araştırmadan elde edilen genel sonuç, burun ucunun aşırı döndürülmesi olmaksızın b-şekilli bir KSG kullanılarak optimal şekilli bir kolumella elde edilebileceğidir.

Anahtar kelimeler: Açık rinoplasti, kolumella dikme grefti, kolumella rekonstrüksiyonu

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Introduction

Tip control is critical to the functional and cosmetic outcomes of rhinoplasty (1). In rhinoplasty, nasal function and nasal tip (NT) support should be preserved (2). If the NT is left unsupported during surgery, loss of the NT projection and NT ptosis are observed at a high rate; as a result of these, nasal airway obstruction can occur (3).

The columella provides a balanced relationship between the alar rim on both sides and the medial cruras (1). The lateral view of the columella should not retract and overhang for satisfactory aesthetic outcomes. The natural and well-shaped columella provides a pleasant lateral aspect.

In previous studies, there are various methods to increase NT support. A columellar strut graft (CSG) is used to increase NT support (4). Other techniques are caudal extension graft, extended CSG, suturing the medial crura to a long caudal septum, and suspension of lower lateral cartilage to the upper lateral cartilage with suture administration (1). All of the methods that are mentioned above lead to some complications associated with the NT and caudal part of the nose. Retracted columella, the stiffness of the NT, over-rotation of the NT, and acute nasolabial angle (NLA) are the most common complications in the literature (1,5). The value of using the CSG technique as a routine procedure in rhinoplasty is still being debated. The reason for this ambivalence is the increased rotation effect of a CSG on the NT (6).

The upperlip, pre-maxilla, anterior nasal spine, columella and nasal base have complex anatomical relations and variable anthropometrical measurements (8). Preoperative assessment of all facial elements is important to creating harmony of the face. Several measurements are used for the assessment of anthropometrical relations. NLA is an essential parameter of preoperative and postoperative measurement. NLA indicates the quantification of NT rotation and tip position (9). Therefore, NLA measurement was used to detect NT rotation in this study.

The traditional strut's shape was believed to cause excessive NT rotation, thus the strut was created with a modified shape. In this research, "b" (small letter "B") shape CSG was prepared differently from the traditional CSG and two different designs of columellar strut were compared in terms of NLA and lateral columellar views. In this study, we wanted to present the results of the b-shaped CSG.

Materials and Methods

The essential approval was obtained to use the hospital database. Ethical approval was obtained from the Alanya Alaaddin Keykubat University Faculty of Medicine for the study (number: 08-07, date: 28/04/2021). A total of 99 patients who operated open approach rhinoplasty with using CSG were included in this study during the period of September 2018 to March 2020. The research included all patients older than 18 who underwent a rhinoplasty procedure utilizing a traditional or b-shaped strut over the time period specified above. Thus, other changes in the NLA were standardized. Demographic features of patients, a type of CSG which was used, preoperative-postoperative NLA, and postoperative follow-up periods were recorded. The patient should be rotated until the philtral columns are aligned to have standardized lateral view photographs were taken by the same surgeon. The patients' photographs that were preoperatively and postoperatively (2 weeks-1 month-3 months-6 months-1 year) were examined. The patients' photographs which were preoperatively and postoperatively (2 weeks-1 month-3 months-6 months-1 year) were examined.

The optimal NLA was determined to be between 95 and 105 degrees, according to the literature. The measurements were taken by an impartial researcher who was not aware of the procedure using retrospective digital preoperative and postoperative photographs. The degree of NLA was analyzed objectively using two defined lines superimposed on the lateral profile of the face. The 1st line was drawn parallel to the upper lip, and the 2nd line was drawn as the projection of the columella. The NLA between the first line and the second line was measured using Synedra View Personal Version 20.0.0.4 (x64 Community Edition).

Operative Technique

Before the rhinoplasty treatment, a local solution was administered to the subperiosteal and subperichondrial planes under general anesthesia. For the open method, a "W" incision was performed. Nasal skin and soft tissue were harvested from the Osseo-cartilage framework, and then the nasal dorsum was exposed. The septum was dissected subperichondrally, and a cartilaginous graft was created from the septal cartilage. The harvested graft was carved in a "b" shape. The dimensions of the thin part of the b-shaped CSG were approximately 1.5 cm x 0.5 cm, while the dimensions of the distal part of the strut graft were 0.5 cm x 0.7 cm (Figure 1A). During NT plasty, a pocket was formed between the medial crura of the alar cartilages. The pocket was prepared in a way that the distal part of the CSG would fit into it without

accessing the anterior nasal spine (Figure 1B). The CSG was positioned in the prepared pocket. The protruding part of the strut graft was toward the skin, and the bottom part of the b-shaped CSG was located from a third of the distal portion of the columella towards the anterior nasal spine. A polypropylene suture was passed from one medial crura to the distal third of the thin part of the b-shaped CSG, and then it was passed to the other medial crura and tied on one side of the strut graft.

The reduction of the dorsal hump and narrowing of the nasal bone base were performed by nasal osteotomies. Reshaping and refinement of the NT were performed using sutures. After final inspection and palpation, the incisions in the skin were closed. Both groups had the same key surgical methods and approaches to rhinoplasties.

Statistical Analysis

Statistical analysis was performed using SPSS software version 25.0 (IBM, Armonk, NY, USA), and and a p-value less than 5% was considered statistically significant. The Mann-Whitney U test was used to compare the two groups for statistical differences. Firstly, it was examined whether the data has a normal distribution or not with Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the data did not show normal distribution, the Mann-Whitney U test was used to compare two independent measurements. The independent t-test was used to determine whether there was a statistical difference in NLA between the two groups.

Results

We evaluated the preoperative and postoperative lateral view images and case histories of 99 patients who had open rhinoplasty in this retrospective analysis (Figures 2, 3). There were 61 female patients and 38 male participants in the research. The patients' average age was 23 (r=18-53) (Table 1). None of the patients had comorbidities such as diabetes or hypertension, while four patients had a history of smoking. The mean follow-up was 17.3 months. Traditionally shaped and b-shaped struts were used for 33 (33.3%) and 66 (66.6%) of the patients, respectively (Table 2). There was no statistical difference between the two groups in age, gender, or follow-up period.

When the postoperative NLAs were evaluated, it was found that 36.4% and 7.6% of the NLAs were above the optimal range in the traditional strut graft group and in the b-shaped CSG group, respectively (Table 3). The mean postoperative NLA with the traditionally shaped columellar strut was 104.12±9.23, while the mean postoperative NLA with the b-shaped columellar strut was 95.93±6.93. A statistically significant difference was found between the postoperative NLAs (p=0.00) (Table 4). When the measurement was compared between the traditional strut graft group and b-shaped strut graft group, optimal NT rotation was obtained without increasing the NLA degree over the optimal degree in the b-shaped CSG group, unlike the traditional strut graft group.

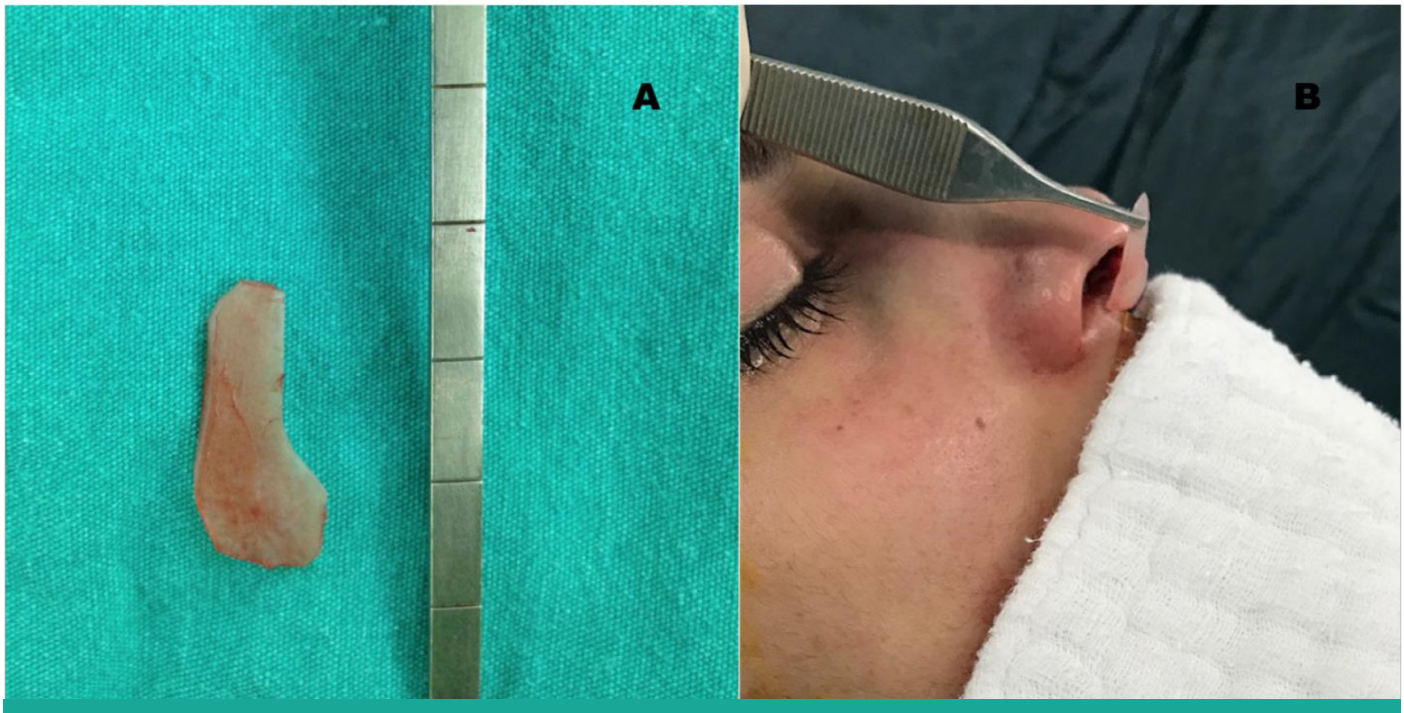

Figure 1. The design and size of the columellar strut (A), the projection of the positioning of the graft in the pocket (B)

Figure 2. Pre-operative view of a 28 years old patient with a nasal dorsal hump, a low NT and thin skin of nose. The "b-shaped" CSG was performed and native lateral columelar show was obtained at the lateral view of patient

CSG: Columellar strut graft, NT: Nasal tip

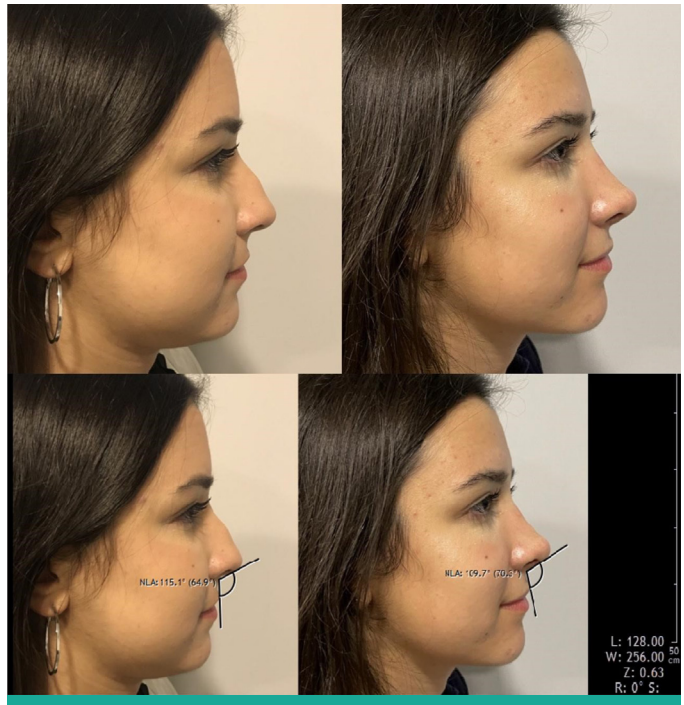

Figure 3. The preoperative lateral profile view shows a nasal dorsal hump and the low degree of the columellar show. The "b-shaped" CSG was performed and native lateral columellar show was obtained at the lateral view of patient

CSG: Columellar strut graft

Table 1. Demographic features of patients and follow-up periods

Type of graft	Age (years)		Gender		Follow-up periods (months)	
Traditional	Min	18	F	24	Min	11
	Max	45	M	9	Max	30
	Mean	26	**Total**	33	**Mean**	14
b-shaped	Min	18	F	37	Min	11
	Max	53	M	29	Max	30
	Mean	23	**Total**	66	**Mean**	15

Table 2. Minimum, maximum, and average preoperative and postoperative angles for each type of columellar strut graft

Type of graft	Preoperative NLA		Postoperative NLA	
Traditional	Min	70	Min	85
	Max	115	Max	125
	Mean	90	**Mean**	104
b-shaped	Min	54	Min	82
	Max	120	Max	120
	Mean	93	**Mean**	95

NLA: Nasolabial angle

Table 3. The frequency and percentage of nasolabial angles above the optimal range for each group

Type of graft			Frequency	Percent	Valid percent	Cumulative percent
Traditional	Valid	Above optimal range	12	36.4	36.4	100.0
		Total	33	100.0	100.0	
b-shaped	Valid	Above optimal range	5	7.6	7.6	100.0
		Total	66	100.0	100.0	

Table 4. The mean of postoperative nasolabial angles

	Type of graft	N	Mean	Standard deviation	Standard error mean
Postop NLA	b-shaped	66	95,9394	6,93459	0,85359
	Traditional	33	104,1212	9,23566	1,60772

p=0.00

Postop: Postoperative, NLA: Nasolabial angle

Complications such as hematoma, wound infection, and skin necrosis were not observed. In the b-shaped CSG group, columella, stiffness of the NT, over-rotation of the NT, and acute NLA were not observed. Only one patient was able to feel the prominent distal part of the b-shaped CSG, but it was not visible. Thus, any revision procedure was not demanded.

Discussion

NT integrity that is formed by healthy and stable attachment is important to ensure good nasal function and to avoid aesthetic problems (7). However, correction of the NT deformity requires a complex procedure and control of the long-term view of the most difficult component of rhinoplasty (2-9). CSG is the most preferred technique for correcting NT deformity. The CSG can help to support a central scaffold, correct asymmetry of the medial crura, provide much-needed support for lower lateral crura and also maintenance and optimization of tip projection (10,11). In this study, CSG was used for all patients depending on various reasons.

Tripod theory is a concept that involves changing the length of the alar cartilage to change the appearance of the NT. The role of both alar cartilages in the base dynamics is highlighted in this theory. A CSG can be placed between the medial crura along the caudal edge of cartilaginous septum to replace medial limb of the tripod (10). In this study, two different shapes of CSGs -a traditional CSG and a b-shaped CSG- were compared in terms of NT rotation. When postoperative NLAs were measured, 36.4% of the NLAs were above the optimal range in cases where the traditional strut was used. Wide NLAs were observed more frequently in cases where the traditional CSG was used than in cases where the b-shaped CSG was used. Both designs of CSG increased the projection of the nose after the operation in agreement with the literature (10,12,13). Therefore, the measurement of tip projection was not included in this study. However, the b-shaped CSG provided gains in projection without extended rotation. When a CSG is used, the NT position changes progressively during the healing period. It is generally believed that the final result is not seen until at least 12 months after rhinoplasty surgery (8). Therefore, the postoperative photos analyzed in this study were taken at least 12 months postoperatively.

The NT includes polygons and breakpoints, and the aesthetically pleasing reconstructed columella should also be designed as a geometric form that has angles similar to those of a natural columella (14). In our clinical experience, the columella is observed as a straight line in cases where a traditional CSG is used; therefore, in this study, a CSG was designed with a geometric shape different from that of the traditional CSG. We believe that the angled appearance of the columella cannot be obtained using a traditional columellar strut, which is prepared in the form of a straight strip. However, when a b-shaped CSG is used, a lateral view of the columella is more pleasing and natural.

Conclusion

The overall conclusion derived from this research is that an optimally shaped columella can be obtained by using a b-shaped CSG without over-rotation of the NT.

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Ethics

Ethics Committee Approval: The essential approval was obtained to use the hospital database. Ethical approval was obtained from the Alanya Alaaddin Keykubat University Faculty of Medicine for the study (number: 08-07, date: 28/04/2021).

Informed Consent: Consents of patient were obtained from all our patients.

Peer-review: Externally and internally peer-reviewed.

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ORIGINAL RESEARCH

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The Usage of Prognostic Nutritional Index to Predict Postoperative Atrial Fibrillation Development

Postoperatif Atriyal Fibrilasyon Gelişimini Öngörmede Prognostik Nutrisyonel İndeks Kullanımı

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Abstract

Objective: Postoperative atrial fibrillation (POAF) is one of the most common complications of cardiac surgery and frequency varies according to the type of surgery. Prognostic nutritional index (PNI), has been shown to be associated with adverse outcomes in heart failure, stroke, chronic renal failure, coronary artery disease, and ST-segment elevation myocardial infarction. In this study, we aimed to evaluate the relationship between PNI and POAF development in patients with a diagnosis of chronic coronary syndrome who underwent coronary angiography and decided to be treated with coronary artery bypass graft (CABG) operation.

Method: Patients diagnosed with chronic coronary syndromes and decided to be treated by CABG surgery at our institution between March 2014 and 2019 were evaluated retrospectively.

Results: A total of 314 patients were included in the study. Two groups were formed according to POAF development. Fifty-eight patients constituted the POAF (+) and 256 patients formed the POAF (-) group. Age, body mass index (BMI), hypertension, coronary artery disease, chronic obstructive pulmonary disease, creatinine were significantly higher and hemoglobin, hematocrit, left ventricular ejection fraction (LVEF) and PNI were found lower in the POAF (+) group. Advanced age, high BMI and creatinine, low LVEF and PNI were determined as independent risk factors for the development of POAF. It was concluded that a cut-off value of 53.13 for PNI could predict the development of POAF with 70.9% sensitivity and 69.6% specificity.

Conclusion: POAF was observed more frequently in patients in lower PNI values. PNI is an easy to use, rapidly measured and widely available index and have good diagnostic accuracy in determining POAF development. Aggressive treatment of malnutrition will be important in addition to personalized dyslipidemia therapy in patients with stable coronary artery disease.

Keywords: Coronary artery bypass graft surgery, postoperative atrial fibrillation, prognostic nutritional index

Öz

Amaç: Postoperatif atriyal fibrilasyon (POAF), kalp cerrahisi sonrası en sık görülen komplikasyonlarından biridir. Kalp yetmezliği, inme, kronik böbrek yetmezliği, koroner arter hastalığı ve ST segment yükselmeli miyokard enfarktüsünde düşük prognostik nütrisyonel indeks (PNI) değerinin olumsuz sonuçlarla ilişkili olduğu gösterilmiştir. Bu çalışmada koroner anjiyografi yapılan ve koroner arter baypas greft operasyonu (KABG) yapılan kronik koroner sendrom tanılı hastalarda PNI ve POAF ilişkisini değerlendirmeyi amaçladık.

Yöntem: Mart 2014 ve 2019 tarihleri arasında hastanemizde, kronik koroner sendrom tanısıyla KABG cerrahisi kararı verilen hastalar geriye dönük olarak değerlendirildi.

Bulgular: Çalışmaya toplam 314 hasta dahil edildi. POAF gelişimine göre 2 grup oluşturuldu. Elli sekiz hasta POAF (+) ve 256 hasta POAF (-) grubunu oluşturdu. Yaş, vücut kitle indeksi (VKİ), hipertansiyon, koroner arter hastalığı, kronik obstrüktif akciğer hastalığı, kreatinin POAF (+) grupta istatistiksel olarak anlamlı yüksek ve hemoglobin, hematokrit, sol ventrikül ejeksiyon fraksiyonu (SVEF) ve PNI ise anlamlı olarak daha düşük saptandı. İleri yaş, yüksek VKİ ve kreatinin, düşük SVEF ve PNI ise POAF gelişimi için bağımsız risk faktörleri olarak saptandı. PNI için 53,13 eşik değerinin POAF gelişimini %70,9 duyarlılık ve %69,6 özgüllük ile öngördürebildiği sonucuna ulaşılmıştır.

Sonuç: Düşük PNI değerlerinde daha sık POAF geliştiği saptanmıştır. PNI, kullanımı kolay ve hızlı sonuç veren bir indeks olup inflamatuar ve nütrisyonel durumun birlikte değerlendirilebilmesini sağlamaktadır. Stabil koroner arter hastalığı olan hastalarda kişiye özel dislipidemi tedavisine ek olarak malnütrisyonun agresif tedavisi önemli olacaktır.

Anahtar kelimeler: Koroner arter bypass greft cerrahisi, postoperatif atriyal fibrilasyon, prognostik nütrisyonel indeks

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Introduction

Postoperative atrial fibrillation (POAF) is one of the most common complications of cardiac surgery and frequency varies according to the type of surgery. It may develop in 15-40% of the patients after coronary artery bypass graft (CABG), whereas its incidence may raise up to 33-49% after valvular surgery (1,2). Perioperative oxidative stress, inflammation, electrolyte disturbance, ischemia, electrical remodeling and pain are known triggers for POAF development (3,4). Since most of the episodes terminate spontaneously, POAF is occasionally linked with myocardial infarction, stroke and death and those patients who experienced POAF has a 4-5-fold risk of persistent atrial fibrillation (AF) occurrence in 5 years follow-up (5).

Lymphocytes and neutrophils play a central role in atherosclerotic plaque rupture via immune reactions. Furthermore, lymphocytes have important roles in modulating the inflammatory response at different stages of the atherosclerotic process. Association between POAF development and inflammatory biomarkers has been shown in many studies (6). On the other hand, malnutrition, accelerates the atherosclerosis development by triggering inflammation (7). Malnutrition can be evaluated with various scoring systems. Prognostic nutritional index (PNI), is an index revealed by calculating the lymphocyte, which is an indicator of inflammation, and albumin, which is an indicator of nutrition, with the formula [serum albumin (g/L) + 0.005x lymphocyte count/mm^3]. Moreover, PNI has been shown to be associated with adverse outcomes in heart failure, stroke, chronic renal failure, coronary artery disease, and ST-segment elevation myocardial infarction (8, 9).

In this study, we aimed to evaluate the relationship between PNI and POAF development in patients with a diagnosis of chronic coronary syndrome (CCS) who underwent coronary angiography and decided to be treated with coronary artery bypass grafting.

Materials and Methods

Patients diagnosed with CCSs and decided to be treated by CABG surgery at our tertiary center between March 2014 and March 2019 were evaluated retrospectively. All patients signed an informed consent form before operation. All transactions were carried out in agreement with the Declaration of Helsinki. Pre-, peri- and postoperative data were retrieved from hospital database and patients' files. Demographic, clinical and laboratory parameters were noted for each patient. The patients with preoperative AF rhythm or history of atrial arrhythmia, moderate to severe valvular disease, congenital heart disease, preoperative renal disease (serum creatinine >2 mg/dL), albuminuria and chronic liver disease, albumin replacement therapy in past 6 months, previous diagnosis of an autoimmune disease, endocrinologic disorders (hypo/hyperthyroidism), malignancy, systemic inflammatory diseases, hematologic diseases, left atrial enlargement (>4.5 cm in echocardiography), active infection, undergone emergency operations (e.g., acute myocardial infarction) were excluded from the study. Those with unavailable serum lymphocyte count or albumin levels were also excluded.

Routine preoperative blood tests before coronary angiography were used in the formula [serum albumin (g/L) + 0.005x lymphocyte count/mm^3] to calculate the PNI value. All 12-lead electrocardiography (ECG) (filter range 0.5 Hz_150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV) which were obtained daily as a routine follow-up procedure in postoperative period and those obtained due to patients' symptoms or abnormality suspected during telemetry monitoring were evaluated to define rhythm abnormalities or AF development during the hospital stay. A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) was regarded as diagnostic of clinical AF (2,10). POAF was defined as an episode of AF requiring treatment related to surgery that developed during hospitalization.

Patients were further grouped into 2 according to the POAF development; POAF developed as POAF (+) and POAF non-developed as POAF (-). The primary endpoint of the study was occurrence of the first documented AF episode during the hospital stay.

This study was approved by Ethical Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 05/07/2022 number: 2022/07/02/002). Patient consent was waived due to retrospective design of the study.

Statistical Analysis

The Statistical Package for the Social Sciences 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The normality of the data was analyzed by Kolmogorov-Smirnov test. Continuous data are stated as mean ± standard deviation, and categorical data are stated as percentages. Chi-square test was applied to assess

differences in categorical variables between groups. Unpaired samples were compared by using Student's t-test or Mann-Whitney U, as needed. Independent variables of POAF were identified by using logistic regression analysis. Receiver operating characteristic (ROC) curve analyses were performed to evaluate diagnostic accuracy of PNI for POAF. Significance was expected at a 2-sided p<0.05.

Results

A total of 314 patients (234 male, 80 female) were included in this retrospective single center study. Mean age of all included patients was 59.8±10.2. POAF developed in 58 patients (18.5%) at a mean time of 2.31±1.47 days postoperatively. We formed 2 groups according to POAF development as defined in methodology. Fifty-eight patients formed POAF (+) and 256 patients formed POAF (-) group. Both groups were similar in terms of gender, presence of hyperlipidemia and history of cerebrovascular accident. Age (63.5±9.4 vs. 59.1±10.2; p=0.002), body mass index (BMI) (29.7±4.4 vs. 27.6±3.4; p<0.0001), hypertension (HT) (65.5% vs. 48.1%; p=0.016), chronic obstructive pulmonary disease (COPD) (41.4% vs. 17.2%; p<0.0001), diabetes mellitus (DM) (56.9% vs. 35.9%, p=0.003), history of coronary artery disease (CAD) (45.7% vs. 28.6%; p=0.013) and smoking status (70.7% vs. 44.9%; p<0.0001) were significantly higher in POAF (+) group. Regarding labaratory markers; creatinine (1.2±0.4 vs. 1.1±0.7; p=0.013) was significantly higher and preoperative haemoglobin (11.6±1.9 vs. 12.5±1.6; p=0.002), hematocrit (36.8±5.1 vs. 39.6±4.8, p=0.001), PNI (52.6±6.1 vs. 55.1±5.7; p=0.005) and left ventricular ejection fraction (46.1±7.8 vs. 50.4±8.3; p<0.0001) were lower in POAF (+) group. When the patients were assessed according to medical therapy on admission β-blocker (26.4% vs. 41.1%, p=0.047) usage were significantly lower in POAF (+) group. Moreover, length of intensive care unit (4.7±2.3 vs. 3.5±3.2; p=0.014) and total length of hospital stay (10.4±4.4 vs. 6.4±4.4; p<0.0001) stay was significantly higher in POAF (+) group. Demographical, baseline clinical, and biochemical characteristics of the cohort based on the presence or absence of POAF are presented in detail in Table 1.

To further evaluate individual risk factors for POAF development, we performed logistic regression analysis for age, BMI, smoking status, history of HT, COPD, DM, CAD, left ventricular ejection fraction, preoperative hemoglobin, creatinine and PNI, respectively. Logistic regression analysis revealed that age [p=0.026, β: 1.065, odds ratio (OR) [95% confidence interval (CI)]: 1.008-1.126], BMI [p=0.001, β: 1.265, OR (95% CI): 1.105-1.447], smoking status [p=0.003, β: 0.202, OR (95% CI): 0.070-0.581], left ventricular ejection fraction [p=0.007, β: 0.923, OR (95% CI): 0.871-0.979], creatinine [p=0.048, β: 1.839, OR (95% CI): 1.006-3.363] and PNI [p=0.038, β: 0.911, OR (95% CI): 0.834-0.995] were independent risk factors associated with POAF development (Table 2). ROC curve analysis was performed to identify the optimal cut-off value and area under the curve (AUC) for PNI. ROC curve for accuracy of PNI for predicting POAF development in CABG patients is shown in Figure 1. The AUC for PNI was 0.730 (95% CI: 0.616-0.844). A cut-off value of 53.13 for PNI was associated with 70.9% sensitivity and 69.6% specificity in prediction of POAF development.

Discussion

In this single-center retrospective study we sought to assess if PNI could predict POAF development in patients presenting with CCS and treated with isolated CABG. The prevalence of POAF was found 18.5% and our results determined low PNI as an independent predictor of POAF development. The results of this study suggest that preprocedural assessment of the PNI may raise suspicion to foresee the incidence of POAF in patients with CCS and treated with isolated CABG. The other independent predictors of POAF were advanced age, higher BMI, smoking, lower left ventricular ejection fraction, and creatinine levels. Consequently, close follow-up of patients with a PNI value <53.13 on admission as an additional clue to other risk factors may help to define patients under risk of POAF.

POAF is the most common arrhythmia after cardiac operations and its incidence may rise up to 40% and is unfavorable due to increased risk of mortality, heart failure, cerebrovascular events as well as financial burden on health care system (11). Valve disease, impaired left ventricular systolic function, left atrial enlargement, previous myocardial infarction, history of AF, advanced age, obesity, HT, DM, COPD, metabolic syndrome, ischemia, hypoxemia are known risk factors (12). In our study, advanced age, obesity, and lower left ventricular ejection fraction were found as independent predictors of POAF development in accordance with the literature. Although, HT, DM, COPD and history CAD were higher in POAF developed group, those were not detected as independent predictor.

Malnutrition is an important public health problem in developing countries. Serum albumin levels represent degree of nutritional status and on the other hand is known as a negative acute phase reactant decreasing

Table 1. Comparison of demographic, clinical and laboratory parameters between groups according to postoperative atrial fibrillation development

Variables	All (n=314)	POAF (-) (n=256)	POAF (+) (n=58)	p
Age (years)	59.8±10.2	59.1±10.2	63.5±9.4	0.002
Gender				0.282
Male, n (%)	234 (74.5)	194 (75.8)	40 (68.9)	
Female, n (%)	80(25.4)	62 (24.2)	18 (31.1)	
Body mass index	28.1±3.7	27.6±3.4	29.7±4.4	**<0.0001**
Hypertension, n (%)	161 (51.3)	123 (48.1)	38 (65.5)	0.016
Chronic obstructive pulmonary disease, n (%)	68 (21.7)	44 (17.2)	24 (41.4)	**<0.0001**
Diabetes mellitus, n (%)	125 (39.8)	92 (35.9)	33 (56.9)	0.003
Hyperlipidemia, n (%)	169 (53.8)	140 (54.7)	29 (50.0)	0.518
Cerebrovascular accident, n (%)	9 (2.9)	7 (2.7)	2 (3.4)	0.769
Coronary artery disease, n (%)	99 (31.5)	73 (28.6)	26 (45.7)	0.013
Smoking, n (%)	156 (49.7)	115 (44.9)	41 (70.7)	**<0.0001**
Left atrial diameter (mm)	36.4±4.4	36.6±4.8	35.6±3.9	0.128
Left ventricular ejection fraction, (%)	49.6±8.4	50.4±8.3	46.1±7.8	**<0.0001**
Thyroid stimulating hormone, (mU/L)	2.1±1.9	2.1±1.2	1.9±1.3	0.790
White blood cell, (10^3/μL)	7.9±1.9	7.9±1.9	7.9±2.1	0.908
Preoperative hemoglobin (g/dL)	12.3±1.7	12.5±1.6	11.6±1.9	0.002
Preoperative hematocrit (%)	38.9±5.1	39.6±4.8	36.8±5.1	0.001
Creatinine, (mg/dL)	1.1±0.7	1.1±0.7	1.2±0.4	0.013
C-reactive protein (mg/L)	12.2±8.2	13.2±8.5	14.3±6.7	0.361
HbA1c (%)	6.8±2.3	6.7±2.1	7.2±2.5	0.062
Prognostic nutritional index	55.0±5.9	55.1±5.7	52.6±6.1	0.005
Intensive care unit stay (days)	3.8±3.1	3.5±3.2	4.7±2.3	0.014
Total length of hospital stay (days)	7.2±4.7	6.4±4.4	10.4±4.4	**<0.0001**
Preoperative treatment, n (%)				
β-blockers	115 (36.6)	101 (41.1)	14 (26.4)	0.047
ACEI/ARB	139 (44.3)	118 (50.0)	21 (41.2)	0.253

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor block, POAF: Postoperative atrial fibrillation

Table 2. Logistic regression analysis for predictors of postoperative atrial fibrillation development

Variables	p	OR (95% CI)
Age	**0.026**	1.065 (1.008-1.126)
Body mass index	**0.001**	1.265 (1.105-1.447)
Hypertension	0.144	0.450 (0.154-1.314)
Chronic obstructive pulmonary disease	0.364	0.610 (0.210-1.774)
Diabetes mellitus	0.607	0.767 (0.280-2.105)
Coronary artery disease	0.193	0.483 (0.161-1.446)
Smoking	**0.003**	0.202 (0.070-0.581)
Left ventricular ejection fraction	**0.007**	0.923 (0.871-0.979)
Preoperative hemoglobin	0.131	0.439 (0.151-1.277)
Creatinine	**0.048**	1.839 (1.006-3.363)
Prognostic nutritional index	**0.038**	0.911 (0.834-0.995)

OR: Odds ratio, CI: Confidence interval

with inflammation. Moreover, as stated before, albumin has antiplatelet effect by modulating arachidonic acid metabolism and a protective effect by anti-oxidant property (13). Hypoalbuminemia, a good predictor of surgical risk, is closely associated with malnutrition. The relationship between hypoalbuminemia and acute coronary syndromes, cardiovascular ischemic disease, and stroke was reported previously (14,15). Besides, in atherosclerotic cardiovascular diseases, lymphopenia is reported to be associated with major adverse events (16). High neutrophil/lymphocyte ratio is widely used as an indicator of inflammation and have been widely studied in various cardiac conditions formerly (17-19). Both decreased lymphocyte count or increased neutrophil count may end up with an increased ratio. Thus, the 5xlymphocyte count used in the calculation of PNI seems to be a more reliable variable. PNI easily calculated and offers valuable information about nutritional status especially in hemodialysis and malignancy patients (20,21). The role of PNI was assessed in stable coronary patients who were treated by percutaneous coronary intervention (PCI) and PNI was established to be associated with long-term cardiovascular outcomes (8). On the other hand, its predictive usefulness for early outcomes after CABG was documented (22). In our study, PNI was documented as an independent predictor of POAF, which is one of the essential morbidities after CABG.

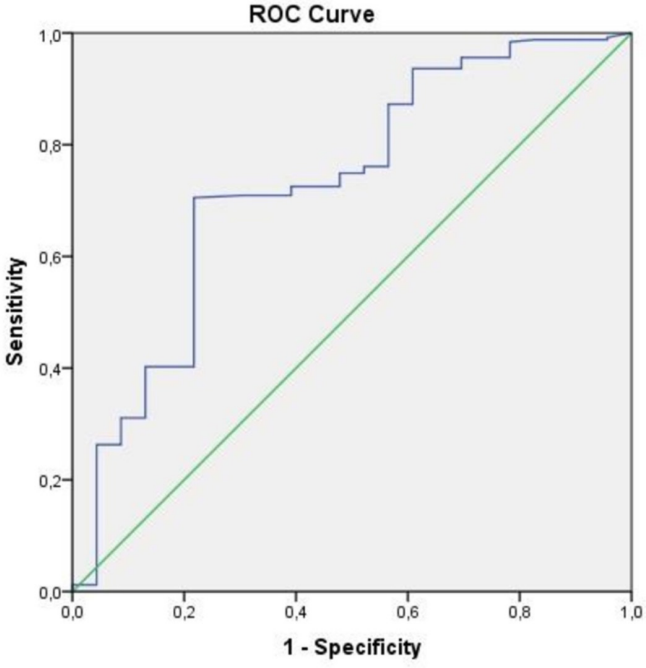

Figure 1. ROC curve for the diagnostic accuracy of prognostic nutritional index for predicting postoperative atrial fibrillation development

ROC: Receiver operating characteristic

Study Limitations

Retrospective and single center design with a relatively lower patient number are the main limitations of study. Moreover, comparison with other malnutrition and inflammation indices would give more reliable evidence. Also, our data is limited to in-hospital detection of POAF development where a longer duration would give better diagnostic ability. Although smoking is known to be associated with cardiovascular disorders, smoking was found as a negative predictor in our study. Relative small sample size may be related with this conflicting result, further studies are needed to evaluate the relation between smoking and POAF development.

Conclusion

This study demonstrated that malnutrition as evaluated using the PNI at admission may predict the POAF development in patients with stable coronary artery disease who underwent CABG for revascularization. POAF was observed more frequently in patients in lower PNI values. PNI is an easy to use, rapidly measured and widely available index and have good diagnostic accuracy in determining POAF development. As a result, aggressive treatment of malnutrition may be important in addition to personalized dyslipidemia therapy in patients with stable coronary artery disease. Further studies with longer follow-up and greater patient numbers are required to improve the clinical utility of PNI.

Ethics

Ethics Committee Approval: This study was approved by Ethical Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 05/07/2022 number: 2022/07/02/002).

Informed Consent: Patient consent waived due to retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.Ö., E.D., E.O., İ.Ş., Design: S.Ö., E.D., E.O., İ.Ş., B.M., A.P., Data Collection or Processing: S.Ö., E.D., B.M., A.P., Analysis or Interpretation: S.Ö., E.D., Drafting Manuscript: S.Ö., E.D., Critical Revision of Manuscript: S.Ö., E.D., E.O., İ.Ş., Writing: S.Ö., E.D., E.O., İ.Ş., Final Approval and Accountability: S.Ö., E.D., E.O., İ.Ş., B.M., A.P.

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ORIGINAL RESEARCH

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Relationship Between Trochlear Dysplasia and Chondromalacia Patellae

Troklear Displazi ve Kondromalazi Patella Arasındaki İlişki

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Abstract

Objective: Purpose of the study is to analyze the association between trochlear dysplasia and chondromalacia patellae.

Method: Knee magnetic resonance imaging of 191 patients (103 female and 88 male, mean age: 33±3.1, range: 18-49) with trochlear dysplasia were involved in the retrospective study. Patients without trochlear dysplasia (100 female and 91 male, mean age: 31±4.2 years, range: 18-49) were considered as the controls. Trochlear dysplasia was classified (type A, type B, type C, type D). Tibial tuberosity-trochlear groove distance was detected. Chondromalacia patellae was examined separately at the medial and lateral facet.

Results: The distribution of trochlear dysplasia was as follows; type A (50.2%), Type B (30.3%), type C (13.6%), type D (5.9%). Chondromalacia patellae was detected in 81 (42.4%) of patients with trochlear dysplasia and in 39 (20.4%) of the controls (p<0.05). Chondromalacia patellae was significantly more frequent at the lateral facet. There was significant association between the type of trochlear dysplasia and chondromalacia patellae. As the degree of dysplasia increases, the frequency of chondromalacia patellae increases (p<0.05).

Conclusion: Trochlear dysplasia and degree of trochlear dysplasia is a significant risk factor for chondromalacia patellae especially in lateral facet.

Keywords: Cartilage, chondromalacia patellae, knee, trochlear dysplasia

Öz

Amaç: Bu çalışmanın amacı, troklear displazi ile kondromalazi patella arasındaki ilişkiyi araştırmaktır.

Yöntem: Retrospektif çalışmaya troklear displazili 191 hastanın (103 kadın ve 88 erkek, ortalama yaş: 33±3,1, dağılım: 18-49) diz manyetik rezonans görüntülemesi dahil edildi. Troklear displazisi olmayan hastalar (100 kadın ve 91 erkek, ortalama yaş: 31±4,2 yıl, dağılım: 18-49) kontrol olarak kabul edildi. Troklear displazi sınıflandırıldı (tip A, tip B, tip C, tip D). Tibial tuberosity-trochlear groove mesafesi ölçüldü. Kondromalazi patella medial ve lateral fasette ayrı ayrı incelendi.

Bulgular: Troklear displazi dağılımı şu şekildeydi; tip A (%50,2), tip B (%30,3), tip C (%13,6), tip D (%5,9). Troklear displazili hastaların 81'inde (%42,4), kontrol grubun 39'unda (%20,4) kondromalazi patella saptandı (p<0,05). Kondromalazi patella lateral fasette anlamlı olarak daha sıktı. Troklear displazi tipi ile kondromalazi patella arasında anlamlı bir ilişki saptandı. Displazi derecesi arttıkça kondromalazi patella sıklığı da artmaktadır (p<0,05).

Sonuç: Troklear displazi ve troklear displazi derecesi özellikle lateral faset düzeyindeki kondromalazi patella için önemli bir risk faktörüdür.

Anahtar kelimeler: Diz, kartilaj, kondromalazi patella, troklear displazi

Introduction

Trochlear dysplasia (TD) refers to the pathological appearance in the morphology and depth of the femoral trochlear groove. It is a condition associated with patellofemoral instability and is classified into 4 types by Dejour (1,2). Chondromalacia patella (CP) is characterized by degeneration of the patellar cartilage and is a common cause of pain in the anterior region of the knee (3). There are some studies investigating the relationship between CP and TD in the literature in terms of patellar and trochlear

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cartilage damage. In addition to this relationship, in our study, relationship of CP with the grade of TD and patellar translation was examined. There is no study investigating this situation.

The aim of present study was to investigate the CP in patients with TD and evaluate whether there were relation between CP and grade of TD and patellar translation. In our opinion, the prevalence of CP significantly increases in patients with TD compared to the general population.

Materials and Methods

2230 knee MR examinations performed at our institution between February 2022 and July 2022 were reviewed. One hundred ninety-one patients with TD between the ages of 18-49 were identified. Patients without TD with the same number and age range were considered as the control group. TD was graded according to Dejour classification (type A, type B, type C, and type D). Type A: Shallow trochlea, type B: Flat trochlea, type C: Asymmetry of trochlear facets with a hypoplastic medial condyle and type D: Asymmetry of trochlear facets plus cliff pattern (4,5). CP were evaluated in accordance with Modified International Cartilage Repair Society classification, grade 0 indicates normal cartilage; grade 1 indicates superficial fissuring and softening; grade 2 indicates <50% depth to the subchondral plate; grade 3 indicates >50% depth into the subchondral plate; and grade 4 indicates penetration into the subchondral plate (6). The presence of CP in the patients was examined separately at the medial and lateral facet. A statistically significant difference in terms of CP between the two patient groups and the existence of a correlation between the degree of dysplasia and CP were investigated.

Tibial Tuberosity-Trochlear Groove (TT-TG) distance was also measured. TT-TG distance measured less than 15 mm considered as normal. Measurements were divided into 3 groups; <15 mm, 15-20 mm and >20 mm (7). Postoperative knee MR examinations, presence of previous history of acute trauma, history of rheumatologic diseases, subjects older than 50 years due to risk of dejenerative osteoarthritis and insufficient MR were excluded.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee (Bezmialem Vakıf University Faculty of Medicine, reference number: 15.03.2022-E.54758) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In keeping with the policies for a retrospective review, informed consent was not required.

Magnetic Resonance Imaging (MRI) Protocol

Unenhanced MRI of the knee was performed using a 1.5-T MR unit (Siemens, Avanto, Erlangen, Germany) with a knee coil a 20- to 26 cm FOV, and a 4-mm slice thickness with a 1-mm gap and a 320x256 matrix. Sequences used were sagittal T2 turbo spin echo (TR 2,300, TE 82, FA 150), sagittal proton density with fat saturation (TR 2140, TE 41, FA 150), coronal proton density with fat saturation (TR 2450, TE 41, FA 150), axial proton density with FS (TR 3330, TE 47, FA 150), and sagittal T1 SE (TR 307, TE 22, FA 150).

Statistical Analysis

Statistical analyses were performed using IBM SPSS 20.0. In statistical analysis, Pearson chi-squared test (x^2) or Fischer's Exact test, was used to compare the distribution of categorical data relative to each other. A p-value <0.05 was considered to show a statistically significant result.

Results

In our study, there were 191 patients with TD (103 female and 88 male, mean age: 33±3.1, range: 18-49) and 191 patients without TD (100 female and 91 male, mean age: 31±4.2 years, range: 18-49). The distribution of patients with TD was; type A [96/191(50.2%)], type B [58/191 (30.3%)], type C [26/191 (13.6%)], type D [11/191 (5.9%)] (Figure 1). CP was detected in 81 (42.4%) of patients with TD, and it was significantly higher compared to the control group. Chondromalacia was detected in 51 patients (26.7%) at the lateral facet and in 30 (15.7%) patients at the medial facet, and 17 (8.9%) had chondromalacia at both the medial and lateral facets (p<0.05). It was significantly higher only in the lateral facet compared to the controls (Figure 2). CP was detected in 39 (20.4%) of the control group. Chondromalacia was detected in 16 patients (8.3%) at the lateral facet

Figure 1. Type B femoral trochlear dysplasia in 28 year-old-man. Axial PD and sagittal T1 W images shows flat trochlea (arrow)

and in 23 patients (12.1%) at the medial facet, and 7 had chondromalacia at both the medial and lateral facet (Table 1). There was statistically significant association between the CP and type of TD. As the degree of dysplasia increases, the frequency of CP increases ($p<0.05$) (Table 2).

TT-TG values were; TT-TG <15 mm [115/191 (60.2%)], TT-TG: 15-20 mm [59/191 (30.8%), TT-TG > 20 mm (17/191 (9%)]. Although there was no statistically significant association between the TT-TG and CP, the highest rate of CP was in the patients with TT-TG distance >20 mm (Table 3).

Discussion

The main parameters of present study shows that the risk of CP increases in cases with TD. Our study showed increased incidence (42%) of CP in young-middle age patients with TD, compared to controls and general population stated in the literature. Variable CP prevalence rates such as 20.1 or 40.7 have been reported (8,9). There are some studies in the literature investigating the relationship between CP and patellofemoral instability. In study of Lu et al. (10), stated that the risk of CP is increased in patients with abnormal patellar height. In study of Dursun et al. (11), relationship between CP and patella type was investigated and they found an increased risk of CP in patients with type 2 and type 3 patella. Fan et al. (12) reported that thickness of lateral trochlear cartilage decreases in patients with TD. In study of Jungmann et al. (13), stated that patellar and trochlear cartilage volume decreased in patients with TD. In our study, unlike these studies, the presence of CP was specifically examined separately at medial and lateral facet levels, rather than patellar cartilage thickness or volume measurement in patients with TD. Also, differently, the relationship between grade of TD, patellar translation (TT-TG distance) and CP was investigated. In line with the studies mentioned above, we think that TD and TD grade increases the risk of CP especially in lateral facet. This may be related to the degree of dysplasia increasing patellofemoral instability. There was no significant correlation between CP and TT-TG, but the CP ratio was higher in patients with TT-TG >20 mm. This may releated with sample size of these patients (n=17). However, this high rate may support that patellar instability increases the risk of CP.

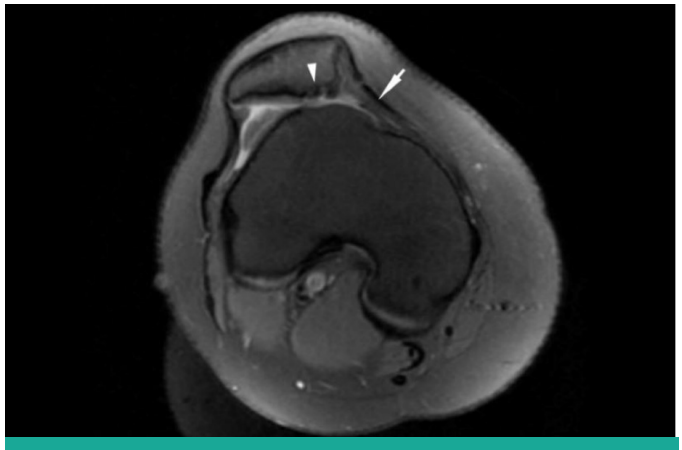

Figure 2. Axial PD image shows cartilage defect at the lateral patellar facet (arrowhead) and significant flattened trochlear groove (arrow) in a patient with trochlear dysplasia. Also lateral patellar tilt was seen

Study Limitations

This study has some limitations. First, there is no interobserver agreement test. Second, small number of Type D patients.

Conclusion

This study shows increased risk of CP especially in lateral patellofemoral region in young patients with TD. Increasing degree of TD can be a serious risk factor for early or advanced stage patellofemoral degeneration. Early and appropriate treatment for high-grade TD is important for the control of patellofemoral degeneration.

Table 1. Distribution of CP in patients with TD and without TD

	MF	LF	MF + LF
TD (+) n=191	30 (15.7%)	51 (26.7%)	17 (8.9%)
TD (-) n=191	23 (12.1%)	16 (8.3%)	7 (3.6%)

MP: Medial facet, LF: Lateral facet, CP: Chondromalacia patella, TD: Trochlear dysplasia

Table 2. CP distribution by type of trochlear dysplasia

	CP (+)	CP (-)	Total
Type A	36 (37.5%)	60 (62.5%)	n=96 (100%)
Type B	25 (43.1%)	33 (56.9%)	n=58 (100%)
Type C	13 (50%)	13 (50%)	n=26 (100%)
Type D	7 (63.6%)	4 (36.4%)	n=11 (100%)
Total	81 (10%)	110 (100%)	191

CP: Chondromalacia patella

Table 3. CP distribution by TT-TG distance

	CP (+)	CP (-)	Total
TT-TG <15 mm	50 (43.4%)	65 (56.6%)	n=15 (100%)
TT-TG: 15-20 mm	23 (38.9%)	36 (61.1%)	n=59 (100%)
TT-TG >20 mm	8 (47%)	9 (53%)	n=17 (100%)

CP: Chondromalacia patella, TT-TG: Tibial tuberosity-trochlear groove

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee (Bezmialem Vakıf University Faculty Of Medicine, reference number: 15.03.2022-E.54758) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: In keeping with the policies for a retrospective review, informed consent was not required.

Peer-review: Externally and internally peer-reviewed.

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ORIGINAL RESEARCH

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Evaluation of Videos with COVID-19 and CPR Content on YouTube

YouTube'da COVID-19 ve CPR İçerikli Videoların Değerlendirilmesi

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Abstract

Objective: The aim of this study is to evaluate the compliance of the scientific, quality, and educational content of YouTube videos with cardiopulmonary resuscitation (CPR) with the American Health Association 2020 current resuscitation guideline.

Method: The first 70 most watched videos were recorded for evaluation by typing Coronavirus disease-2019 (COVID-19) and CPR as keywords in the search engine of the YouTube homepage. The videos were evaluated according to the criteria of inclusion in the study, and the source of the videos, by whom they were uploaded, the length of the video, the number of days uploaded, the number of views and likes, the global quality score (GQS), the Journal of the American Medical Association (JAMA) score and the m-DISCERN scoring systems were recorded to detect the characteristics of the videos. These data were evaluated statistically.

Results: 21% of the evaluated videos were uploaded by doctors and 79% by healthcare providers. The average video length was 3.945 seconds, the average number of views was 9104.37, and the average number of like was 61.70. The mean GQS was 4.24, mean JAMA score was 3.06, and mean m-DISCERN score was 3.76. There was no statistically significant difference between both the loaders.

Conclusion: YouTube videos were found to be accurate and appropriate for scientific content. The reliability of YouTube, which is a visual video content, is significantly meaningful, especially about how healthcare professionals will perform CPR during the COVID-19 pandemic.

Keywords: COVID-19, CPR, GQS, JAMA, m-DISCERN, YouTube

Öz

Amaç: Bu çalışmanın amacı Koronavirüs hastalığı-2019 (COVID-19) hastalığı ile birlikte yapılan kardiyopulmoner resüsitasyon (CPR) içerikli YouTube videolarının bilimselliğinin, kalitesinin ve eğiticiliğinin American Health Association 2020 güncel resüsitasyon kılavuzuna uygunluğunu değerlendirmektir.

Yöntem: YouTube anasayfasının arama motoruna anahtar kelime olarak COVID-19 ve CPR yazılarak en çok izlenen ilk 70 video değerlendirilmek üzere kaydedildi. Videoların çalışmaya dahil edilme kriterlerine göre değerlendirmesi yapılarak videoların kaynağı, kim tarafından yüklendiği, video uzunluğunun süresi, yüklenme gün sayısı, izlenme ve beğenilme sayıları, global quality skoru (GQS), Journal of the American Medical Association (JAMA) skoru ve m-DISCERN skorlama sistemleri videoların özelliklerini saptamak için kaydedildi. Bu veriler istatistiksel olarak değerlendirildi.

Bulgular: Değerlendirilen videoların %21'i doktorlar, %79'u sağlık kuruluşu tarafından yüklenmişti. Ortalama video uzunluğu 3,945 saniye, ortalama izlenme sayısı 9104.37, ortalama beğenilme sayısı 61,70 idi. Ortalama GQS'u 4,24, ortalama JAMA skoru 3,06, ortalama m-DISCERN skoru 3,76 idi. Her iki yükleyici arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: YouTube videolarının doğru ve bilimsel içeriğe uygun olduğu bulundu. COVID-19 pandemi sırasında özellikle sağlık profesyonellerinin nasıl CPR yapacağı konusunda görsel anlamda video içeriği olan YouTube'un güvenirliği önemli ölçüde anlamlıdır.

Anahtar kelimeler: CPR, COVID-19, GQS, JAMA, m-DISCERN, YouTube

Introduction

The internet is an easily accessible source of information. Especially in the field of health, the video-based YouTube site is a very preferred option for accessing appliable medical information. Every month, more than 1.9 million people visit YouTube and watch a huge number of medical education videos (1). On the other hand, the Coronavirus disease-2019 (COVID-19) pandemic, which has affected the world since December 2019, has caused concern about how to perform the vital cardiopulmonary resuscitation (CPR).

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As a result of the studies, many guidelines that are published have started to be followed. American Heart Association (AHA) guideline is generally preferred as the main guideline (2). Because it is easy to access and share the latest and up-to-date information on the Internet, more over the information distributors have shared on the YouTube website to explain CPR better. People need video content with higher quality and information (3). With the advance of the Internet, people can easily obtain health information online more and have made it the most prominent source of health information. However, online platforms may also contain inaccurate medical information that may cause one from making wrong decisions about the treatment of diseases (4). Our study was conducted to investigate the compliance of CPR videos added to YouTube due to the COVID-19 pandemic with AHA guidelines.

Materials and Methods

On March 14, 2021, the keywords CPR and COVID-19 were written into the YouTube search engine and the first 100 videos related to these keywords were evaluated. Out of 100 videos, 30 videos with exclusion criteria were not included in the study (Figure 1). Non-English, repeated, pre-study-start video, non-medical content and unrelated to keywords were not included in the study. The ethics committee approval was not obtained because this study included publicly available video-sourced data. The videos were evaluated by two experienced emergency medicine specialists and the evaluations were averaged. After typing keywords into the search engine, the videos that came out were examined. The videos that were decided to be included in the study were written one by one by recording their links to the research form. All information showing the general features of the videos, whose links are recorded, is recorded at the bottom of the window. The length of the video, who uploaded the video, the number of likes, the number of days uploaded, and the view rate (views/day) were recorded.

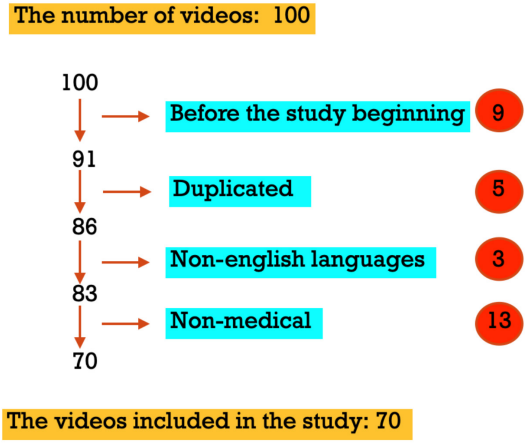

Figure 1. Study flow chart

Reliability, Quality and Utility Assessment

The m-DISCERN (quality criteria for consumer health information) scores, which determine the video quality, were recorded by calculating the modified (GQS) and JAMA (Journal of American Medical Association) scores. The reliability of the video content was assessed by Charnock et al. (5) using the modified DISCERN scale (m-DISCERN) adapted from the original DISCERN for the evaluation of written health information, and the consumer health information quality criteria scoring system was applied. What is DISCERN for? There is currently a great deal of written consumer health information available about treatment options from a variety of sources, including the internet. Not all of this information is of good quality, and only a small portion is based on good evidence. Many of

1. Are the goals clear and achievable?
2. Are reliable sources of information used?
3. Is the information presented balanced and unbiased?
4. Are additional sources of information listed for patient reference?
5. Have areas of uncertainty been mentioned?

Figure 2. m-DISCERN scoring

Score	Description of quality
1	poor quality; is unlikely of be to us efor patient education
2	poor quality; is of limited use to patients because only some information is present.
3	Suboptimal quality and flow; is somewhat useful to patients; important topics are missing, some information is present.
4	Good quality and flow; useful to patients because most important topics are corvered.
5	Excellent quality and flow; is highly useful to patients.

Figure 3. Global quality score

Criteria	Description
Authorship	Author and contributor credentials and their affiliations should be provided.
Attribution	Clearly lists all copyright information and states references and sources for content.
Disclosure	Conflicts of interest, funding, sponsorship, advertising, support, and video ownership should be fully disclosed.
Currency	Initial date of posted content and subsequent updates to content should be provided.

Figure 4. JAMA scoring system
JAMA: Journal of the American Medical Association

the posts available provide false or confusing advice, and it can be difficult to know what information to use and which to discard. DISCERN is a tool designed to help users of consumer health information judge the quality of written information about their treatment options. There are a total of 5 questions in m-DISCERN scoring. The ladeste 0 and the highest 5 points are awarded in Figure 2. Ratings above 3 indicate a high degree of reliability (6,7). The GQS was used to assess the quality of the video content. This assessment tool was originally developed to evaluate website resources and assess the flow of available information and ease of use. In GQS, the information is classified in Figure 3. GQS is a system that scores between 0 and 5, from the lowest quality to the highest quality. A higher GQS score means higher quality information. In addition, each video was evaluated for the JAMA scoring system as shown in Figure 4. The JAMA scoring system is a non-specific and objective tool for online videos and resources. Basically, it includes authorship, bibliography, patent right and actuality. Each criterion gets 1 point. 1 indicates the weakest quality, while 4 indicates the highest quality (8,9).

Statistical Analysis

The Statistical Package for the Social Sciences 22 (IBM, Armonk, NY, USA) was used for the statistical analysis. The Mann-Whitney Utest was used to evaluate statistically significant differences in the general features of the videos between groups. A statistical significance was set at $p<0.05$. Spearman's correlation coefficients between the scores were used for concurrent validity.

Results

In our study, 70 videos were evaluated. Fifteen of the videos were uploaded by doctors (21.43%) and 55 by health institutions (78.57%). The average viewing rate of the videos was found to be 13.20. The average broadcast history (days) was 650.04, the broadcast time (seconds) was 777.16, the number of views was 9104.37, and the number of like was 61.70. When the number of views of all videos was added together, it was found to be 640321. m-DISCERN score, JAMA score and GQS values were evaluated as having high quality (Table 1). When the characteristic distribution of the videos was examined, those with audio and spoken content (97.1%) were found to be the highest (Table 2). When the video was evaluated according to the upload source, no significant difference was found between JAMA, GQS score and m-DISCERN scores (Table 3). The relationship between viewing rates and quality assessment scores was not found (Table 4). Since there was no number of dislikes within the framework of YouTube publishing policies within the changing criteria, the liking rate and video power index could not be calculated in the data [like ratio = like x100/ (like+dislike) (Video power index = like ratio x view ratio].

Discussion

In our study, we tried to determine the characteristics of the video content that people, especially health workers, encountered when they researched CPR on the YouTube website during the COVID-19 outbreak. In this study, we found that the videos were of sufficient quality by looking at the m-DISCERN, GQS score and JAMA scores. However, when we examined the first 100 videos, we found that 30 videos did not have medical content. Future studies should consider a significant number of potential videos that may be excluded before data collection, but this is difficult to predict in advance. YouTube is growing in popularity, with more and more people using the internet to access health information, social media, and free access to videos from content creators, including health professionals (10). Since this information, uploaded to YouTube, which has become the largest online source for medical information, is published without quality control, incorrect and incomplete information can be easily spread and accurately detected through this virtual platform. According to the

Table 1. General characteristics of videos

	n	Minimum	Maximum	Mean	Standard deviation
Average broadcast (days)	**70**	**46**	**821**	**650.04**	**171.95**
Broadcast time (seconds)	70	36	3945	777.16	980.67
View numbers	70	12	134243	9104.37	19046.83
Like numbers	70	0	814	61.70	117.35
View rates	70	0.01	168.20	13.20	25.24
m-DISCERN score	70	2	5	3.76	1.06
GQS	70	3	5	4.24	0.77
JAMA score	70	1	4	3.06	0.931

JAMA: Journal of the American Medical Association

2015 AHA resuscitation guide by Katipoglu et al. (11), a study on the evaluation of the accuracy of English CPR videos on YouTube showed that it was not suitable in terms of providing basic information to the general population. In our study, it was determined that the videos were sufficient quality, and the reason for this was the high effort and desire of health workers to transfer their more accurate and important approaches to the information recipients with the concern about how there was a change in CPR during the COVID-19 pandemic. In addition, uploading video uploaders by healthcare companies or organizations has increased reliability even more. The m-DISCERN score was found to be higher than other studies. Li HO-Y et al. (12) included 69 of the 150 videos displayed in their study. They recorded the total number of views of 69 videos included in this study, which was examined by typing COVID-19 into the search engine, as 257,804,146. The study was conducted on 21 March 2020. Our study was conducted on March 14, 2021. Although our study was conducted later than it, the reason for the low number of views is that the video content is more specific because the words COVID-19 and CPR are written together in the search engine (12).There are limitations to be considered in this study. First, it's a cross-sectional study, but since YouTube is already a dynamic platform, any search strategy will have this limitation. And because it's supported by other studies, this limitation is unlikely to affect our outcome (13,14). In the study conducted on contact lens use, 200 videos were analyzed and 79 of them were included in the study and the m-DISCERN score of these videos was found to be 2.34 (1), JAMA score was 1.20 (0.99) and GQS score was 3.47 (1.28) (15). Regarding the effect of vitamin C on COVID-19 conducted by Lee and Chang (16), the YouTube study evaluated 50 videos and found that their m-DISCERN and GQS scores were 2.2 (1.4) and 2.2 (1.1), respectively, and when these values were examined, it was seen that the videos were of poor quality, weak and misleading. Although the videos were made by medical doctors, their reliability did not differ significantly from those in other groups (16). In our study, the quality assessment scores were found to be higher. In the study about lateral epicondylitis and YouTube contents, Aydın and Mert (17) reported the mean GQS, JAMA and DISCERN scores as 3.06, 1.96 and 43.94, respectively. Consedering these findings, the video quality in our study was found better than this study. In the COVID-19 pandemic, which has affected the whole world, source servers have taken care to have better, high quality and reliable videos while producing videos.

Table 2. Distribution of video characteristics

	Yes n (%)	No n (%)
Speaking	68 (97.1%)	2 (2.9%)
Sub-title	34 (48.6%)	36 (51.4%)
Voice	68 (97.1%)	2 (2.9%)
Practice	49 (70%)	21(30%)

Table 3. Evaluation of the scores by video sources

	Points	Healthcare provider	Doctor	p
m-DISCERN	2	9	1	0.929
	3	18	1	
	4	18	1	
	5	20	2	
GQS	3	13	1	0.975
	4	23	2	
	5	29	2	
JAMA	1	3	0	0.686
	2	17	2	
	3	17	2	
	4	28	1	

Mann-Whitney U was used (non-parametric test), JAMA: Journal of the American Medical Association, GQS: Global quality score

Table 4. Comparation of view rates with the scores

	GQS	m-DISCERN	JAMA
View rates (p-value)	0.082 (r=-0.3)	0.352 (r=0.11)	0.252 (r=0.14)

Spearman corralation test was used, JAMA: Journal of the American Medical Association, GQS: Global quality score

Study Limitations

This was a cross-sectional study that only captured snapshots. YouTube is a dynamic video-sharing platform with content that is refreshed every day, and therefore this limitation is expected for all similar studies. Another limitation is that only English videos were analyzed. However, English is considered the dominant language for accessing information online. The rating was also limited to the top 100 videos for each search term. This number was decided based on previous data showing that the majority of searchers don't look beyond the first few pages when searching on YouTube. Finally, only YouTube videos were analyzed, and other social media sites were not evaluated.

Conclusion

The analysis of 70 videos releated COVID-19 and CPR on YouTube has good quality and useful for all the people. According to this results everyone who investigated how to make CPR at the COVID-19 pandemia can easly learn and practice this situation compliant with the guidelines.

Ethics

Ethics Committee Approval: This study does not involve any human or animal resources, ethical approval was not required for the study.

Informed Consent: Patient information was not used in this study. Therefore, the patient consent certificate was not obtained.

Peer-review: Internally and externally peer-reviewed.

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

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ORIGINAL RESEARCH

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The Analysis of Serum Calcium and Urine Calcium/Creatinine Ratio in Diagnosis of Preeclampsia

Preeklampsi Tanısında Serum Kalsiyum ve İdrar Kalsiyum/Kreatinin Oranının Analizi

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Abstract

Objective: Preeclampsia is one of the primary reasons for maternal and fetal morbidity and mortality. Maternal and fetal complications can be prevented by early diagnosis, treatment, and follow-up of preeclampsia. This study aimed to determine the clinical diagnostic value of serum calcium (Ca) levels and urinary calcium/creatinine (Ca/cr) ratio in preeclampsia.

Method: A retrospective study was conducted on a sample population of 183 pregnant patients diagnosed with preeclampsia who delivered singleton babies at the Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Şişli Etfal Training and Research Hospital, İstanbul, Turkey, between January 2010 and January 2012. The patients were divided into two groups. Group 1: Preeclampsia; group 2: Preeclampsia with severe features. Serum Ca levels and urinary Ca/cr ratios of the patients were evaluated and compared.

Results: Hypocalcemia rates were higher in group 2 (93%) than in group 1 (58%). There was a statistically significant difference between the distribution of patients in the two groups according to serum Ca levels (28.339; 1; p=0.0001). The urinary Ca/cr ratios were lower in group 2 due to the decreased Ca extraction (58.481;1; p<0.0001). The mean Ca/cr ratio was 0.032 in group 2 and 0.11 in group 1.

Conclusion: Low serum Ca levels were detected in preeclamptic patients, and as the severity of preeclampsia increased, the Ca/cr ratio decreased due to decreased urinary Ca excretion. These findings were more significant for group 1; however, beyond a certain threshold, lower serum Ca levels and urinary Ca/cr ratio did not diagnose preeclampsia with severe features in group 2.

Keywords: Preeclampsia, serum calcium, urinary calcium/creatinine ratio

Öz

Amaç: Preeklampsi maternal ve fetal morbidite ve mortalitenin önde gelen nedenlerinden biridir. Erken tanı, tedavi ve takibi ile gelişebilecek maternal ve fetal komplikasyonlar önlenebilir. Bu çalışma, preeklampside serum kalsiyum (Ca) düzeyleri ve idrar kalsiyum/kreatinin (Ca/cr) oranının klinik tanısal değerini belirlemeyi amaçlamaktadır.

Yöntem: Ocak 2010 ile Ocak 2012 tarihleri arasında Sağlık Bilimleri Üniversitesi, Şişli Etfal Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde preeklampsi tanısı alan ve tekiz gebeliği bulunup doğum yapan 183 gebe hasta üzerinden retrospektif bir çalışma yapılmıştır. Hastalar iki gruba ayrıldılar. Grup 1: Preeklampsi; grup 2: Şiddetli özelliklere sahip preeklampsi. Hastaların serum Ca seviyeleri ve idrar Ca/cr oranları değerlendirildi ve karşılaştırıldı.

Bulgular: Hipokalsemi oranları grup 2'de (%93), Grup 1'e (%58) göre daha yüksekti. Serum Ca düzeylerine göre iki gruptaki hastaların dağılımı arasında istatistiksel olarak anlamlı fark vardı (28.339; 1; p=0,0001). Grup 2'de Ca ekstraksiyonundaki azalma nedeniyle idrar Ca/cr oranları daha düşüktü (58.481;1; p<0,0001). Ortalama Ca/cr oranı grup 2'de 0.032 ve grup 1'de 0,11 idi.

Sonuç: Preeklamptik hastalarda düşük serum Ca düzeyleri saptandı ve preeklampsinin şiddeti arttıkça idrarla Ca atılımının azalmasına bağlı olarak Ca/cr oranı azaldı. Bu bulgular grup 1 için daha anlamlıydı; ancak, belirli bir eşiğin ötesinde, düşük serum Ca seviyeleri ve idr Ca/cr oranı grup 2'de şiddetli özelliklere sahip preeklampsiyi teşhis edemedi.

Anahtar kelimeler: İdrar kalsiyum/kreatinin oranı, preeklampsi, serum kalsiyumu

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Introduction

Preeclampsia, a multisystemic condition caused by placental and maternal vascular dysfunction, is seen in an average of 4.6% of all pregnancies worldwide (1). 10-15% of maternal mortality due to complications during pregnancy is related to preeclampsia/eclampsia (2). Preeclampsia can cause serious complications that can affect many organ systems and result in end-organ dysfunction. Maternal and fetal complications of preeclampsia can be avoided or limited by early identification of at- risk pregnancies.

Preeclampsia is described as new-onset hypertension; systolic blood pressure of ≥140 mmHg and diastolic blood pressure of ≥90 mmH or both, after 20 weeks of gestation in a previously normotensive patient, with or without proteinuria. The following of the criterias can list in the absence of proteinuria: Thrombocytopenia; platelet count <100,000/μL, renal failure; serum creatinine levels above 1.1 mg/dL or a doubling of the serum creatinine levels in the absence of other renal diseases, hepatic dysfunction; elevation of serum hepatic transaminases to twice the normal concentration, pulmonary edema, new-beginning headache unrelieved with medications and not unexplained with a different diagnose or visual symptoms (3).

Preeclampsia with severe features is characterized by systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥110 mmHg or both. The other criterias as follows: Thrombocytopenia; platelet count <100,000/μL, hepatic dysfunction, unexplained by a different diagnosis; the elevation of serum hepatic transaminases to twice the normal concentration or by severe right upper quadrant or epigastric pain that can not be relieved with medications, renal failure; serum creatinine levels above 1.1 mg/dL or a doubling of the serum creatinine levels in the absence of another renal disease, pulmonary edema, new-beginning headache unrelieved with medications and unexplained by a different diagnose, visual disturbances (3).

Many physiological changes occur during pregnancy. One of these is the increased renal glomerular filtration rate in the kidneys and consequent increased urinary calcium (Ca) excretion (4). The normal range for 24-hour Ca urine excretion in women is 100 to 250 mg/day. It increases to 350-620 mg/day during pregnancy, but renal ionized Ca excretion considerably decreases in preeclampsia (5).

Various methods and tests based on Ca metabolic changes have been investigated for the early diagnosis or prediction of preeclampsia. Studies such as Ca supplementation, evaluation of serum Ca, urinary Ca, urinary calcium/creatinine (Ca/cr) levels in preeclamptic and normotensive patients, ionized calcium studies in the umbilical cord, and the Ca-ATPase activity of plasma membranes from human myometrium have been performed on preeclamptic patients. Some studies observed significant findings, while others did not. In addition, some study sample sizes were not extensive enough.

However, the relationship between Ca metabolism and preeclampsia is still unclear. Our study evaluated serum Ca and urinary Ca/cr ratios, whose diagnostic value is still controversial in predicting preeclampsia. This study aimed to analyze the diagnostic value of serum Ca and urinary Ca/cr ratios in preeclampsia.

Materials and Methods

This retrospective study included 183 pregnant patients who were diagnosed with preeclampsia and delivered singleton babies at the Clinic of Obstetrics and Gynecology, University of Health Sciences Turkey, Şişli Etfal Training and Research Hospital, İstanbul, Turkey between January 2010 and January 2012. Due to its retrospective design, this study was considered exempt from clinical studies ethics committee approval.

Preeclampsia was diagnosed based on new-onset hypertension after 20 weeks of gestation with or without proteinuria. Patients with any of the following features in the absence of proteinuria were diagnosed with preeclampsia: Thrombocytopenia; platelet count <100,000/μL, renal failure; serum creatinine levels above 1.1 mg/dL or a doubling of the serum creatinine levels in the absence of other renal diseases, hepatic dysfunction; elevation of serum hepatic transaminases to twice the normal concentration, pulmonary edema, new-beginning headache unrelieved with medications and not unexplained with a different diagnose or visual symptoms (3).

Patients were divided into two groups based on their hypertension. Patients with systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥110 mmHg were diagnosed as preeclampsia with severe features and added to group 2. Group 1: Preeclampsia; group 2: Preeclampsia with severe features. Patients with chronic hypertension, diabetes mellitus, urinary infection, renal disease, or multifetal pregnancy were excluded from the study.

Age, gravidity, parity, a gestational week at birth, fetal birth weight, and delivery type (cesarean or vaginal delivery) of eligible patience were recorded. The patient's serum Ca, 24-hour urine protein, Ca, and creatinine values were also

recorded. Hypocalcemia was defined as a serum Ca level of less than 8.8 mg/dL, with a normal range defined as 8.8-10.7 mg/dL. A standard reference interval for the urine Ca (mg/dL)/urine creatinine (mg/dL) ratio is <0.14. Due to possible changes in glomerular filtration, Ca/cr ratio in the 24-h urine specimens was measured instead of the urine's direct Ca concentration. The serum Ca and urinary Ca/cr ratios were evaluated and compared in both groups.

Statistical Analysis

The Power Analysis method was applied with the GPower 3.1.9.7 program to examine the adequacy of the sample size of the study. When the power (1-β) value is 0.80, and the α value is taken as 0.05, it is concluded that the minimum sample size for serum Ca analysis should be 24 and the minimum sample size for urinary Ca/cr analysis should be 75. Overall, there are 183 pregnant patients in the study, which is a sufficient sample size to have statistical power for both variables.

SPSS Version 18.0 for Windows was used for statistical analysis. The means, standard deviations, frequencies, and correlations of patient demographic variables were calculated. The statistical significance of serum Ca and urinary Ca/cr was evaluated by using an independent two-sample t-test (two-sided). According to the result of the t-test of serum calcium, the effect size is 1.16, and it is the large effect size according to the criterion of Cohen's d (6). Besides, urinary Ca/cr has a large effect size according to the criterion of Cohen's d by 0.87 (6).

With a 95% confidence interval, values of p<0.05, t-test results were accepted as being statistically significant. For determining the predictive threshold value of urinary Ca/cr ratio in the development of preeclampsia, the "receiver operating characteristic curve (ROC)" was used. Negative and positive predictive values were calculated using the cross tables.

Results

A total of 183 pregnant patients with preeclampsia were included in the study. Group 1 included 100 (54.6%) patients, while group 2 included 83 patients (45.4%). No significant differences were observed regarding age, gravidity and parity between groups. However, gestational age at delivery and fetal birth weight were significantly lower in group 2 than in group 1. While the rate of cesarean delivery was higher in group 2 (78%), the rate of vaginal delivery was higher in group 1 (58%).

There was an inverse relationship between serum Ca and urinary Ca/cr ratios in preeclampsia. In this study, serum Ca levels were low in 73.8% of patients, whereas 26.2% had a serum Ca level within the normal reference range. The average serum Ca level was 8.5 mg/dL in group 1 and 7.9 mg/dL in group 2. There was a statistically significant difference in serum Ca levels between the groups (28.339;1; p<0.0001). Hypocalcemia was more prevalent in group 2 (93%) than in group 1 (58%). There was also a statistically significant difference between the two groups concerning the urinary Ca/cr ratio (58.481;1; p<0.0001). Ca extraction was lower in group 2 (72%) than in group 1 (16%). The mean Ca/cr ratio was 0.032 in group 2 and 0.11 in group 1 (Table 1).

Table 1. Baseline demographic features and distribution of the patients between group-1 and group-2 preeclampsia

	Group 1 preeclampsia (n=100)	Group 2 preeclampsia (n=83)	Total (n=183)	p-value*
Age (years)	29.6±6.1	28.43±6.64	29.1±6.3	
Gravidity	1.7±0.98	1.59±0.86	1.64±0.92	
Parity	1.34±0.89	1.2±0.92	1.27±0.90	
Gestational age (weeks)	35±3.9	33.94±3.76	34.5±3.8	
Fetal birth weight (gr)	2400±800	2100±700	2200±800	
Proteinuria (mg/24 hours)	871.9±443.5	4727.18±2643.42	2620.5±2638.02	
Serum calcium (mg/dL)	8.58±0.6	7.9±0.57	8.27±0.67	<0.0001
Urinary calcium/creatinine	0.11±0.12	0.032±0.04	0.07±0.10	<0.0001
Hypocalcemia	58 (58%)	77 (93%)	135 (74%)	
Low urinary Ca/cr	16 (16%)	60 (72%)	76 (42%)	
High urinary Ca/cr	83 (84%)	23 (28%)	106 (58%)	
Delivery mode (n)				
Caesarian section	42 (42%)	65 (78%)		
Vaginal delivery	58 (58%)	18 (12%)		

* Two-sample t-tests (two-sided) were applied, Ca/cr: Calcium/creatinine

On the ROC curve for group 1, the sensitivity to diagnose preeclampsia was more significant. The serum Ca and urinary Ca/cr ratios were more diagnostic of preeclampsia for group 1 (Figure 1). Specificity was more significant on the ROC curve for group 2, and serum Ca and urinary Ca/cr ratios did not diagnose the development of preeclampsia with severe features in group 2. The cut-off point for urinary Ca/cr was 0.35, whereas serum Ca was 8.1 (Figure 2).

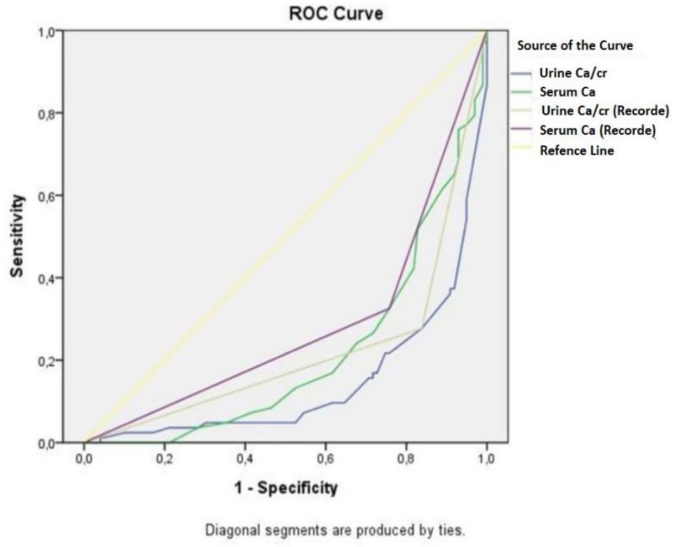

Figure 1. The ROC curve for group 1, sensitivity and specificity for the diagnosis of preeclampsia

Ca/cr: Calcium/creatinine, ROC: Receiver operating characteristic

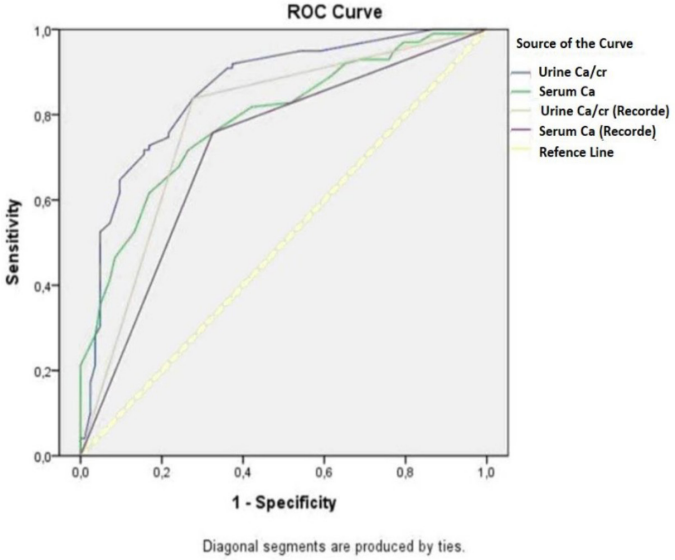

Figure 2. The ROC curve for group 2, sensitivity and specificity for the diagnosis of preeclampsia

Ca/cr: Calcium/creatinine, ROC: Receiver operating characteristic

Discussion

Many studies have been conducted to investigate how maternal serum Ca levels can be used for the early diagnosis and prevention of preeclampsia. The role of Ca in the development of hypertension emphasizes the circulatory and vascular bioactive factors that affect hypertension and draws attention to the quantity and activity of mediators secreted by the endothelium, vascular smooth muscle, and extracellular matrix during pregnancy. Researchers have stressed the importance of intracellular free Ca concentration, which controls smooth muscle contraction and the subsequent chain of activation (7).

Some studies have demonstrated that low serum Ca level are associated with greater preeclampsia risk. Punthumapol and Kittichotpanich (8), and Tuli et al. (9) reported that serum Ca levels were remarkably decreased in preeclamptic women compared to normotensive patients. Seely et al. (10) studied serum and urinary Ca levels in third-trimester preeclampsia and normotensive pregnancies and revealed that preeclamptic pregnancies had lower serum Ca values than normotensives. In addition, Jain et al. (7) compared the serum Ca levels between normal, mild and severe preeclamptic patients and determined that serum Ca levels decreased even more as the severity of preeclampsia increased.

In our study, serum Ca levels decreased by 73.8% and remained within the normal range for 26.2% of preeclamptic patients. We observed a statistically significant difference in serum Ca levels between group 1 and group 2, with average values of 8.58 mg/dL and 7.9 mg/dL, respectively.

Despite these results, some studies have not found an association between hypocalcemia and preeclampsia. Darkwa et al. (11) reported that serum Ca levels did not differ in preeclamptic patients compared to non-preeclamptic patients. Wadhwani et al. (12) studied maternal serum Ca levels from early pregnancy until delivery and cord levels in women with preeclampsia and compared them to normotensive patients. They observed that Ca levels were similar between the groups at all time points (12).

Studies have been published showing that renal Ca extraction decreases with the development of preeclampsia. Sanchez-Ramos et al. (4) observed that preeclamptic patients had less excretion of total calcium than normotensives and gestational hypertension patients. Sirohiwai et al. (13) reported that urinary Ca excretion was remarkably lower in preeclamptic patients than in normotensives and stated that a drop in 24-

hour urinary Ca and a rise in protein are risk factors for preeclampsia. Seely et al. (10) measured preeclamptic and normotensive women's urinary Ca levels in the third- trimester and confirmed that preeclamptic patients have relative hypocalciuria. A meta-analysis reported that urinary Ca excretion was lower in women with preeclampsia than in normotensive pregnancies. However, as the severity of pregnancy-related hypertensive disorders increases, urinary Ca excretion decreases; however, this same decrease is not observed in non-pregnancy-related hypertension (14). Rodriguez et al. (15) examined the Ca/cr ratio in spot urine from normal pregnant women. Subsequently, preeclampsia developed in an average of 80% of the patients with low Ca/cr values. Therefore, their study remarked that the Ca/Cr ratio could be a helpful screening test in predicting preeclampsia (15). Also, Vahdat et al. (16) performed a prospective study to evaluate the predictive value of Ca/cr ratio in preeclamptic patients. In their study, the mean Ca/cr ratio was significantly lower in preeclamptic women and suggested that it may be used as a screening test (16).

However, Saudan et al. (17) found that hypocalciuria precedes the onset of preeclampsia in gestational hypertensive women, and Ca/cr was not sensitive enough to be proposed as a screening test for preeclampsia. Ibrahimi et al. (18) conducted a prospective case-control study to determine the predictive value of the Ca/cr ratio in the 24-h urine sample in predicting preeclampsia in pregnant women between 24-34 weeks. They found that the role of Ca/cr ratio in predicting preeclampsia was lower than that of proteinuria and uric acid (18). Also, Ingec et al. (19) reported that urinary Ca excretion was reduced in severe preeclamptic and eclamptic patients, but it cannot be used to identify or predict the severity of preeclampsia.

In our study, we also observed a decrease in urinary Ca, especially in group 2 patients; 72% had hypocalciuria. The mean urinary Ca/cr ratio was 0.032. There is seen statistically significant differences in the urinary Ca/cr ratio in 24-h urine specimens between the two groups (58.481;1; $p<0.0001$). Ca excretion was reduced significantly in group 2, but the urinary Ca/cr ratio did not diagnose severe preeclampsia on the ROC curve. Therefore, the cut-off point for urinary Ca/Cr was 0.35.

Conclusion

Low serum Ca levels and decreased urinary Ca excretion were detected in preeclamptic patients. The serum Ca levels and urinary Ca/cr ratios were more likely to diagnose preeclampsia in group 1.

However, we were not able to diagnose the eventual severity of preeclampsia in group 2 using this method. Further studies with more extensive sample sizes are required to confirm and validate the diagnostic value of serum Ca and urinary Ca/cr for preeclampsia.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Our study is retrospective and was carried out on data processing data without using patient names.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: E.B., S.Ö., Design: E.B., S.Ö., Data Collection or Processing: E.B., Analysis or Interpretation: E.B., S.Ö., Drafting Manuscript: E.B., Critical Revision of Manuscript: S.Ö., Writing: E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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ORIGINAL RESEARCH

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Single-centre Microsurgery Treatment Methods for Unruptured Intracranial Aneurysms of the Anterior Circulation and Results

Kanamamış İntrakraniyal Ön Sirkülasyon Arter Anevrizmaları Tek Merkez Mikrocerrahi Tedavi Yöntemi ve Sonuçları

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Abstract

Objective: Intracranial artery aneurysms can result in high morbidity and mortality when ruptured. Preventive treatments might be necessary to avoid adverse results. This paper aims to discuss and share the first-term findings of unruptured intracranial artery aneurysms (UIAs) of the anterior circulation surgery at a newly established clinic in light of our clinical principles and surgical approaches.

Method: Patients diagnosed with UIAs of the anterior circulation in our establishment in September 2020 and November 2022 and treated with microsurgery clipping operations were retrospectively evaluated. Assistive devices such as a sodium fluorescein integrated microscope, videoangiography, and micro-Doppler ultrasonography were intraoperatively used. We actively used a second surgeon with a third hand in the microscopic field. With case studies, we provided various techniques, and our experiences were used to avoid complications. We compared our surgical findings with radiological and clinical data.

Results: In our institution, 44 aneurysms and 40 patients diagnosed with UIAs of the anterior circulation were treated with 42 operations. The mean age was 50 years (31/69 years), and the follow-up time was 379 days (30/828 days). The modified Rankin scale (mRS) of the patients was evaluated; the mRS of patients was evaluated as three due to previous subarachnoid haemorrhage history, and postoperative change was not detected. Three patients had postoperative epileptic seizures; therefore, their mRS was evaluated as 1, and the mRS of 36 patients was 0 after follow-up. In the postoperative digital subtraction angiography of two patients, a rest was detected in the aneurysm neck; therefore, one patient underwent another surgery, and the endovascular team treated the other patient. Infarction due to loss of

Öz

Amaç: İntrakraniyal arter anevrizmaları, yırtıldığı takdirde yüksek morbidite ve mortalite ile sonuçlanmaktadır. Olumsuz sonuçlarla karşılaşmamak için önleyici tedavi gerekebilmektedir. Bu makale ile yeni bir kliniğin kanamamış intrakraniyal ön sirkülasyon arter anevrizması (KİKAA) cerrahisinde klinik prensip ve cerrahi yaklaşımlarımızın ışığında ilk dönem sonuçlarımızı tartışmayı ve paylaşmayı amaçladık.

Yöntem: Eylül 2020-Kasım 2022 tarihleri arasında merkezimizde KİKAA saptanan ve mikrocerrahi klipleme operasyonu ile tedavi edilen hastalar retrospektif değerlendirildi. İntraoperatif olarak, mikroskopa entegre sodyum floresein video anjiyografi ve mikro-Doppler ultrasonografi gibi yardımcı cihazlar kullanıldı. Mikroskopik sahada ikinci cerrahı üçüncü bir el ile sahada aktif olarak deneyimledik. Komplikasyonlardan kaçınmak için kullandığımız çeşitli teknikleri ve deneyimizi olgu örnekleri ile sunduk. Cerrahi sonuçlarımızı radyolojik ve klinik verilerle karşılaştırdık.

Bulgular: Kurumumuzda KİKAA tanısı ile toplam 40 hasta, 44 anevrizma 42 operasyon ile tedavi edilmiştir. Ortalama yaş 50 yıl (31/69 yıl), takip süresi 379 gündür (30/828 gün). Hastaların modifiye Rankin skoru (mRS) bir hasta daha önce geçirilmiş subaraknoid kanamaya bağlı mRS 3 olarak değerlendirilmiş ve postoperatif değişiklik saptanmamıştır, üç hasta postoperatif epileptik nöbet geçirmesi nedeniyle mRS 1 olarak değerlendirildi, 36 hasta ise takip süresi sonunda mRS 0'dı. İki hastada postoperatif dijital subtraksiyon anjiyografide anevrizma boynunda rest saptanması üzerine bir hasta tekrar cerrahiye alınırken, diğer hasta endovasküler ekip tarafından tedavi edildi. Hiçbir hastada parent arter ve perforan arter kaybına bağlı enfarkt görülmedi. %20 hastada minor komplikasyon görüldü.

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Abstract

the parent artery and the perforating artery was not observed in any patient. Minor complications were seen in 20% of the patients.

Conclusion: An increase in the variety and use of intraoperative assistive techniques and the active participation of the second surgeon using a third hand can decrease the complication rate. Additionally, the complication rate will decrease as the surgical experience increases in vascular institutions dealing with such cases.

Keywords: Aneurysm clipping, micro-Doppler ultrasonography, microsurgery, sodium fluorescein, videoangiography

Öz

Sonuç: İntraoperatif yardımcı tekniklerin çeşitliliğinin ve kullanımının artması, ikinci cerrahın üçüncü bir el ile sahada operasyona aktif katılımı komplikasyon oranının düşmesini sağlayabilir. Ayrıca olgu akışının sağlandığı vasküler merkezlerde cerrahi tecrübenin de artmasıyla komplikasyon oranı azalacağı kanaatindeyiz.

Anahtar kelimeler: Anevrizma klipleme, mikrocerrahi, mikro-Doppler ultrasonografi, sodyum floresein, videoanjiyografi

Introduction

An aneurysm is the outward expansion of the wall of a blood vessel due to a weakness in the blood vessel walls (1). It is seen in ≈3.2% (95% confidence interval, 1.9-5.2% of the adult population (mean age: 50) (2). Aneurysms are observed 1.5 times more in women than men (3,4). In 90% of the cases, aneurysms are smaller than 10 mm and are generally located in the anterior cerebral circulation. Between 20% to 30% of the patients have multiple aneurysms (5).

In cases of growth in the follow-ups of unruptured intracranial artery aneurysms (UIAs) diagnosed with secondary findings with the increasing use of imaging methods, the rupturing risk can change between 2% to 10% based on the size, location, and shape of the aneurysm (6). The 5-year rupturing risk of aneurysms can change between 1.5% to 50% according to factors such as localization and size (7,8). If an aneurysm is ruptured, mortality and morbidity rates increase severely. In the ruptured aneurysm series, the mortality rate was revealed to vary between 27% to 47% based on their locations (9). Precisely 30% of surviving patients have to live with neurological and neurocognitive deficits. (10)

Mortality in UIAs is 1-3%, and the severe morbidity rate is 4-10.9% (8). The aim of the treatment is to avoid complications and ensure the clipping of the aneurysm neck by protecting the parent artery, distal extension, and perforating arteries (11,12). Even though vascular structures can be observed using an operational microscope, vessel patency and a residual aneurysm cannot be observed with microscopes; therefore, intraoperative monitoring methods are required. High-technique resources such as angiography conducted with microscope-integrated sodium fluorescein were developed to achieve this goal (13-15). Technical equipment such as micro-Doppler ultrasonography is also used intraoperatively (17-19). The literature mentions that intraoperative assistive techniques help mortality and morbidity decrease in vascular surgery for giant and complex aneurysms, as well (16,20-23).

UIAs have critical mortality and morbidity rates in the follow-up and treatment processes. In addition to the experience of the institution and learning curve, surgical approaches and principles also change according to the technical equipment used. This paper aims to discuss and share the findings of a single center with 40 patients and 44 intracranial artery aneurysm cases in light of our specific clinical principles and surgical approaches.

Materials and Methods

Patient Selection

Patients include those who underwent microsurgery UIAs of the anterior circulation clipping operations in our institution. This single-cantered study presents the results of operations conducted by two vascular neurosurgeons. All 40 patients operated on in September 2020 and November 2022 were included in the study. All data were retrospectively examined and compiled after approval (no. 2022-281) was granted by the ethical Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital.

Patients generally arrived at the neurology or neurosurgery outpatient clinic with headache complaints. Those with UIAs of the anterior circulation on computed tomography (CT)-angiography or magnetic resonance imaging (MRI)-angiography were correlated with digital subtraction angiography (DSA).

Pre-surgical Procedure

The microsurgical clipping indications of patients were decided on during a meeting held with the interventional radiology team of our institution. For preoperative diagnosis, a four-system of DSA was carried out on all patients.

Surgical Procedure

Conventional pterional craniotomy was used for anterior circulation aneurysms as a surgical technique. In accordance with microsurgical principles, chiasmatic,

carotid (if necessary), the opening of lamina terminalis cistern and dissection of the Sylvian fissure, exploration of the proximal artery starting from the periphery of the aneurysm, and dissection of the perforating arteries and venous structures adhered to the dome, especially in large aneurysms, from the aneurysm neck, were performed (Figure 1).

We tended to apply temporary clipping for proximal parent arteries, except for small aneurysms. A temporary clip application enabled the aneurysm dome's internal pressure to decrease and be compatible circumferential dissection (Figure 2). Temporary clipping areas were chosen as places that would be affected the least because they are suitable for recurring manipulations. Placing the pilot clips specifically helped the domes in large aneurysms needing to be wrapped and revealed the relationship with the surrounding anatomical structures; pilot clip placement also minimized the risk of rupture until placement of the final clipping. The presence of an active second surgeon with a third hand in the field, in terms of dynamic retraction and manipulation, helped with clipping repositioning and placement of multiple clips in additional ways when needed (Figure 3).

In all operations, a Leica 530 OH-X surgical microscope with an FL560-integrated fluorescence module was used (Leica Microsystems GmbH, Wetzlar, Germany).

After the optimum clip position was confirmed with surgical observation and micro-Doppler following the aneurysm clipping (Hadeco Inc. Japan, Koven Technology Inc., USA), sodium fluorescein videoangiography was made with the FL560 module of the microscope. Sodium fluorescein (Flusible 500 mg/5 mL IV solution for injection) was administered to all patients in bolus using a central venous catheter. This method was used at least once and at most three times during any given operation. The maximum dose to be administered to patients was accepted as 20 mg/kg (16). A total of 5 mg/kg was calculated for every application during the operations (Figures 2, 4-7).

CT were examined in the postoperative period (2-6 h) for future comparisons and to exclude the possible complications of cases and asymptomatic structural changes, such as silent stroke and contusion. In postoperative follow-up, patients were evaluated with CT,

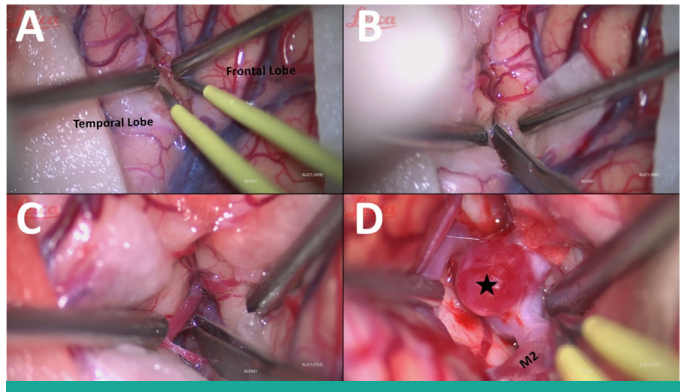

Figure 1. Various images of left sylvian fissure dissection in surgery for an unruptured aneurysm in the left middle cerebral artery bifurcation. Finally, the pre-clip view of the aneurysm dome (star) dissected from the surrounding structures

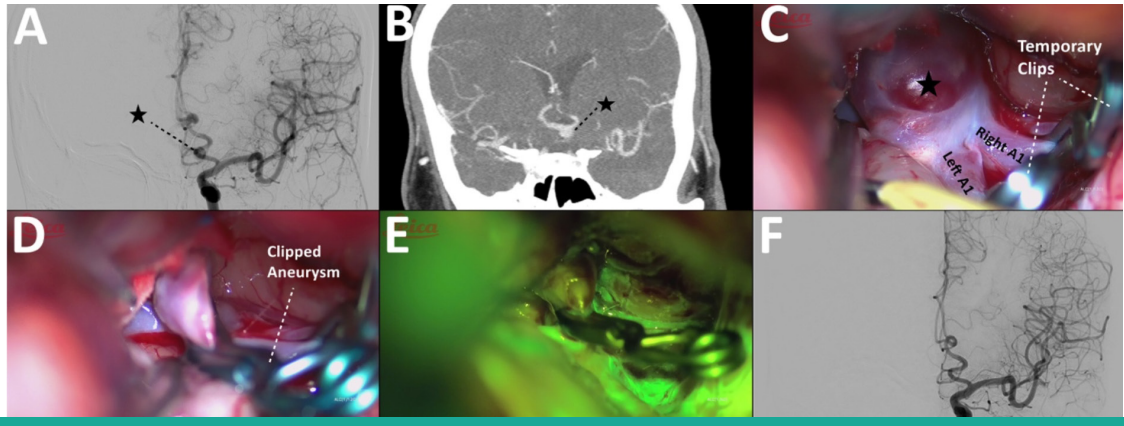

Figure 2. A 56-year-old male patient was operated on due to an unruptured anterior communicating segment (Acom) artery aneurysm. **A.** In preoperative digital subtraction angiography (DSA), in the anterior-posterior view, an aneurysm (star) with a wide neck, approximately 6×5 mm in size, at the A1 segment-Acom junction of the left anterior cerebral artery can be seen. **B.** In the coronal slice of preoperative computed tomography brain angiography, an aneurysm dome (star) is visible. **C.** The aneurysm dome (star) and the temporary clips placed in the A1 segment of the left-right anterior cerebral artery are seen. **D.** The aneurysm is closed with a single permanent clip. **E.** In videoangiography mode after sodium fluorescein injection, the aneurysm dome did not fill up. **F.** In the anterior-posterior view of postoperative DSA, the residual aneurysm filling was not detected, and parent artery loss was not seen

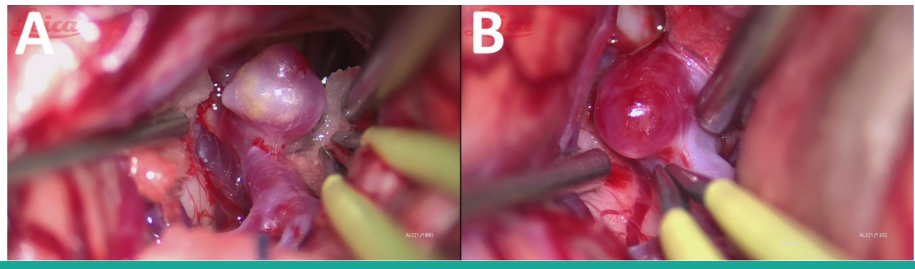

Figure 3. Before and after aneurysm clipping, the retraction and aspiration conducted with the help of an aspirator by the second surgeon using the third hand of the second surgeon technique can be seen in two different phenomena

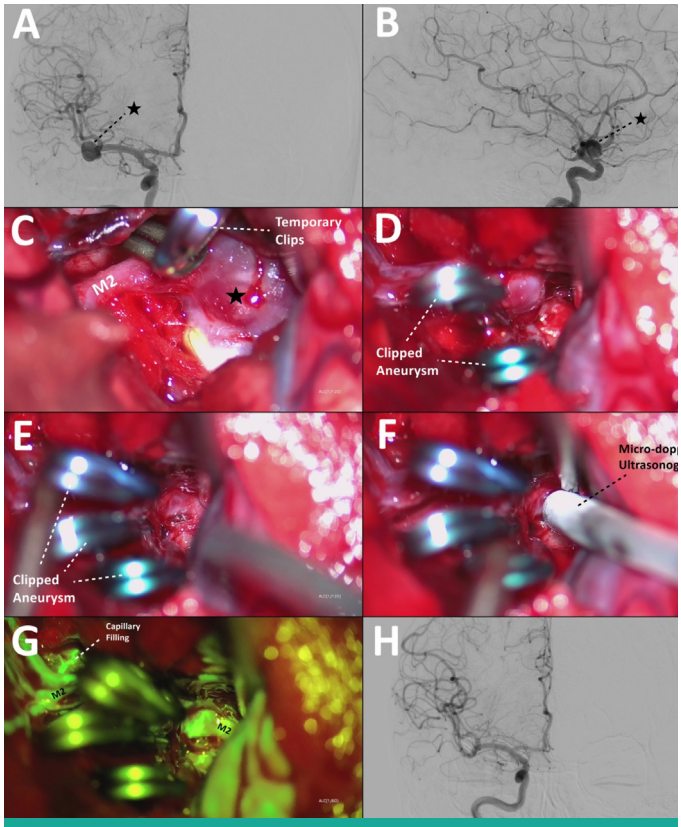

Figure 4. A 45-year-old female patient was operated on due to an aneurysm incidentally detected in the bifurcation of the right middle cerebral artery (MCA). **A, B.** In the anterior-posterior and lateral views of the preoperative digital subtraction angiography (DSA), laterally and superiorly oriented, a wide neck saccular aneurysm (star), 9×6.7 mm in size at the widest point, originating from the right MCA bifurcation can be seen. **C.** The aneurysm dome (star) and the temporary clip placed in the M1 segment of the right MCA can be seen. **D, E.** The aneurysm was vertically serial clipped with three permanent aneurysm clips. **F.** The flow in MCA branches and aneurysm dome are checked using micro-Doppler USG. **G.** In videoangiography mode after sodium fluorescein injection, the aneurysm dome did not fill up, and MCA distal branches were coloured. **H.** In the anterior-posterior views of the DSA, residual aneurysm filling was not detected, and parent artery loss was not seen

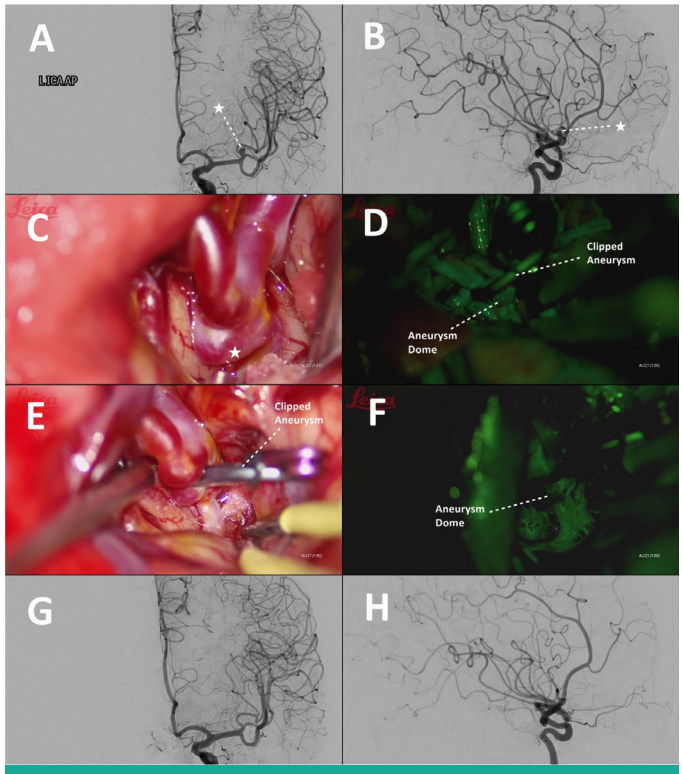

Figure 5. A 61-year-old female patient was coiled with endovascular treatment by interventional radiology due to a ruptured saccular aneurysm in the posterior communicating segment of the right internal carotid artery. The unruptured left middle cerebral artery (MCA) at the trifurcation level was operated on due to an aneurysm. **A, B.** In the anterior-posterior and lateral views of the preoperative digital subtraction angiography, a saccular aneurysm (star) with a regular surface and wide neck, approximately 4×3 mm in size, located at the upper trunk at the left MCA trifurcation level can be observed. **C.** Aneurysm morphology (star-aneurysm) **D.** After the aneurysm clip and sodium fluorescein injection, it can be seen that the aneurysm dome was coloured. **E.** Image after the revision of aneurysm clipping. **F.** In the videoangiography mode after revision of the aneurysm clipping and second sodium fluorescein injection, the aneurysm dome did not fill up. **G.** In the anterior-posterior and lateral views of the postoperative digital subtraction angiography, residual aneurysm filling was not detected, and parent artery loss was not seen

MRI, brain diffusion sequence, and computed perfusion tomography. First, DSA was chosen in all postoperative patients to see whether aneurysms demonstrated rest and to evaluate parent artery occlusion or stenosis. In 12 patients, CT and brain angiography were preferred because of the invasive DSA and the potential for complications (the tendency of patients to experience thrombosis, the development of complications in the previous DSA, or patients not giving consent).

Statistical Analysis

The analysis of the data was made using the SPSS 24.0 package program.

Results

During the study phase, 40 patients and 44 UIAs of the anterior circulation were treated with 42 operations. The mean age of the patients was 50 years (min/max: 31/69 years). The mean follow-up time of the patients was 379 days (30^{th}-828^{th} day). Multiple aneurysms were detected in 16 patients. Two different aneurysms of three patients were clipped in the same operation. One patient was operated twice for two different aneurysms. Re-operation was performed in one patient after a residual aneurysm was detected. The other aneurysms of 12 patients were followed up radiologically because operations took place in different surgical corridors and due to low bleeding risk.

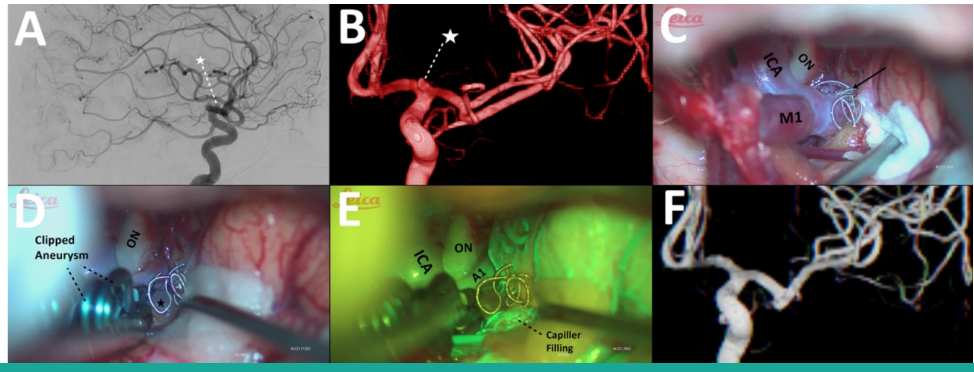

Figure 6. A 35-year-old female patient with a twenty-year history of endovascular coil embolization operation for an aneurysm in the left internal carotid artery (ICA) bifurcation was operated on after recurrence was detected. **A, B.** In the lateral and three-dimensional views of the preoperative digital subtraction angiography (DSA), a superior oriented recurring aneurysm (star), 3.3×2.6 mm in size, in the left ICA bifurcation, with opacities attached to the coils can be seen. **C.** The left ICA, the M1 segment of the middle cerebral artery (MCA), the optic nerve, and the coil (arrow), a portion of which protruded outside the aneurysm dome. **D.** The aneurysm (star) is closed with two permanent clips. The remaining coil after a portion is removed can be seen. **E.** In videoangiography mode after sodium fluorescein injection, the aneurysm dome did not fill up, and ICA, middle cerebral artery, and its branches were coloured. **F.** In the three-dimensional view of the postoperative DSA, residue aneurysm filling was not detected, and parent artery loss was not perceived

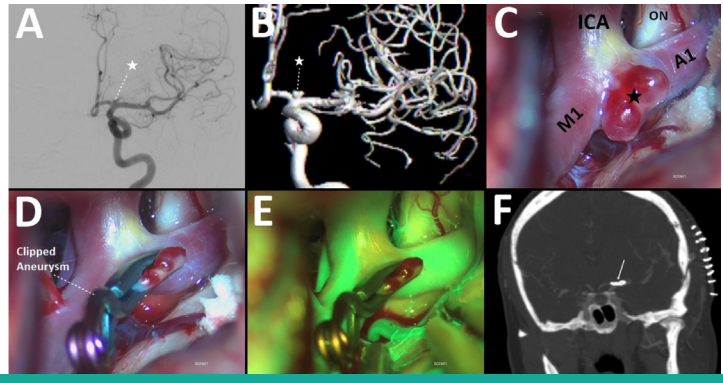

Figure 7. A 52-year-old female patient was operated on due to an unruptured aneurysm in the left internal carotid artery (ICA) bifurcation. **A, B.** In the anterior-posterior and three-dimensional views of the preoperative digital subtraction angiography, a saccular aneurysm (star), 3.5×2.5 mm in size, in the left ICA terminus, superiorly oriented, bilobed, contoured, with a narrow neck can be seen. **C.** The left ICA and its branches, optic nerve, and aneurysm dome (star) can be observed. **D.** The aneurysm is closed with a permanent clip. **E.** In videoangiography mode after sodium fluorescein injection, the aneurysm dome did not fill up, and ICA and its branches were coloured. **F.** In the coronal slice of the postoperative brain computed tomography-angio, an aneurysm clip is seen (arrow), residue aneurysm filling was not detected, and parent artery loss was not observed

The demographic data of the patients are given in Table 1. The aneurysm location and patient numbers were recorded and can be seen in Table 2. A total of nine patients had subarachnoid haemorrhage and treatment history. At the end of the 379th-day follow-up after treatment, the patients were evaluated using their modified Rankin scale (mRS) scores. One patient's preoperative mRS was 3 due to a prior subarachnoid haemorrhage; the postoperative follow-ups continued with mRS 3, and the mRS of three patients was evaluated as 1 due to postoperative epileptic seizure. The mRS of 36 patients was 0.

Rest was found in the aneurysm neck in the postoperative DSA imaginings of two patients. One of the patients with rest was operated on again, and the other patient was treated by the endovascular team using a flow diverter stent.

Considering the surgical complications, no cerebral infarction was seen in any patient due to the parent artery and the perforating artery.

Two patients had CSF fistulas. One of these patients showed symptoms of rhinorrhoea, and the other showed signs of CFS leakage from a skin defect. These two patients were operated on using revision surgery; the patient with CSF leakage from the skin also developed meningitis and was given antibiotic therapy.

Three patients had epileptic seizures, and antiepileptic treatments were applied. Cerebral hyperperfusion syndrome was found in the further examination of a patient with seizure attacks following postoperative DSA. This patient was diagnosed with CT-perfusion (Figure 8). The patient who developed cerebral hyperperfusion syndrome was followed up in the intensive care unit for three days. The patient's blood pressure was reduced to normal limits in a controlled and gradual manner. Triple antiepileptic therapy was given, and no postoperative bleeding was observed. The patient was discharged with no deficits after follow-up.

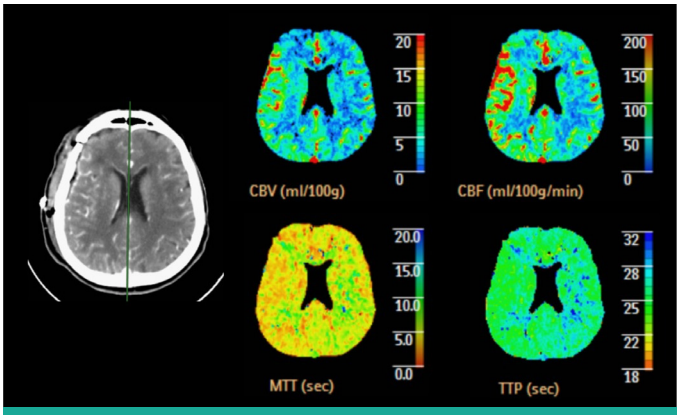

Figure 8. A 69-year-old male patient was operated for an aneurysm in the unruptured right middle cerebral artery (MCA) M2 bifurcation. On the 4th postoperative day, after digital subtraction angiography, computed perfusion tomography images show increased cerebral blood volume (CBV), increased cerebral blood flow (CBF), decreased mean-transient time (MTT), and decreased time-to-peak (TTP). Hyperperfusion is observed in the right MCA feeding area. Reference values are located on the right side of all images

Two patients had skin healing problems. The source of the problem experienced by one of our patients was thought to have stemmed from immunosuppressive treatments for existing rheumatic diseases. For the other patient, the source of the problem was the production of *Staphylococcus aureus* in the wound swab culture; it was treated with antibiotics.

In one patient, a cerebral contusion was observed outside the surgical field. Data on the complications are summarized in Table 3.

Table 1. Demographic characteristics of patients

Total amount of patients	**40**
Patient's age, range and mean (years)	31-69 (50.6)
Patient sex, female/male	27/13
Total amount of aneurysms	44
Total number of surgery	42
Multipl/single aneurysms	16/24
Follow-up period of patients, range and mean (days)	2-828 (379)

Table 2. Aneurysm localizations

Aneurysms	**Value**	**Percent**
Anterior communicating artery	7	15%
Middle cerebral artery bifurcation/ trifurcation	26	60%
Middle cerebral artery-M1 branches	2	4%
Middle cerebral artery-M2 branches	1	3%
Posterior communicating artery	2	4%
Internal carotid artery-distal	5	11%
Anterior cerebral artery-A1 branches	1	3%
Total	44	100%

Table 3. Post-surgical complications

Complications	**Value**	**Percent**
Seizure	3	7.5
Meningitis	1	2.5
Cerebrospinal fluid leaks	2	5
Hyperperfusion syndrome	1	2.5
Contusion	1	2.5
Skin wound problem	1	2.5

Discussion

With the recent increase in imaging techniques, UIAs can be detected at higher rates (24). Although some standards are accepted in deciding indications for treatment and treatment methods, discussions continue on this topic in the literature (2,8,24-27). The size, location, and other morphological characteristics of aneurysms, growth patterns documented in serial imaging, patient age, previous subarachnoid haemorrhage history, and the presence of multiple aneurysms or other cerebrovascular pathologies affect the decision process in terms of indications and treatments (2,8,26,27). Therefore, a decision must be taken in a multidisciplinary way by the endovascular and neurovascular teams in the treatment planning process (2,9). Various reviews and guidelines have revealed that aneurysms showing a growth of 7-10 mm in radiological follow-ups, those with previous subarachnoid haemorrhage history, and those located in anterior and posterior communicating arteries tend to have higher rupturing risks (2,9,24). In this study, 40 patients and 44 aneurysms were treated with 42 operations. Guideline criteria were taken into consideration for surgical indications. During the operations, we used assistive devices such as sodium fluorescein videoangiography and micro-Doppler ultrasonography. For more efficient dissection, we used microsurgery, the participation of a second surgeon with a third hand to the field, and various clipping methods such as pilot, serial, and temporary clipping during our surgical practices.

Subarachnoid haemorrhage has a very complex pathogenesis and can cause mortality and morbidity in ruptured cerebral aneurysms (27). However, in UIA treatment, permanent neurological deficits or death, specifically, are completely neurosurgical intervention complications. Some suggestions were introduced to prevent complications. In institutions with 20 or more annual cases, surgeries and assistive preoperative modern equipment are used (2,27,28).

Sodium fluorescein videoangiography is a practical intraoperative device that can show the aneurysm sac occlusion and the patency of the cerebral vessels surrounding the aneurysm after clipping (10). The most significant advantage of sodium fluorescein videoangiography is its ability to obtain three-dimensional scans simultaneously with the microscope while continuing the surgical operation. It is advantageous, especially in deep-localized aneurysms or small perforating arteries in danger (16). Some studies indicated that the main disadvantage of the intravenous use of sodium fluorescein is its long-term stay in the artery walls and aneurysm dome because of its long half-life, which will limit its recurrent use in case of reclipping (29). However, we benefitted from the recurring use in suitable doses, as mentioned in one of our previous studies (30).

Sodium fluorescein videoangiography's advantages in micro-Doppler ultrasonography aneurysm surgery are its practicality, low complication, and reusable structure (18,31). However, micro-Doppler ultrasonography can be insufficient in evaluating small perforations. Also, neighbourhood vascular structures can produce false positive results (32). We gradually used the micro-Doppler alongside sodium fluorescein videoangiography in our study. We believe combining various methods can positively impact perfecting surgical results. Every piece of equipment has its advantages and disadvantages.

It is essential to minimize the neural tissue and vascular injury during dissection and clip placement using microsurgical techniques. In the standard approach, the minimal use of retractors directly decreased brain damage (33-35). Some highly-regarded institutions stated that they included a second surgeon in the field (36). In our series, instead of keeping Leyla retractors constantly in the field, we had a second surgeon with a third hand participate in the surgery field. Various studies have reported 3% to 9% of brain damage associated with retractor use (37,38). Spetzler et al. (39) reported an incidence of approximately 10% in retraction-related complications in skull base surgery. In our study, we observed a 2.5% postoperative contusion. The contusion was not related to retraction. In addition, we experienced more practicality with a dynamic retraction in a narrow space in the surgical field compared to a fixed retraction.

When intraluminal thrombosis is present, the first part closer to the aneurysm neck is generally seen as easily closable with a permanent clip. However, the artery wall around the aneurysm neck is usually thick and calcific, making it very difficult and risky to clip (20). Therefore, some researchers have suggested thrombectomy in such cases, which notably increases the time the temporary clips stay in place (20,36). We did not operate on a giant aneurysm in our series; however, we should mention that we experienced an increase in thrombus visibility with the growth of the aneurysm dome. Closing with a single clip was nearly impossible in cases with calcified thrombus. We did not apply thrombectomy in our cases, but we ensured vascular modelling using serial-multiple clips.

A previously coiled aneurysm makes the surgery and the total obliteration of the dome difficult (36), and it was present in one of the patients in our series. We observed that coils punctured through the aneurysm dome and protruded out, and not knowing the exact localization of the defect posed an additional risk for rupture. Instead of completely removing the coil pieces from the dome, we ensured the closure of the dome using multiple clippings.

Complications occurring in intracranial aneurysm surgery can be categorized into two groups: Vascular and non-vascular. Vascular complications include thromboembolism during the perforating artery injury, parent artery occlusion, premature aneurysm rupture, and atherosclerotic lesion manipulation. The non-vascular complication class includes focal brain contusion, cranial nerve damage, excessive CSF drainage, intracerebral hematoma, and surgical wound infection. The mortality and permanent neurologic deficit rates are higher in vascular complications compared to the other group (21). We treated 40 patients and 44 aneurysms in this study with 42 operations. We did not encounter any mortalities or severe morbidities in patients. The mRS was evaluated as 1 in three the patients due to the detection of a newly developed epileptic seizure.

Proximal artery control should be ensured to prevent early rupture in aneurysm surgery. A sensitive approach is required for proximal control. Proximal artery control should be used to avoid premature rupture during aneurysm surgery. Some studies have reported vasospasm associated with the use of temporary clips (40). We did not detect vasospasm due to temporary clip use in our research.

Patients developing hyperperfusion syndrome because of temporary clips have been reported in the literature. Araki et al. (41) stated that a temporary clipping time longer than 20 minutes increased risk. In our study, one patient developed hyperperfusion syndrome after DSA, but a temporary clip was not used.

Sylvian, frontobasal, and frontal bridge veins should be protected with a good microdissection. In addition, ensuring that the perforators and distal branches are protected using assistive equipment after clipping is necessary (22). Minor complications such as bone flap infection and postoperative hematoma can be prevented by paying close attention to sterile conditions and careful haemostasis towards the end of the surgery (21).

Particular attention should be paid to the aneurysms oriented to the M1 segment of the middle cerebral artery, the A1 segment of the anterior cerebral artery, and the anterior communicating posterior due to its close relationship with the lenticulostriate artery (22). While the neck of an aneurysm that has simple, narrow, and non-complex anatomy can be closed with a single clip, using fenestra and clips at various angles might be required in cases where the complex-wide neck, perforating, and parent arteries stick to the neck or move away from the neck of the aneurysm (22,36). Additionally, bifurcation might require reconstruction with multiple clips using different approaches (23). It should be noted that it would not be inappropriate to wrap the aneurysm without clipping when faced with complications, despite experience in the field (36). Studies have shown that rests can remain after clipping the aneurysms at a 3.8% to 8% ratio; it was previously stated that these rests show a growth pattern in later years (42,43). We diagnosed two patients in our series (5%) with postoperative rest, and this was treated with secondary intervention.

Study Limitations

We are sharing the first-term findings of a newly established clinic. Therefore, having a small number of complicated cases with high difficulty levels, such as bypass surgery limits our study.

Conclusion

The variety and use of assistive devices such as sodium fluorescence videoangiography and micro-Doppler ultrasonography can ensure reliable results and lead to few complications without hindering surgical flow during the operation. A good preoperative evaluation always ensures better postoperative performance. The second surgeon joining the field as the third hand will help with the retraction and minimize the damage to neural tissue and vessels. Additionally, the complication rate will decrease as surgical experience increases in vascular institutions that deal with such cases.

Ethics

Ethics Committee Approval: All data were retrospectively examined and compiled after approval (no. 2022-281) was granted by the ethical Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital.

Informed Consent: The waiver of consent was not required due to the retrospective design of the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: B.E., E.A., S.D., L.Ş.P., Design: B.E., E.A., S.D., L.Ş.P., Data Collection or Processing: Y.K., S.D., E.A., O.B., Analysis or Interpretation: B.E., L.Ş.P., Y.K., Critical Review: L.Ş.P., Final Approval and Accountability: B.E., S.D., O.B., Technical or Material Support: O.B., Y.K., S.D., Supervision: L.Ş.P., Writing: B.E., S.D.

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ORIGINAL RESEARCH

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Cytology May not be Sufficient for Cervical Screening in Women with HPV Types Other than Type 16-type 18

Tip 16 ve 18 Dışı HPV Taşıyan Kadınlarda Kanser Taraması için Sitoloji Yeterli Olmayabilir

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Abstract

Objective: The aim of this study was to examine the relationship between human papilloma virus (HPV) types 16-18 and other high risk HPV types and final pathology in HPV positive women who underwent colposcopy and loop electroincision procedure (LEEP).

Method: The data of 528 HPV positive women hospitalized at tertiary center between January 2017 and January 2019 were recorded retrospectively. The ages of the patients, smear results, HPV types, pathology results of colposcopic biopsies and pathology results of LEEP material in LEEP patients were evaluated. Women with HPV DNA type 16 and/or 18 named as high risk group (HRG) and women with high risk HPV DNA types other than type 16 and/or 18 (31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 types) named as other high risk group (OHRG). Pregnant women were not included in the study. Women with vaginal infections were included in the study after treatment. Both groups were statistically analyzed according their colposcopical and pathological findings.

Results: There were 322 women (61%) in the OHRG. While there were benign findings in the colposcopy in approximately 75% of OHRG, cervical cancer was suspected in 3 (1%) of them. Benign colposcopic findings were the most common in the HRG, and CIN1 (30%) was the second most common. CIN3 and cancer were more common in the HRG (6.8% and 2.9%, respectively). 75% of the patients in the OHRG were followed up; 25% had LEEP. CIN1 was found in 18% of the women who underwent LEEP.

Conclusion: In the OHRG, invasive cervical cancer was diagnosed in 2 patients, even if the smear was negative; for this reason, colposcopy may be required regardless of cytology, as in HPV 16 and 18 positivity in these patients.

Keywords: Cervical cancer, colposcopy, cytology, human papilloma virus, smear

Öz

Amaç: Bu çalışmanın amacı, kolposkopi ve loop elektroensizyon prosedür (LEEP) yapılan human papilloma virüsü (HPV) pozitif kadınlarda HPV tip 16-18 ve diğer yüksek riskli HPV tipleri ile final patolojisi arasındaki ilişkiyi incelemektir.

Yöntem: Ocak 2017-Ocak 2019 tarihleri arasında tersiyer bir merkezde tedavileri yapılan 528 HPV pozitif kadının verileri geriye dönük olarak incelendi. LEEP yapılan hastaların yaşları, smear sonuçları, HPV tipleri, kolposkopik biyopsilerin ve LEEP materyallerinin patoloji sonuçları değerlendirildi. HPV tip 16 ve/veya 18 olan grup yüksek risk grubu (HRG), tip 16 ve/veya 18 dışında olup da genital kanserlere neden olabilen HPV tiplerini (31, 33, 35, 39, 45, 51, 52, 56, 58, 59 ve 68 tipleri) diğer yüksek riskli HPV grubu (OHRG) olarak tanımladık. Gebeler çalışmaya dahil edilmedi. Vajinal enfeksiyonu olan kadınlar tedavi sonrası çalışmaya dahil edilmiştir. Kolposkopi ve patoloji sonuçları mevcut HPV tipine göre istatistiksel olarak değerlendirildi.

Bulgular: OHRG grubunda 322 kadın (%61) vardı. Bu grupta HPV'li kadınların yaklaşık %75'inde kolposkopide benign bulgular, 3 (%0,9) kadında serviks kanseri tespit edildi. HRG grubunda en yaygın kolposkopik bulgu benign bulgulardı, CIN1 (%30) ikinci sıklıktaydı. CIN3 ve serviks kanseri yüksek risk grubunda daha yaygındı (sırasıyla %6,8 ve %2,9). OHRG grubunda %75 kadına LEEP yapılmadan takip yapılmıştı, LEEP yapılan (%25) kadınlarda %18 CIN1 tespit edildi.

Sonuç: OHRG'de smear negatif olsa bile 2 hastada kanser görüldü; bu nedenle bu gruptaki hastalarda da HPV 16 ve 18 pozitifliğinde olduğu gibi sitolojiden bağımsız olarak kolposkopi yapılması gerekebilir.

Anahtar kelimeler: İnsan papilloma virüsü, kolposkopi, rahim ağzı kanseri, sitoloji, yayma

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Introduction

There are more than 200 subtypes of human papilloma virus (HPV) virus that invade through microcracks in the epithelium. In women, the vulva, vagina, cervix, perianal area, and anal canal are affected. The incidence of HPV was 10% worldwide (1). It is most common in Africa. HPV can be seen in patients of all ages. The frequency of HPV decreases after the age of 25, with a small peak in some populations after menopause (2).

Genital HPV is mainly transmitted by sexual contact. However, intravaginal cleaning also causes HPV positivity in young girls without a history of sexual contact (8%) (3).

There are more than 40 types of HPV that infect anogenital skin and mucous membranes. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are high risk HPV types for the development of malignancy. Condyloma acuminata (types 6 and 11 being the most common), squamous intraepithelial lesions and cancer (types 16 and 18 being the most common) are associated with HPV.

With a cervical smear, it is possible to diagnose and follow-up lesions due to HPV. Colposcopy is performed for the diagnosis and follow-up of precancerous lesions and cancer following an abnormal cervical screening test or in cases of clinical suspicion. If there are suspicious findings in colposcopy, the pathological examination should be detailed by performing the loop electrosurgical excision procedure (LEEP). LEEP describes a conical excision of the cervix, including the transformation zone and areas that appear suspicious on colposcopy. Moreover, LEEP is also a treatment method.

In routine practice, post-smear colposcopy and LEEP follow-up are recommended for women with high risk HPV. However, if there are abnormal examination findings and clinical complaints for patients with non-16/18 HPV, colposcopy and LEEP follow-up are recommended. Moreover, malignancy can also develop with other high risk group HPV (4).

Other than HPV types 16 and 18, we planned this study to investigate the frequency of precancerous and malignant lesions developing with high risk HPV types and to compare them with patients with high risk types of HPV.

Materials and Methods

Our study was conducted retrospectively in a secondary center after obtaining the permission of the Local Ethics Committee of Batman State Hospital (no: 2020/232). Data were collected in the pilot province where mobile HPV screening was performed. In the study, a retrospective evaluation of the data of 528 female patients aged between 27 and 65 whose cervical smears were taken and HPV DNA examined. The US Food and Drug Administration approved ThinPrep Imaging System was used for primary screening.

The cervix was first visualized by applying saline, then 3-5% acetic acid was applied to the cervix and upper vagina, waited for 30-60 seconds, and the squamocolumnar junction and ectocervix were examined. Finally, Schiller's test was done with 5% Lugol solution. Cervical biopsy was taken under local anesthesia from the abnormal epithelium. A Kevorkian cervical biopsy instrument was used for the cervical biopsy. Monsel's solution (ferric subsulfate) was applied to the biopsy site, and if the bleeding did not stop, bleeding site was sutured with 2/0 polyglactin, absorbable, synthetic, monofilament material.

Endocervical curettage was performed all women with a pathological appearance in colposcopy, and in women with ASCH, HSIL, AGC, LSIL or ASCUS smear results without lesions in colposcopy.

Statistical Analysis

All analyses were performed using the SPSS v21 program (SPSS Inc., Chicago, IL, USA). The compliance of the quantitative data with the normal distribution was checked with the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables with the normal distribution are the mean ± standard deviation, and the median (smallest value-maximum value) of the other variables given in the form. Frequency and percentage values were preferred in the presentation of categorical data. The chi-square test was used in the analysis of the categorical data. The Fisher's Exact test was used for the HPV subtype and different category comparisons. A p-value less than 0.05 was considered significant.

Results

Five hundred twenty-eight HPV positive women were included in the study. The mean age of the HPV detected patients is 42 years. Considering HPV positive patients; it is positive in 38% at 35 years of age, in approximately 48% at 40 years of age, and in approximately 22% at 50 years of age. Considering each demographic characteristics, no similarity was found between the two groups in terms of age, body mass index, literacy and smoking rates (Table 1).

Non-16/18 HPV was detected in 322 women (61%). While there were benign findings in the colposcopic evaluation in approximately 75% of the women with OHRG, cervical cancer was detected in three women (0.9%). In the OHRG and HRG groups, there was a difference between the patients with and without LEEP (p=0.027 <0.05). Benign colposcopic findings were the most common finding in the HRG, and cervical intraepithelial neoplasia-1 (CIN1) (30%) was the second most common pathological diagnosis of colposcopic biopsy materials. CIN2 was seen at the same rate in both groups. CIN3 and cervical cancer (6.8% and 2.9%, respectively) were more common in the HRG (Table 2). Seventy-five percent of the patients in the OHRG were followed up; 25% had LEEP. CIN1 were found in 18% of the women who underwent LEEP (Table 3).

Table 1. Demographic characteristics of patients

	HRG (Mean + SD)	OHRG (Mean + SD)	p-value
Age	44+0.9	39+0.8	0.120
Gravida	4+0.3	3.8+0.8	0.08
Parity	3+0.4	2.67+0.7	0.62
Abortus	1+0.5	1+0.7	0.65

HRG: High risk group, OHRG: Other high risk group, SD: Standard deviation

Table 2. Comparison of histopathologic findings in colposcopicaly directed biopsies of patients in HRG and OHRG

Cervical biopsy	OHRG	HRG	p-value
Benign	241	123	**0.039**
CIN1	63	61	0.125
CIN2	3	2	0.143
CIN3	12	14	0.134
Cervical cancer	3	6	**0.04**
Total	322	206	-

HRG: High risk group, OHRG: Other high risk group, CIN: Cervical intraepithelial neoplasia

Table 3. Comparison of histopathologic findings of LEEP materials in HRG and OHRG

LEEP results	OHRG	HRG	p-value
CIN1	57	51	0.157
CIN2	15	11	0.190
CIN3	7	12	**0.034**
Cervical cancer	1	1	-
Total	80	75	

HRG: High risk group, OHRG: Other high risk group, CIN: Cervical intraepithelial neoplasia, LEEP: Loop electroincision procedure

Discussion

In our study, we found out that the women with the HRG had a higher rate of cervical pathologies than OHRG. The frequency of benign lesions was approximately 75% in the women with OHRG and approximately 60% in patients with HRG. We found that performing a colposcopy and LEEP in addition to smear tests in women with carcinogenic HPV has a higher diagnostic value for the diagnosis of precancerous lesions and cancer.

ThinPrep, which we used for cervical evaluation, uses programmed algorithms. If abnormalities are found, the entire slide is reviewed by a cytopathologist. With the use of this device, HSIL and LSIL diagnoses are detected at a higher rate than in traditional pathological examinations (5). However, the clinical efficacy of automated systems and their role in cervical cancer screening are still unclear.

In our study group, non-16/18 HPV types were detected in 133 and high risk HPV types in 85 of 218 patients with normal smear results. In the colposcopy results of these patients with normal smear results in OHRG; CIN1, 2 and 3 was detected in 17%, 0.7% and 5.2%, respectively. The CIN1, CIN2, and CIN3 rates of the patients in HRG detected and normal smear results were analyzed as 21%, 1.2%, and 5.9%, respectively. High risk HPV was detected in 22 of 68 patients whose smear results were ASCUS, and cervical cancer was detected in one patient as a result of colposcopic biopsy. One of the reasons for the inconsistency of the smear results and colposcopy results may be that the person performing the examination is not a gyneco-oncopathologist.

Not every infection with HPV type 16 or 18 will necessarily progress to cervical, vaginal, or vulvar cancer. In several studies in women, the presence of anti-HPV antibodies, which are indicative of prior infection, has been associated with a reduced risk of subsequent HPV infection, particularly for types 16 and 18, suggesting the potential for protective immunity following natural infection (6). In cervical cancer prevention guidelines, age is also important in HPV follow-up along with HPV16/18 typing to determine the risk of CIN3 and cancer in terms of cytology and cervical cancer risk. According to ASCCP recommendations, if HPV type 16/18 or HPV positive and genotype is uncertain, the management of these patients is colposcopy or repeat cytology 2-4 months later (4). In our study, CIN2 was observed as the same rate in both groups and it was found to differ from the literature.

LEEP is a treatment method that can provide remission in persistent HPV infections in the treatment of SIL (7).

In fact, it is not HPV that is treated, but lesions caused by HPV. According to the data of 141 women who underwent LEEP for CIN and had clean surgical margins, LEEP can effectively eliminate HPV infections. Most HPV positive women had HPV eradicated at six months. While the HPV persistence rate is 45% in the 3rd month, it decreased to 2.1% by the 12th month. The most common persistence rate is in HPV type 16. In women with high risk HPV, recurrence and residual disease are more common after LEEP (8). In our study, we found a higher rate of CIN3 in HRG. (5.8%, 2.1%) ($p<0.05$) (Table 3).

Study Limitations

In our study, we considered the absence of previous HPV anamnesis a limitation. Moreover, the tests were performed by different physicians at different instutitions.

Conclusion

According to the results of our study, we believe that the presence of HPV types other than HPV 16 and 18 is a risk of precancerous and cancerous lesions and should be evaluated further with colposcopy.

Ethics

Ethics Committee Approval: Our study was conducted retrospectively in a secondary center after obtaining the permission of the Local Ethics Committee of Batman State Hospital (no: 2020/232).

Informed Consent: Written and verbal consent was obtained from all patients before starting the study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.O., Ö.K.A., Design: E.O., Ö.K.A., Data Collection or Processing: E.O., Ö.K.A., Analysis or Interpretation: E.O., Ö.K.A., Critical Revision of Manuscript: E.O., Ö.K.A., Final Approval and Accountability: E.O., Ö.K.A., Technical or Material Support: E.O., Supversion: Ö.K.A., Writing: E.O., Ö.K.A.

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ORIGINAL RESEARCH

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Comparison of the Protective Effect of Alpha Lipoic Acid and Quercetin in Methotrexate-Induced Lung Damage

Metotreksat ile Oluşturulan Akciğer Hasarında Alfa Lipoik Asit ve Kuersetinin Koruyucu Etkilerinin Karşılaştırılması

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Abstract

Objective: The aim of this experiment is to investigate and compare the effects of alpha lipoic acid (ALA) and quercetin (QUE) on methotrexate (MTX)-induced lung injury in rats.

Method: Wistar Albino rats were distributed into control, MTX, MTX+ALA and MTX+QUE groups with each consisting of 6 rats. Except control group, MTX administrated to rats as a single dose (20 mg/kg) intraperitoneally (i.p.) on the first day. Saline (0.1 cc/100 gr/day, i.p.) was injected to rats in control and MTX groups for 5 days. In MTX+ALA and MTX+QUE groups, rats had injections of ALA (50 mg/kg/day, i.p.) and QUE (50 mg/kg/day, i.p.) for 5 days. After sacrification on day 6, lung tissues were excised out for histopathologic and biochemical investigation.

Results: MTX group showed massive hemorrhage with edema in the interstitium, significant inflammatory cell infiltration, and severe alveolar destruction and vascular congestion. Additionally, significant increases in oxidative stress markers as malondialdehyde and sialic acid and significant decreases in antioxidants as glutathione, superoxide dismutase and catalase were detected at the tissue level in MTX group ($p<0.0001$, $p<0.0001$, $p<0.0001$, $p=0.03$ and $p<0.0001$, respectively). Both ALA and QUE treatment led to a prominent improvement in morphologic damage. Moreover, ALA and QUE resulted in the reversal of the alterations seen in the tissue oxidative damage markers and antioxidant activities as well. We could not reveal a significant difference between MTX+ALA and MTX+QUE group in terms of morphologic damage and biochemical markers of oxidative injury ($p>0.05$).

Öz

Amaç: Bu çalışmanın amacı sıçanlarda metotreksat (MTX) ile oluşturulan akciğer hasarında alfa lipoik asit (ALA) ve kuersetinin (QUE) koruyucu etkilerinin araştırılması ve karşılaştırılmasıdır.

Yöntem: Wistar Albino her biri 6 adet sıçandan oluşan kontrol, MTX, MTX+ALA ve MTX+QUE gruplarına ayrıldı. Kontrol grubu hariç tüm gruplarda deneyin ilk gününde sıçanlara tek doz MTX (20 mg/kg) intraperitoneal (i.p.) olarak verildi. Kontrol ve MTX gruplarındaki sıçanlara 5 gün serum fizyolojik (0,1 cc/100 gr/gün, i.p.) verildi. MTX+ALA ve MTX+QUE gruplarındaki sıçanlara 5 gün ALA (50 mg/kg/gün, i.p.) ve QUE (50 mg/kg/gün, i.p.) enjeksiyonu yapıldı. Deneyin 6. gününde sıçanlar sakrifiye edilerek akciğer dokuları histopatolojik ve biyokimyasal inceleme için çıkartıldı.

Bulgular: MTX grubunda interstisyumda yoğun hemorajiyle birlikte ödem, belirgin enflamatuvar hücre infiltrasyonu ve ciddi alveolar yıkımı ve vasküler konjesyon görüldü. Bu bulgulara ek olarak, MTX grubunda malondialdehit ve sialik asit gibi oksidatif stres belirteçlerinde önemli bir artış ve glutatyon, süperoksit dismutaz ve katalaz gibi antioksidanlarda önemli bir azalış olduğu doku düzeyinde saptandı (sırasıyla $p<0,0001$, $p<0,0001$, $p<0,0001$, $p=0,03$ ve $p<0,0001$). Hem ALA hem de QUE tedavisinin morfolojik hasar üzerinde belirgin bir iyileşmeye neden olduğu tespit edildi. Ayrıca ALA ve QUE tedavisi MTX'in yol açtığı doku oksidatif hasar belirteçlerinde ve antioksidan aktivitedeki olumsuz değişimleri tersine çevrilmesine neden olduğu tespit edildi. Morfolojik hasar ve oksidatif hasarın biyokimyasal belirteçleri açısından MTX+ALA ve MTX+QUE grupları arasında anlamlı bir fark saptanmadı ($p>0,05$).

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Abstract

Conclusion: Our study showed the similar protective effect of ALA and QUE in MTX induced lung damage. Further studies are warranted to verify the results of our outcome.

Keywords: Alpha lipoic acid, lung, methotrexate, quercetin

Öz

Sonuç: Çalışmamız MTX ile oluşturulan akciğer hasarı üzerinde ALA ve QUE'nin benzer koruyucu etkilerinin olduğunu gösterdi. Sonuçlarımızı doğrulamak için daha ileri çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Akciğer, alfa lipoik asit, kuersetin, metotreksat

Introduction

Methotrexate (MTX) is a folic acid analog that frequently preferred in the treatment of both systemic and inflammatory diseases like psoriasis, rheumatoid arthritis and malignancies. The basic mechanism of its action occurs through the inhibition of folate metabolism and suppression of the synthesis of inflammatory cytokines such as like tumor necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β), and thereby leading to the downregulation of inflammatory reactions (1,2). Pulmonary toxicity has been regarded as the main adverse effect of the long-term treatment with MTX or its overdose. In a dose-dependent fashion, MTX could cause pneumonitis, interstitial lung disease, and lung fibrosis and the development of these adverse effects usually ends up with early discontinuation of the therapy (3). Oxidative stress caused by overproduction of reactive oxygen species (ROS) is regarded as the underlying mechanism behind MTX-induced lung toxicity (4).

Recently there has been an on-going effort to tackle MTX-induced pulmonary toxicity and many natural and synthetic agents with a proposed antioxidant action have been used in the treatment of this dismal complication. Quercetin (QUE), its name originating from quercetum (oak forest), is a natural product which acts as a pigment giving color to fruits and vegetables (5). It was shown that QUE has a role in prevention of many chronic diseases like diabetes mellitus (DM), obesity and cardiovascular diseases via its antioxidant effects (5, 6). Several investigators revealed that QUE supplementation in rats treated with MTX caused a beneficial effect against the development of lung, liver and renal toxicities (7-9). Furthermore, alpha lipoic acid (ALA) is a commonly used herbal medicine and it is a synthetic form of lipoic acid produced by plants and animals (10). ALA has a crucial role in energy metabolism and regeneration of cellular antioxidant stores, therefore inducing an antioxidant action in the body (11). Clinically, ALA supplementation in diabetic patients regulates the blood sugar and improves DM-related complications (12). In a study by Arpag et al. (13), combination of ALA with MTX was found to reduce the MTX-related tissue damage in rats. In MTX-related pulmonary toxicity, although the organ protective effects of the above-given herbals, ALA and QUE, have been shown in several studies, the evidence has still remained weak. In our study, we aimed to study the effect of ALA and QUE in pulmonary toxicity related to MTX experimentally and compare the effects of these two agents.

Materials and Methods

Chemicals

Quercetin (Q4951, catalog number:117-39-5) and ALA (T1395, catalog number: 1077-28-7) were obtained from Sigma-Aldrich Chemical Company (St. Louis, MO, USA). Methotrexate (Metotrexate, 50 mg/5 mL) was obtained from Koçak Farma İlaç ve Kimya Sanayi A.Ş., Turkey.

Animals

Twenty-four adult male Wistar Albino rats (2 months old, 200-250 gr) were housed under the standard laboratory conditions. They received standard rat pellet and water ad libitum. Throughout the experiment, "the Guide for the Care and Use of Laboratory Animals" process guidelines were followed. The experimental procedure was approved by Marmara University Animal Care and Use Committee (protocol number: 50.2022.mar and date: 11.10.2022).

Experimental Design

Rats were distributed into four group: In control group (C, n=6), rats were injected with saline (0.1 cc/100 gr/day) intraperitoneally (i.p.) for 5 days. In MTX group (n=6), rats were injected with a single dose of MTX (20 mg/kg, i.p.) on the first day and saline (0.1 cc/100 g/day, i.p.) for 5 days. In MTX+ALA group (n=6), rats were injected with a single dose of MTX (20 mg/kg, i.p.) on the first day and ALA (dissolved in saline, 50 mg/kg/day, i.p.) for 5 days. In MTX+QUE group (n=6), rats were injected with a single dose of MTX (20 mg/kg, i.p.) on the first day and QUE (dissolved in saline, 50 mg/kg/day i.p.) for 5 days. On the sixth day of the experiment, all rats were sacrificed under general anesthesia with sodium pentothal (50 mg/kg, i.p.) and lung tissues were excised out for histopathological and biochemical investigation.

Histopathologic Analysis

For light microscopic analysis, fixation of lung tissue samples was done with 10% formaldehyde. After routine tissue processing, they were embedded in paraffin blocks. For detection of the morphological alterations, hematoxylin and eosin staining was applied to approximately 5 µm thick paraffin section. All stained section was investigated by a microscope (Olympus CX41, Tokyo, Japan) and photographed with a camera (Kameram Dijital Mikroskopi, Türkiye). Histopathologic scoring for each sample was done at least 5 microscopic areas and four criteria were evaluated including (1) congestion, (2) interstitial edema, (3) inflammatory cell infiltration and (4) alveolar degeneration. Each criterion was semiquantitatively scored on a scale ranging from 0-3 (0: Absent, 1: Mild, 2: Moderate and 3: Severe) (14).

Biochemical Analysis

To assess the biochemical parameters, lung tissue homogenates (10% w/v) were made using saline solution and kept in the freezer at -20 °C. Malondialdehyde (MDA), glutathione (GSH) and sialic acid (SA) levels and superoxide dismutase (SOD), catalase (CAT) activities were determined via following previously described methods (15).

Statistical Analysis

All data was analyzed by GraphPad Prism 8.42 (GraphPad Software, San Diego, CA, USA). Following the normal distribution of data was identified by Shapiro-Wilk test, the One-Way Analysis of Variance (ANOVA) test and Tukey's multiple comparison tests were done. The results were given as mean ± standard deviation and a value of $p<0.05$ was accepted as significant.

Results

Histopathologic Results

Microscopic investigation revealed normal lung architecture in control group. In MTX group, massive hemorrhage with edema in the interstitium, significant inflammatory cell infiltration, and severe alveolar destruction and vascular congestion were observed. In addition to a quite regular alveolar structure in most areas of the tissue, a reduction in hemorrhage with edema in the interstitium, a decrease in inflammatory cell infiltration and mild vascular congestion were seen in MTX+ALA group. In MTX+QUE group, a prominent amelioration in alveolar structure, regression in hemorrhage with edema in the interstitium, reduced inflammatory cell inflammation and a moderate vascular congestion were present (Figure 1).

Compared to control group, exposure to MTX resulted in a significantly higher histopathologic score ($p<0.0001$). In comparison, the histopathologic score was found to be lower in MTX+ALA and MTX+QUE groups when compared to MTX group ($p<0.0001$, for both). Additionally, there was no significant difference in the histopathologic score between MTX+ALA and MTX+QUE groups ($p>0.05$, Table 1).

Biochemical Results

The MDA and SA levels in MTX group were found to be significantly higher in comparison with control group ($p<0.0001$, for both). However, MDA level significantly decreased in both MTX+ALA and MTX+QUE groups when compared with MTX group ($p=0.006$ and $p=0.02$, respectively). Moreover, SA level significantly decreased in both MTX+ALA and MTX+QUE groups in comparison with MTX group ($p=0.001$, for both). Contrasted with the control, the GSH level, SOD and CAT activities significantly reduced in MTX group ($p<0.0001$, $p=0.03$ and $p<0.0001$, respectively). The level of GSH significantly increased in

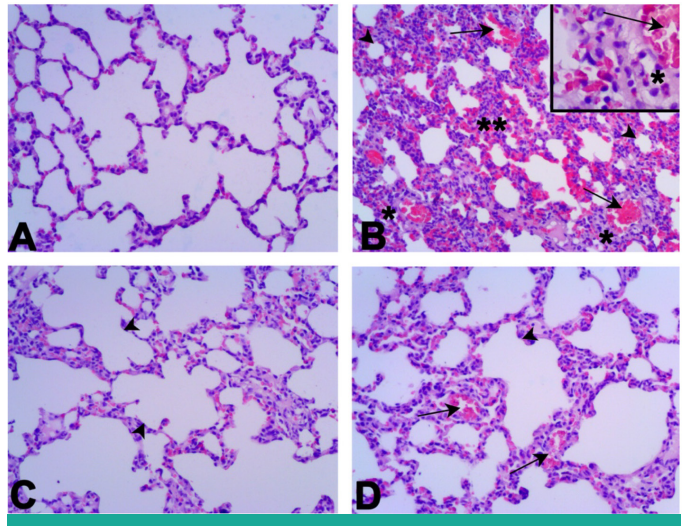

Figure 1. Representative light photomicrographs of lung tissues in experimental groups. In control group (**A**), normal lung morphology were observed. In methotrexate (MTX) group (**B**), Massive hemorrhage with edema in the interstitium (**), inflammatory cell inflammation (*), severe vascular congestion (arrows) and alveolar destruction (arrows) were seen. In MTX + alpha lipoic acid (ALA) group (**C**), Quite regular alveolar structure (arrow heads) were observed in most areas of the tissue. In MTX+quercetin (QUE) group (**D**), Quite regular alveolar structure (arrow heads) in many areas of the tissue and moderate vascular congestion (arrows) were seen. Original magnification x 100 and x200 (inset), Hematoxylin and eosin staining

both MTX+ALA and MTX+QUE groups compared to MTX group (p=0.0005 and p=0.005, respectively). Also, CAT activity was significantly increased in both MTX+ALA and MTX+QUE groups compared to MTX group (p=0.009 and p=0.007 respectively). There was no a significant difference in SOD activity in both MTX+ALA and MTX+QUE groups compared to MTX group (p>0.05, Table 2).

Discussion

Our results showed that both ALA and QUE have the antioxidant potential to suppress the generation of ROS in the lung tissue of the animals treated with MTX. The benefit of these agents was also verified at the morphologic level and administration of both ALA and QUE with MTX lessened the inflammation in the lung tissue and preserved the alveolar structure in the similar fashion.

In our study, MTX treatment resulted in the generation of ROS and lung damage that was in accordance with the current literature data. As a folate antagonist and S-phase active agent, MTX inhibits the activity of dihydrofolate reductase enzyme and synthesis of purine and pyrimidine bases necessary for production of nucleic acids in rapidly dividing malignant cells (16). It was shown that most of the patients treated with MTX for malignancy and inflammatory conditions like rheumatoid arthritis have pulmonary symptoms such as dyspnea, cough, pneumonitis and interstitial lung disease (3,4,17). In patients with MTX-associated pneumonitis, IL-8 and chemotactic factors secreted by the airway epithelium increase (18). Toxic doses of MTX promotes a more profound lung inflammation by increasing the secretion of IL-1 and TNF-α, MDA and myeloperoxidase (MPO) which were shown to be the most crucial players of chronic inflammation and pneumonitis (2,19).

To tackle the pulmonary toxicity, anti-inflammatory and antioxidant agents have been increasingly tested in many experimental studies. Kurt et al. (20) revealed that infliximab, TNF-α inhibitor, is protective against MTX overdose-associated lung damage by decreasing endothelin-1 release and oxidative stress. In an experimental study by Kaymak et al. (21), Vitamin B12 pretreatment was shown to lessen oxidative damage and inflammation in MTX-induced lung toxicity. Moreover, immunohistochemically, expressions of TNF-α, alpha-smooth muscle actin (α-SMA), laminin, and the number of apoptotic cells were found to decrease significantly with vitamin B12 in the lung tissue samples. The protective

Table 1. Comparison of histopathologic score in experimental groups

Parameters	C (n=6)	MTX (n=6)	MTX+ALA (n=6)	MTX+QUE (n=6)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Histopathologic score	1.08±0.37	10.17±1.16	4.91±0.91	5.91±0.66
p-values		<0.0001*	<0.0001*; <0.0001$^{\alpha}$	<0.0001*; <0.0001$^{\alpha}$

Tukey's multiple comparison test. Value of p<0.05 was accepted as significant. *represents comparisons with control group; $^{\alpha}$ represents comparisons with MTX group. SD: Standard deviation, C: Control, MTX: Methotrexate, ALA: Alpha lipoic acid, QUE: Quercetin

Table 2. Comparison of biochemical markers in experimental groups

Parameters	C (n=6)	MTX (n=6)	MTX+ALA (n=6)	MTX+QUE (n=6)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
MDA (nmol/mg protein)	39.92±6.79	65.49±11.34	49.09±6.72	51.94±3.04
p-values		<0.0001*	0.006$^{\alpha}$	0.02$^{\alpha}$
SA (ng/g protein)	12.75±1.73	21.31±2.31	16.85±1.22	17.10±1.31
p-values		<0.0001*	0.002*; 0.001$^{\alpha}$	0.001*; 0.001$^{\alpha}$
GSH (mg/g protein)	4.14±0.29	2.59±0.38	3.52±0.31	3.32±0.31
p-values		<0.0001*	0.02*; 0.0005$^{\alpha}$	0.001*; 0.005$^{\alpha}$
SOD (U/mg protein)	1.26±0.10	1.08±0.08	1.63±0.14	1.13±0.07
p-values		0.03*		
CAT (kU/mg protein)	5.52±0.42	4.31±0.35	5.03±0.24	5.05±0.32
p-values		<0.0001*	0.009$^{\alpha}$	0.007$^{\alpha}$

Tukey's multiple comparison test. Value of p<0.05 was accepted as significant. *represents comparisons with control group; $^{\alpha}$represents comparisons with MTX group. SD: Standard deviation, C: Control, MTX: Methotrexate, ALA: Alpha lipoic acid, QUE: Quercetin, MDA: Malondialdehyde, GSH: Glutathione, SA: Sialic acid, SOD: Superoxide dismutase, CAT: Catalase

roles of N-acetylcysteine and erythropoietin in MTX-related lung damage were also demonstrated in the literature (22).

The balance between ROS and antioxidants determines the sensitivity and resistance of the organism to oxidative stress. Endogenous and/or exogenous factors that change this balance cause cell injury. Antioxidant defense systems protect the cell against the harmful effects of ROS. These molecules are divided into two groups as enzymatic, such as SOD and CAT activity, and nonenzymatic, such as GSH, and are involved in antioxidant defense mechanisms at different levels in the cell (23).

As a flavonoid, QUE is extensively found in plants in nature, including berries, grapes, apples, brassica vegetables, tomatoes and onions as well as in many seeds, nuts, and leaves (5). Flavonoids are natural products and have several therapeutic effects such as antioxidant, antitumor, and anti-inflammation properties. QUE is an active flavonoid and has the ability to scavenge free radicals (24). Owing to these properties, it has been remained as a popular herbal agent (25). The impact of QUE in MTX-induced organ damage was studied in several studies. Aydin (26) demonstrated the hepatoprotective effect of QUE in MTX-related hepatotoxicity experimentally. In a study by David et al. (9), numerous inflammatory cell infiltration, congested septal capillaries and abnormally large alveoli in lungs were detected with MTX (0.125 mg/kg) and increasing the dosage of MTX to 0.250 mg/kg resulted in more severe damage. Co-administration of QUE with MTX inhibited the most of the pathologic alterations in the lung tissue. In our study, QUE treatment increased the antioxidant capacity of the lung tissue exposed to MTX by increasing the tissue levels of GSH, CAT and SOD. Moreover, MDA, a product of lipid peroxidation, decreased with QUE treatment. The benefit of QUE treatment was also evident in histopathologic evaluation with amelioration of alveolar structure and regression in hemorrhage, edema, inflammatory cell inflammation and vascular congestion after MTX treatment.

Biochemically, ALA, as a cofactor, is fat and water soluble and involves in the conversion of glucose into energy. The antioxidant capacity of ALA has been shown in many *in vitro* and *in vivo* studies as it acts like a metal chelator, free radical scavenger, regenerator of antioxidant defense and repairer of already injured tissues by ROS (27). Its anti-inflammatory and antioxidant action was shown in many studies (12). The antioxidant effect of ALA on kidney, liver and peripheral nerves, and kidney was shown experimentally (28-30). Guais et al. (31) gathered attention on the fact that when cellular cofactors like lipoic acid and hydroxy citrate were combined with chemotherapeutic agents in cancer models, it resulted in a better basic treatment protocol efficacy. The role of ALA in MTX-induced lung damage was questioned in only one study performed by Arpag et al. (13). The investigators treated animals with ALA (60 mg/kg) for 5 days after a single dose of MTX and found that ALA treatment resulted in significant decreases in the production of MDA, MPO, IL-1 and TNF-α. Also, in histologic evaluation, ALA reduced chronic inflammation and damage. In our study, MTX and ALA were applied in similar doses as those given in literature. In accordance with the above mentioned study, our study also proved the antioxidant effect of ALA in MTX induced pulmonary toxicity. We could not reveal a superiority of QUE on ALA or vice versa in terms of antioxidant capacity or tissue protection.

Study Limitations

Our study has a few apparent limitations. First, to test the protective roles of ALA and QUE, we mainly focused on the tissue markers of oxidative stress. Incorporating immunohistochemical tests of tissue cytokines like IL-6 and TNF-α and apoptosis would certainly increase the power of the study. Second, while demonstrated the protective effect of ALA and QUE individually against MTX-induced lung damage, it would be better to test the combination of two agents in a separate group to understand whether they exert a synergistic effect when used in combination.

Conclusion

Our study verified the fact that MTX causes lung damage through augmentation of oxidative stress in the tissue. Moreover, both ALA and QUE exert a protective role in lung injury by lessening the oxidative stress related to methotrexate exposure. We could not detect any difference in the magnitude of the tissue protection between ALA and QUE against MTX-induced lung damage.

Ethics

Ethics Committee Approval: The experimental procedure was approved by Marmara University Animal Care and Use Committee (protocol number: 50.2022.mar and date: 11.10.2022).

Informed Consent: N/A.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., A.M., Ş.Ç., Ş.O., Concept: E.A., Ş.O., Design: E.A., Ş.O., Data Collection or Processing: E.A., A.M., Ş.Ç., Ş.O., Analysis or Interpretation: E.A., A.M., Ş.Ç., Ş.O., Literature Search: E.A., A.M., Ş.Ç., Ş.O., Writing: E.A., A.M., Ş.Ç., Ş.O.

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ORIGINAL RESEARCH

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The Impact of Differential Atrioventricular Delays on Arterial Distensibility Measured by Pulse Wave Velocity in Patients with Dual-chamber Pacing

Çift Odacıklı Kalp Pili olan Hastalarda Değişken Atriyoventriküler Gecikme Zamanlarının Nabız Dalga Hızı ile Ölçülen Arteriyel Genişleyebilirlik Üzerine Etkisi

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Abstract

Objective: Atrioventricular (AV) delay optimization improves hemodynamics and clinical parameters of patients treated with dual-chamber (DDD) pacemakers. Pulse wave velocity (PWV) is an index of arterial stiffness and a marker of cardiovascular events. Increased levels of PWV is an indicator of diffuse atherosclerosis and rigid arteries. We aimed to investigate the impact of differential AV delay intervals (100, 150 and 200 ms respectively) on arterial distensibility measured by carotid-femoral PWV in patients with DDD pacing.

Method: A total of 40 patients with DDD pacing were enrolled in our prospective study. PWV was measured for each AV delay (100 ms, 150 ms and 200 ms respectively) with 10 minute resting intervals. Pacing was programmed at least 10 beats/minute above the resting heart rate. PWV was automatically calculated by using the device, Complior Colson (France), which allows online pulse wave recording according to this formula: PWV(m/s) = distance (meter)/transit time (second).

Results: There was a statistically obvious positive correlation between carotid-femoral PWV and prolongation of AV delay interval ($p<0.001$). According to gender analysis; weight, height and waist-hip ratio values were significantly higher in male group. Additionally, there was not a statistically significant difference between groups in terms of age, body mass index, mean, systolic and diastolic blood pressure, pulse pressure and PWV measured at differential AV delay intervals.

Conclusion: Prolongation of AV delay interval increased carotid-femoral PWV values thereby decreased arterial distensibility in patients with DDD pacing. Therefore, optimum AV delay adjustment may provide better hemodynamics in these patients.

Keywords: Atrioventricular delay interval, dual-chamber pacemaker, pulse wave velocity

Öz

Amaç: Atriyoventriküler (AV) gecikme optimizasyonu, çift odacıklı (DDD) kalp pilleri ile tedavi edilen hastaların hemodinamiklerini ve klinik parametrelerini iyileştirir. Nabız dalga hızı (NDH), arteriyel sertliğin bir indeksi ve kardiyovasküler olayların bir belirtecidir. Artan NDH seviyeleri, yaygın ateroskleroz ve sertleşmiş arterlerin bir göstergesidir. Diferansiyel AV gecikme aralıklarının (sırasıyla 100, 150 ve 200 ms) DDD pacingli hastalarda karotis-femoral NDH ile ölçülen arteriyel esneyebilirlik üzerindeki etkisini araştırmayı amaçladık.

Yöntem: Prospektif çalışmamıza DDD pacingli toplam 40 hasta alındı. NDH, her AV gecikmesi için (sırasıyla 100 ms, 150 ms ve 200 ms) 10 dakikalık dinlenme aralıklarıyla ölçüldü. Pacing, dinlenme kalp hızının en az 10 vuruş/dakika üzerine programlandı. NDH çevrimiçi nabız dalgası kaydına izin veren Complior Colson (Fransa) cihazı kullanılarak, şu formüle göre otomatik olarak hesaplandı: PWV(m/s) = mesafe (metre)/geçiş süresi (saniye).

Bulgular: Karotis-femoral NDH ile AV gecikme aralığının uzaması arasında istatistiksel olarak belirgin pozitif korelasyon vardı ($p<0,001$). Cinsiyet analizine göre; ağırlık, boy ve bel-kalça oranı değerleri erkek grubunda anlamlı olarak daha yüksekti. Ayrıca yaş, vücut kitle indeksi, ortalama, sistolik ve diyastolik kan basıncı, nabız basıncı ve diferansiyel AV gecikme aralıklarında ölçülen NDH açısından gruplar arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: AV gecikme aralığının uzaması karotis-femoral NDH değerlerini artırdı ve bu nedenle DDD pacingli hastalarda arteriyel distensibiliteyi azalttı. Optimum AV gecikmenin ayarlanması bu hastalarda daha iyi bir hemodinami sağlayabilir.

Anahtar kelimeler: Atriyoventiküler gecikme aralığı, çift odacıklı kalp pili, nabız dalga hızı

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Introduction

Newer generation dual-chamber (DDD) pacemakers have been widely used as they are considered to be more physiological (1). However, DDD pacemakers require more timers than other devices as they include several types of intervals, such as the basic and atrioventricular (AV) delay intervals.

Arterial stiffness is an indicator of atherosclerosis and caused by loss of elasticity and thickening of the arterial wall. Increased arterial stiffness is not only an indicator of vascular aging, but also a predictor of target organ damage and increased cardiovascular events (2). Due to the insidious nature of the atherosclerotic process, early recognition of arterial changes and functional and/or structural lesions may help to identify patients with high risk for clinical complications.

Pulse wave velocity (PWV) is one of the most important parameters used to evaluate elastic properties of large arteries (3,4). Also, using PWV measurements provides an easy and reproducible method to assess arterial stiffness (5). PWV is measured by using two ultrasound or pressure sensitive transducers fixed transcutaneously on the trace of a couple of artery at a certain distance from each other (such as carotid-femoral or brachial-radial arteries) (3). Increase in PWV values, which is defined as the velocity of the pressure wave over an arterial segment, is an important indicator of the diffuse atherosclerotic process (6). Arterial PWV is inversely proportional to arterial compliance and PWV propagation time (PWVPT) (3,4).

In addition, increased heart rate causes an increase in arterial PWV (7); thereby a decrease in arterial distensibility and compliance. Previous studies have shown that changes in AV delay interval affect both the left ventricular filling time and stroke volume of the patients (8,9). It is unknown whether other different factors such as AV conduction time affects PWV or not in case of a fixed heart rate.

Therefore, we assumed that PWV values calculated at different AV delay intervals may guide optimal programming to provide better hemodynamics in patients with DDD pacemakers. Due to the lack of data regarding this issue, we aimed to investigate the effect of differential AV delay intervals (100, 150 and 200 ms, respectively) on arterial distensibility measured by the carotid-femoral PWV in patients with DDD pacing.

Materials and Methods

Fourty consecutive patients with DDD pacemakers who were admitted to our outpatient clinic between January to July 2015, were recruited in our single-center and prospective clinical study. Written informed consent was taken from each participant. Our study was conducted in concordance with the Declaration of Helsinki and approved by the Local Ethics Committee of İstanbul University (09/07/2014, no: B.08.06.YOK.2.I.U.E.50.0.05.00/10).

None of the patients had a pacemaker other than DDD mode. Exclusion criteria included patients with coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, liver or kidney failure, atrial fibrillation and patients using non-steroidal anti-inflammatory or steroid drugs during the study. We also excluded patients with body mass index (BMI) ≥35 kg/m² and waist-hip ratio (WHR) ≥1.

Patients were asked to rest in a supine position for 10 minutes before starting the measurements. Following each 10 minute period of haemodynamic stabilization, AV delay intervals were gradually prolonged and programmed as 100, 150 and 200 ms, respectively. Three different AV delays were used for testing by AV sequential pacing. Carotid-femoral artery PWV and blood pressure (BP) were measured by same researcher. Pacing was programmed at a minimum of 10 beats/minute above the resting heart rate. Also, pacing rate was further increased when continuous capture could not be obtained (8). Weight measurements of the patients were made by scale, whereas height measurements by meter. BMI was calculated by dividing the weight in kilogramme by the height calculated in square meters (kg/m^2). The waist circumference (cm) was measured from the mid point of the distance between the lowest rib and the crista iliaca when the patient was in upright position. The hip circumference (cm) was measured from the major trochanter femoris level. WHR was calculated by dividing waist circumference by hip circumference. Arterial BP was measured with a standard mercury manometer in supine position following a 10-minute period of rest. Systolic BP (SBP) was accepted as the value at which Korotkoff sounds were heard first and diastolic BP (DBP) as the value at which sounds disappeared (phase 5). Pulse pressure (PP) was calculated by subtracting DBP from SBP. Mean BP (MBP) was determined using the formula MBP = SBP + 2xDKB/3.PWV measurements were taken immediately after obtaining the brachial BP. Aortic PWV was calculated using the Complior device (Createch Industrie, France), which allows automatic online pulse wave recording

and automatic calculation of PWV (3). Common carotid and femoral artery pressure waveforms were measured non-invasively using a pressure sensitive transducer TY-306 Fukuda (Fukuda, Tokyo, Japan). An average of ten repeated measurements was taken for final analysis. PWV was automatically calculated with the formula ΔD/Δt [ΔD: distance traveled by the pulse wave on the body surface (meters) between two recording points, Δt: Pulse wave transit time (seconds) automatically determined by the Complior device].

Statistical Analysis

Statistical analysis was performed by using the SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) packet program. Continuous variables were reported as mean ± standard deviation while categorical variables were presented as numbers and percentages. The significance between different measurements of the same participant was determined by using the non-parametric Friedman test. If significance was detected in the Friedman test, the non-parametric Wilcoxon test was used to determine the source of significance. As AV delay parameters were non-normally distributed, Friedman and Wilcoxon tests were used. The non-parametric Mann-Whitney U test was used for comparison between the female and male groups. Student t-test was used for normally distributed data. The relationship between PWV and other variables was evaluated by Pearson correlation test. Values of $p<0.05$ were considered statistically significant.

Results

Of the 40 cases included in the study, 21 (52.5%) were male and 19 (47.5%) were female. Demographic characteristics and anthropometric measurements of the patients were shown in Table 1. Type II diabetes mellitus was present in 7 (36.8%) of 19 female cases and 5 (23.8%) of 21 male cases. Hypertension was found in 15 (78.9%) patients among women and 11 (52.3%) patients among men. Eight (42.1%) female and five (23.8%) male patients had hyperlipidemia.

The change in BP with respect to increasing AV delay intervals was shown in Table 2. No statistically significant difference was found between SBP, DBP, MBP and PP values measured at differential AV delay intervals ($p=0.105$, $p=0.264$, $p=0.449$ and $p=1.000$, respectively).

A statistically significant increase in PWV and a decrease in PWVPT were detected with the prolongation of AV delay intervals ($p<0.001$ and $p<0.001$, respectively) and graphically shown in Figure 1A and 1B. When the groups were compared among themselves by the Wilcoxon test; a statistically significant difference was found between PWV 100-150 ms, 100-200 ms and 150-200 ms (for PWV 100 ms vs. 150 ms, $p<0.001$; PWV 100 ms vs. 200 ms, $p<0.001$; PWV 150 ms vs. 200 ms $p=0.001$). Similarly, statistically significant results were obtained in the comparison between the groups in terms of PWVPT (for PWVPT 100 ms vs. 150 ms, $p=0.002$; PWVPT 100 ms vs 200 ms, $p<0.001$; PWVPT 150 ms vs. 200 ms $p<0.001$, respectively). A strong positive correlation ($p<0.001$, $r=0.590$) was found between age and the PWV values taken at 100 ms. Likewise, there was a strong positive correlation between age and PWV values taken at 150 ms and 200 ms (respectively $p<0.001$, $p<0.001$; $r=0.611$, $r=0.562$).

According to gender analysis that was given in Table 3; height, weight and WHR values of men were significantly higher than those of women ($p<0.001$, $p=0.016$ and $p=0.001$, respectively). Also, there was no statistically significant difference between women and men in terms of age, BMI, SBP, DBP, MBP, PP, PWV and PWVPT values measured at differential AV delay intervals (100, 150 and 200 ms, respectively).

Discussion

To the best of our knowledge, this is the first study to investigate the effect of different AV delay intervals on arterial distensibility measured by carotid-femoral PWV in patients with DDD pacing. Our study demonstrated a statistically significant increase in arterial PWV and thereby a decrease in PWVPT with gradually increasing AV delay intervals (100, 150 and 200 ms). In this respect, the results of our study suggest that prolongation of AV conduction time may increase arterial stiffness in patients with classical DDD pacemakers.

Nishimura et al. (10) examined the patients with dilated cardiomyopathy into two groups according to PR intervals whether above or below 200 milliseconds. A significant increase in cardiac output of patients in long PR interval group was noted with AV interval optimization. Likewise, Manisty et al. (8) evaluated hemodynamic changes occurred at different AV delay intervals (40-120 ms) in 19 patients with permanent pacemaker, and observed an acute improvement in hemodynamic parameters (SBP, DBP, MBP, PP and stroke volume) as the AV delay interval approached from non-physiological (40 ms) to physiological values (120 ms). Contrary to this study, no significant difference was found in our study in terms of hemodynamic parameters. This may be due to the fact that

we recorded our measurements in a more physiological range of AV delay, such as 100 ms to 200 ms.

Patients whose arterial PWV values increase may have worse cardiac functions due to the increased workload in front of the left ventricle. Also, decrease in arterial distensibility may lead to decreased effective coronary blood flow and increased myocardial ischemia (11). Various studies have suggested that increased PWV values may be related to increased adverse cardiovascular events and mortality (3,6,11,12).

PWV may be affected by different parameters such as age, heart rate, SBP, DBP, MBP, and PP (12,13). In the present study, a significant relationship was found between PWV and age. As the age increases, the elastic tissue of the aorta gradually decreases and therefore stiffness increases. Additionally, increasing the right ventricular pacing rate may increase arterial stiffness. Yıldız et al. (14) compared 17 patients with classical DDD pacemakers with healthy subjects in terms of arterial distensibility determined by PWV, and found an increase in arterial PWV and a decrease in distensibility in patients with pacemakers in terms of gender and age compared to the control group. Similarly, Wilkinson et al. (15) reported a linear relationship between heart rate and arterial stiffness in patients with permanent atrial or dual pacemakers. Krishnamoorthy et al. (16)

Table 1. Demographic characteristics and anthropometric measurements of the study group

	Mean ± SD; or n (%)	Range
Age (years)	62.4±15.9	(23-84)
Male gender	21 (52.5)	
Body height (cm)	165.0±8.12	(150-180)
Body weight (kg)	75.3±12.02	(48-97)
Waist circumference (cm)	96.43±10.39	(67-110)
Hip circumference (cm)	105.95±7.75	(87-125)
WHR	0.90±0.00	(0.73-0.99)
BMI (kg/m^2)	27.63±3.75	(34.17-17.63)
Diabetes, n (%)	12 (30)	
Hypertension, n (%)	26 (65)	
Hyperlipidemia, n (%)	13 (32.5)	

BMI: Body mass index, SD: Standard deviation, WHR: Waist-to-hip ratio, SD: Standard deviation

Table 2. Blood pressure values according to different AV delay intervals

	AV delay 100 ms	AV delay 150 ms	AV delay 200 ms	p-value
SBP (mmHg)	129.50±20.12	128.75±19.90	128.75±19.37	0.105
DBP (mmHg)	78.75±10.42	78.25±10.10	78.25±9.84	0.264
MBP (mmHg)	95.66±12.78	95.08±12.56	95.08±12.15	0.449
PP (mmHg)	50.25±13.68	50.50±13.77	50.50±13.77	1.000

AV: Atrioventricular, DBP: Diastolic blood pressure, MBP: Mean blood pressure, PP: Pulse pressure, SBP: Systolic blood pressure

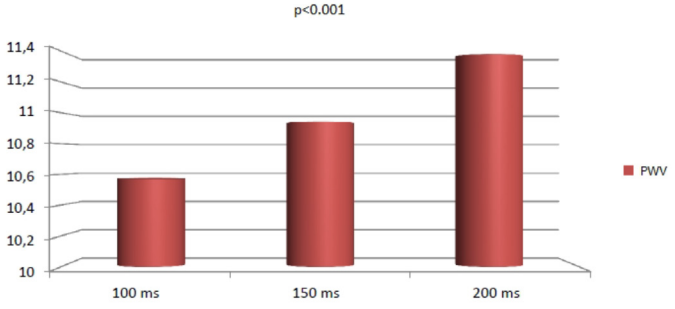

Figure 1A. PWV values measured at different AV delay intervals

PWV: Pulse wave velocity, AV: Atrioventricular

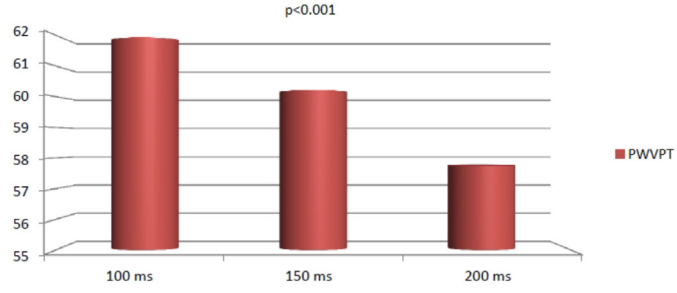

Figure 1B. PWVPT values measured at different AV delay intervals

AV: Atrioventricular, PWVPT: Pulse wave velocity propagation time

Table 3. Comparison of anthropometric and hemodynamic measurements between the groups

	Female	Male	p-value
Body weight (kg)	70.16±12.04	79.95±10.17	0.016
Body height (cm)	158.11±4.58	171.24±4.86	<0.001
BMI (kg/m^2)	28.04±4.44	27.25±3.22	0.523
WHR	0.87±0.06	0.93±0.03	0.001
SBP-100 msec (mmHg)	132.63±21.56	126.67±18.80	0.361
SBP-150 msec (mmHg)	131.05±21.32	126.67±18.80	0.469
SBP-200 msec (mmHg)	131.05±20.25	126.67±18.80	0.486
DBP-100 msec (mmHg)	80.00±11.06	77.62±9.95	0.503
DBP-150 msec (mmHg)	78.95±10.49	77.62±9.95	0.668
DBP-200 msec (mmHg)	78.95±9.94	77.62±9.95	0.668
MBP-100 msec (mmHg)	97.53±13.67	93.97±12.00	0.376
MBP-150 msec (mmHg)	96.32±13.37	93.97±12.00	0.486
MBP-200 msec (mmHg)	96.32±12.52	93.97±12.00	0.503
PP-100 msec (mmHg)	52.63±14.85	48.10±12.50	0.333
PP-150 msec (mmHg)	52.11±14.37	49.05±13.38	0.520
PP-200 msec (mmHg)	52.11±14.37	49.05±13.38	0.520
PWV-100 msec (m/s)	10.82±2.67	10.35±2.05	0.630
PWV-150 msec (m/s)	11.29±2.97	10.62±2.04	0.421
PWV-200 msec (m/s)	11.81±3.30	11.00±2.36	0.537
PWVPT-100 msec (m/s)	59.36±14.82	64.23±11.68	0.145
PWVPT-150 msec (m/s)	57.21±15.06	62.90±11.78	0.083
PWVPT-200 msec (m/s)	55.10±15.12	60.14±12.53	0.226

BMI: Body mass index, WHR: Waist-to-hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, PP: Pulse pressure, PWV: Pulse wave velocity, PWVPT: Pulse wave velocity propagation time

divided 101 patients with DDD pacemakers into two groups according to the presence of atrial high-rate episodes. An increase in arterial stiffness was detected in the group with atrial high velocity episodes. These studies were not conducted at a constant heart rate unlike our study, in which the effect of heart rate was excluded.

The effect of differential AV delay intervals on arterial stiffness still remains controversial. Differential AV delay intervals may lead to hemodynamic adaptation and lengthen the time of systole or diastole (17). The prolongation of systolic phase, occured by AV conduction programming, may cause an increase in left ventricular stroke volume and thus in the amount of blood passed and consequently an increase in aortic pressure. Chan et al. (18) investigated the changes in vascular function with PR (AV delay interval) prolongation in 88 healthy individuals. As the AV interval prolonged, a decrease in flow-mediated dilatation and an increase in PWV was observed. This also indicates that PR prolongation may a negative effect on arterial mechanics.

Evaluation of arterial stiffness is increasingly important in patients with high cardiac risk such as the presence of a permanent pacemaker. Based on this, measuring arterial expandability besides hemodynamic changes when programming the pacemaker seems to be reasonable in these patients. If their devices are programmed for the optimum AV delay interval, these patients may experience improvement in large artery mechanics such as arterial expansion.

Study Limitations

There were some limitations to be noted in our study. First of all, our results were based on a single-center study and relatively small number of patients were analyzed. Secondly, most of the patients have coexistent medical conditions such as diabetes mellitus and hypertension; therefore our results might not accurately reflect endothelial dysfunction associated with AV delay interval prolongation. Antihypertensive and antidiabetic drugs also may effect our results.

Conclusion

In conclusion, the results of this study indicated that lengthening AV delay interval increased carotid-femoral

PWV in patients with DDD pacemakers. Thus, optimum AV delay adjustment may provide better hemodynamics in these patients. Nevertheless, further prospective studies are needed to confirm our findings in a larger cohort of patients.

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Ethics

Ethics Committee Approval: Fourty consecutive patients with DDD pacemakers who were admitted to our outpatient clinic between January to July 2015, were recruited in our single-center and prospective clinical study. Our study was conducted in concordance with the Declaration of Helsinki and approved by the Local Ethics Committee of İstanbul University (09/07/2014, no: B.08.06. YOK.2.I.U.E.50.0.05.00/10).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.B.K., G.Ç., M.Y., Design: B.B.K., G.Ç., M.Y., Data Collection or Processing: B.B.K., G.Ç., Analysis or Interpretation: B.B.K., G.Ç., M.Y., Literature Search: B.B.K., G.Ç., Writing: B.B.K., G.Ç.

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CASE REPORT

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The Course of COVID-19 in a Patient with Congenital Neutropenia: A Case Report

Konjenital Nötropenili Bir Hastada COVID-19 Hastalığı: Bir Olgu Sunumu

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Abstract

Coronavirus disease-2019 (COVID-19) is a respiratory illness caused by severe acute respiratory syndrome-coronavirus-2. Although it is primarily a respiratory illness, there is growing evidence that it also affects the digestive system and manifests itself through various symptoms such as loss of appetite, diarrhea, nausea and vomiting. In this context, this case report features a 14-year-old female patient with congenital neutropenia who became infected with COVID-19, yet had no respiratory system involvement. Instead, the patient developed primarily gastrointestinal tract involvement and secondarily syndrome of inappropriate antidiuretic hormone secretion.

Keywords: Coronavirus, congenital neutropenia, COVID-19, HAX-1 mutation, primary immunodeficiency

Öz

Koronavirüs hastalığı-2019 (COVID -19), şiddetli akut solunum sendromu-koronavirüs-2'nin neden olduğu bir solunum yolu hastalığıdır. Mart 2020'de Dünya Sağlık Örgütü tarafından pandemi olarak sınıflandırılan bir acil halk sağlığı durumu haline geldi. Öncelikle bir solunum yolu hastalığı olmasına rağmen, sindirim sistemini de etkilediğine ve iştahsızlık, ishal, mide bulantısı ve kusma gibi çeşitli semptomlarla kendini gösterdiğine dair artan kanıtlar vardır. Bu olgu sunumunda, solunum sistemi tutulumu olmayan, sadece gastrointestinal sistem tutulumu ve sekonder uygunsuz antidiüretik hormon salgılanması sendromu gelişen doğuştan nötropenili 14 yaşında bir kız hasta sunulmaktadır.

Anahtar kelimeler: COVID-19, HAX-1 mutasyonu, konjenital nötropeni, koronavirüs, primer immün yetmezlik

Introduction

Coronavirus disease-2019 (COVID-19) is a respiratory illness caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). First cluster of COVID-19 cases were reported in the city of Wuhan located in Hubei Province of China on December 31st, 2019. COVID-19 outbreak was then declared an epidemic, i.e., a public health emergency of international concern, on January 30th, 2020, and later a pandemic, i.e., a public health emergency of global concern, on March 11th, 2020, by the World Health Organization. Clinical findings associated with the disease tend to vary from person to person. While some COVID-19 patients were asymptomatic, others had died due to COVID-19-induced acute respiratory distress syndrome (ARDS). The course of the disease is particularly severe in older men. Other risk factors associated with a poor prognosis are diabetes mellitus, hypertension, chronic respiratory disease, cancer, and cardiovascular disease (1).

This case report features a 14-year-old female congenital neutropenia patient who became infected with COVID-19 and presented with atypical clinical findings such as acute gastroenteritis and syndrome of inappropriate antidiuretic

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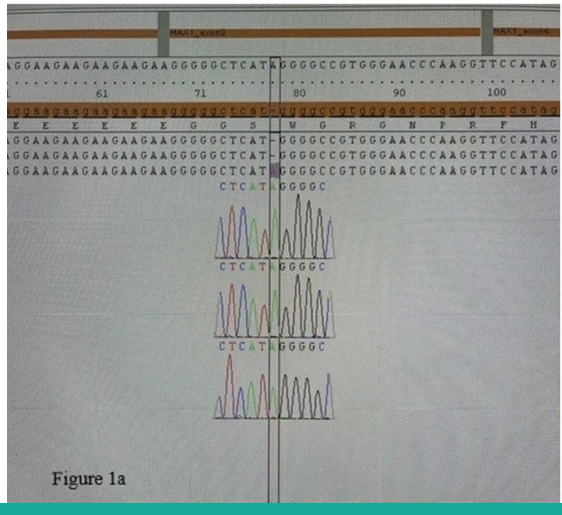
hormone secretion (SIADH), but without respiratory system involvement, similar to most COVID-19 cases reported in the literature.

Case Report

A 14-year-old female patient applied to the emergency service with complaints of loss of appetite, abdominal pain, and diarrhea that have been going on for the last three days. Her anamnesis indicated that she underwent tympanomastoidectomy for recurrent otitis media, suffered from bilateral hearing loss, was observed for chronic neutropenia, and was receiving trimethoprim-sulfamethoxazole prophylaxis. Molecular examination indicated a homozygous hematopoietic cell-specific protein 1-related protein X-1 mutation (Figure 1a). Her physical examination revealed that her general condition was poor, and she was mildly to moderately dehydrated. She had no fever. Examination of the respiratory system did not reveal any features. The patient, who had right lower quadrant pain on abdominal examination, did not have organomegaly. No pathology was noted on abdominal ultrasonography. The results of the complete blood count test indicated leukopenia and neutropenia. C-reactive protein, one of the markers of infection, was measured as 220 mg/dL. The patient was hospitalized with a diagnosis of congenital neutropenia and acute gastroenteritis. Given that the general condition of the patient, who had no fever, was not very good, cefepime treatment and intravenous (IV) fluid therapy were initiated. The results of the SARS-CoV-2 polymerase chain reaction test performed using patient's nasopharyngeal aspirate taken on the second day of hospitalization came out negative. Thoracic tomography of the patient did not reveal any features. Her vomiting and diarrhea symptoms did not regress. No pathogenic bacteria grew in the patient's stool culture. *C. difficile, E. histolytica, rotavirus,* and *adenovirus* were not detected in the microbiological examinations of the stool. The patient's laboratory results are summarized in Table 1. The patient had persistent abdominal tenderness. No air-fluid levels were observed on direct radiography of the abdomen taken in the standing position, yet the bowel loops were pale. Abdominal tomography indicated an increase in adipose tissue at the level of the ascending colon as well as thickening of the peritoneum. Surgical pathology was not considered. Metronidazole was added to patient's treatment due to persistent abdominal pain. Given her severe neutropenia, persistent diarrhea and poor condition in general, she was started on subcutaneous granulocyte colony stimulating factor (G-CSF) treatment at a dose of 10 mcg/kg/day on the sixth day of hospitalization. The patient's serum sodium level, whose diarrhea persisted, was 131 mEq/L (135-145). Patient's hyponatremia persisted despite adequate IV fluid intake. High urinary sodium excretion was noted (191 mEq/L vs. regular value of <20 mEq/L). The patient was diagnosed with SIADH, and subsequently subjected to fluid



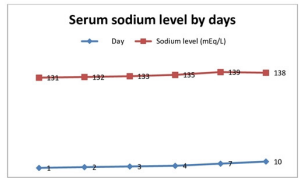


Figure 1b: Distribution of the patient's serum sodium level by days. From the third day, the patient's fluid intake was restricted.

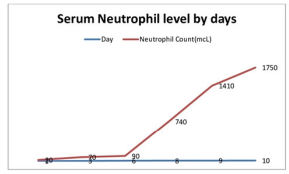


Figure 1c: Distribution of the patient's serum neutrophil level by days. Subcutaneous G-CSF was started at a dose of 10 mcg/kg on the sixth day of hospitalization. mcL; microliter

Figure 1a. A homozygous mutation of c.130_130insA, (p.W44X), (rs1572018284) in the *HAX1* gene was detected. A single nucleotide insertion occurred between positions 130 and 131 in the coding region. A single nucleotide insertion and a die-shifting mutation at position 44 of the protein resulted in a stop codon in the same codon. The RS number reported in the NCBI dbSNP short genetic variations and ClinVar databases has been classified as a pathogenic allele, and Varsome has classified it as a pathogenic. **Figure 1b)** Distribution of the patient's serum sodium level by the time elapsed in days. The patient's fluid intake was restricted starting from the third day of hospitalization. **Figure 1c)** Distribution of the patient's serum neutrophil count by the time elapsed in days. Subcutaneous G-CSF treatment was started at a dose of 10 mcg/kg on the sixth day of hospitalization

mcL: Microliter

Table 1. Characteristics of patients with congenital neutropenia

Parameter	Measurement
White blood cell (1.000/uL)	2.12 (4.19-9.43)
Hemoglobin (g/dL)	9.1 (10.8-13.3)
Platelet (1.000/uL)	298 (150-400)
Total lymphocyte count (1.000/uL)	1.05 (1.16-3.33)
Total neutrophil count (1.000/uL)	0.02 (1.82-7.47)
C-reactive protein (mg/L)	202.5 (0-5)
Erythrocyte sedimentation rate (mm/h)	68 (0-15)
Alanine transaminase (U/L)	2 (0-37)
Aspartate transaminase (U/L)	10 (0-27)
Urea (mg/dL)	25.5 (10.7-38.5)
Uric asit (mg/dL)	5.8 (2.4-5.7)
Creatinine (mg/dL)	0.43 (0.5-0.9)
Sodium (mEq/L)	131 (138-145)
Potassium (mEq/L)	3.59 (3.4-4.7)
Clor (mEq/L)	99 (97-107)
Calcium (mg/dL)	8.28 (8.4-10.2)
Magnesium (mg/dL)	1.78 (1.7-2.2)
Albumin (g/L)	33 (32-45)
Total protein (g/L)	80 (60-80)
Glucose (mg/dL)	94 (74-106)
Alkaline phosphatase (U/L)	116 (50-117)
GGT (U/L)	10 (5-36)
LDH (U/L)	144 (0-250)
Amylase (U/L)	28 (28-100)
Lipase (U/L)	14 (13-60)
Phosphorus (mg/dL)	3.54 (2.5-4.8)
Troponin T (ng/L)	<3 (<14)
Ferritin (ng/mL)	415 (13-150)
Clinical manifestations	Gastroenteritis, inappropriate ADH syndrome
Abdominal ultrasonography	Grade 1 hepatosteatosis
Thorax computed tomography	Normal
Abdominal computed tomography	Normal
Rotavirus	Negative
Adenovirus	Negative
Clostridium dificille	Negative
Entemobia hystolica	Negative
Stool culture	Negative
Sodium spot (mEq/L), in the urine	191.6 (<20)
D-dimer, quantitative (microgram FEU/mL)	1.18 (0-0.5)
Fibrinogen (mg/dL)	428 (193-412)
Blood culture	Negative

LDH: Lactate dehydrogenase, GGT: Gamma-glutamyl transferase, ADH: Antidiuretic hormone

restriction. The patient, who had no fever and whose serum sodium levels returned to normal and absolute neutrophil count increased with treatment with G-CSF during follow-up, was discharged (Figures 1b, c).

Discussion

The coronavirus that causes COVID-19, also known as SARS-CoV-2, is an enveloped, single-stranded RNA virus from the beta-coronavirus subfamily. Severe COVID-19 is usually associated with ARDS and multiorgan failure (2). The most commonly reported clinical symptoms associated with COVID-19 are fever, fatigue, and dry cough. A small percentage of patients infected with COVID-19 present with gastrointestinal symptoms, the most common one being anorexia followed by diarrhea, nausea, and vomiting. The prevalence of gastrointestinal symptoms in COVID-19 patients is 17.6%. COVID-19 patients presenting with only gastrointestinal symptoms are usually diagnosed late, and gastrointestinal involvement is often associated with a poor prognosis (3).

There are several studies in the literature that demonstrated a relationship between primary immunodeficiencies (PIDs) and COVID-19 disease. It was reported that the course of COVID-19 disease in patients with agammaglobulinemia without B-cells is milder than patients with common variable immunodeficiency (CVID) whose B-cells are dysfunctional (1). Based on this finding, the authors of the said study suggested that the absence of B-cells prevents cytokine storm and inflammation and provides an advantage for patients with agammaglobulinemia (1). It has been established that COVID-19 infection has a severe course in patients with PID who have disorders in the antiviral pathway of the innate immune system, e.g., toll-like receptor 3, toll-like receptor 7, or interferon regulatory factor 7, or in the interferon pathway (human interferon alpha/beta receptor chain 2). It has been previously reported that IV immunoglobulin therapy may have a protective effect against COVID-19 in patients with PID (2).

In a multicenter study conducted with COVID-19 patients with neutropenia along with other PIDs such as CVID and phosphoacetylglucosamine mutase 3 deficiency, Meyts et al. determined that neutrophils play a minimal role in the development of immunity against COVID-19 infection based on the observation that the course of COVID-19 in children with chronic granulomatous disease was mild (4). However, cases of congenital neutropenia with COVID-19 are limited to case reports in the literature (5). Vignesh et al. (5) reported COVID-19 infection in a patient with congenital neutropenia who had pulmonary involvement and respiratory distress but did not require mechanical ventilation. Previous studies have reported that the use of G-CSF for febrile neutropenia in adult patients with malignancies exacerbated respiratory symptoms and cytokine storm due to acute COVID-19 infection (6). In comparison, the patient presented herein had only gastrointestinal tract involvement and no respiratory findings. Her chest examination and thoracic computed tomography scan did not reveal any abnormal finding. The patient was started on cefepime for empirical treatment but not G-CSF at first since she had no fever. Nevertheless, G-CSF treatment had to be started on the sixth day of hospitalization since her general condition was deteriorating as also indicated by the increase in her neutrophil count. The G-CSF treatment resulted in an improvement in patient's general condition and her absolute neutrophil count returned to normal levels by tenth day of hospitalization.

Hyponatremia (<135 mmol/L) is the most common electrolyte disturbance in COVID-19 patients and is generally associated with poor prognosis. Although there are many factors that cause hyponatremia, the most common cause is SIADH, which occurs in approximately 40-50% of patients. This rate may increase in brain injury, subarachnoid hemorrhage, and pneumonia (7). In comparison, the serum sodium level of the patient presented herein was 131 mEq/L at the time of admission. Initially, it was thought that the hyponatremia might be due to diarrhea, and, therefore, the patient was given fluids. Subsequently, given that her hyponatremia did not improve despite fluid intake, her urine sodium level was measured considering that she might have SIADH. Accordingly, the patient, who a had high urinary sodium level, was subjected to fluid restriction from the third day of hospitalization, and then her serum sodium level returned to normal.

SARS-CoV-2 activates angiotensin-converting enzyme 2 receptors in the gut, leading to inflammation and diarrhea. A high viral load due to SARS-CoV-2 causes intestinal problems in the early phase of COVID-19, whereas a cytokine storm affecting T and B-cells occurs in the late phase of COVID-19. In parallel, in the late phase, the intestinal symptoms regress, the respiratory tract is affected, and ARDS emerges (8). In comparison, the T and B-cell counts of the patient presented herein were normal. There are insufficient data in the literature on the course of COVID-19 disease in patients with congenital neutropenia. In this context, the findings of this case report featuring a 14-year-old female COVID-19 patient

who had no respiratory involvement and presented with only gastrointestinal involvement and SIADH would likely contribute to the literature in that regard. Nevertheless, further studies are needed on the prognosis of COVID-19 disease in patients with congenital neutropenia.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.H.Ç., S.N., Design: M.H.Ç., S.N., Data Collection or Processing: M.H.Ç., S.N., A.Ö.K., H.Ö., I.T., S.U., Ç.A., Analysis or Interpretation: M.H.Ç., S.N., A.Ö.K., H.Ö., I.T., S.U., Ç.A., Drafting Manuscript: M.H.Ç., S.N., Critical Revision of Manuscript: M.H.Ç., S.N., Technical and Material Support: M.H.Ç., S.N., A.Ö.K., H.Ö., I.T., S.U., Ç.A., Writing: M.H.Ç., S.N., A.Ö.K., H.Ö., I.T., S.U., Ç.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Surprise Lesion in the Cecum: Benign Multicystic Peritoneal Mesothelioma

Çekumda Sürpriz Bir Lezyon: Benign Multikistik Peritoneal Mezotelyoma

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Abstract

Benign multicystic peritoneal mesothelioma (BMPM) is a rare neoplasm that is difficult to distinguish from other cystic neoplasms radiologically. A 41-year-old female patient was admitted to the emergency service with a complaint of abdominal pain. After the physical examination, and radiological imaging, ovarian torsion was assumed, and a gynecological laparoscopy was planned. A firm mass was observed in the cecal region during gynecological laparoscopy, and a right hemicolectomy was performed. There was a multicystic mass measuring 4x4x2.5 cm in the cecal region of the specimen is sent to the pathology department. Morphological findings on hematoxylin-eosin sections and immunohistochemical studies supported it, and a diagnosis of BMPM was made. The diagnosis of BMPM, which can be a challenging process considering its clinical and radiological features, is mainly made pathologically. These lesions frequently recur and rarely show a malignant transformation. Therefore, it must be evaluated in the pathological differential diagnosis.

Keywords: Benign, cecum, mesothelioma, multicystic, periton

Öz

Benign multikistik peritoneal mezotelyoma (BMPM), radyolojik olarak diğer kistik neoplazmlardan ayırt edilmesi zor olan nadir bir neoplazmdır. Kırk bir yaşında kadın hasta karın ağrısı şikayeti ile acil servise başvurdu. Fizik muayene ve radyolojik görüntüleme sonrasında over torsiyonu düşünülerek jinekolojik laparoskopi planlandı. Jinekolojik laparoskopi sırasında çekum bölgesinde sert kitle görüldü ve sağ hemikolektomi yapıldı. Patoloji bölümüne gönderilen örneğin çekum bölgesinde 4x4x2,5 cm boyutlarında multikistik kitle mevcuttu. Hematoksilen-eozin kesitlerindeki morfolojik bulgular ve immünohistokimyasal çalışmalar ile BMPM tanısı konuldu. Klinik ve radyolojik özellikleri göz önüne alındığında zorlu bir süreç olabilen BMPM'nin tanısı esas olarak patolojik olarak konur. Bu lezyonlar sıklıkla tekrarlar ve nadiren malign transformasyon gösterirler. Bu nedenle ayırıcı tanıda mutlaka akılda bulundurulmalıdır.

Anahtar kelimeler: Benign, çekum, mezotelyoma, multikistik, peritoneal

Introduction

Benign multicystic peritoneal mesothelioma (BMPM) is an exceedingly rare tumor that is more common in women. It accounts for 3-5% of all peritoneal mesotheliomas, with an annual incidence of 2/1,000,000 (1). It is more common in women of reproductive age to an average age of 36 years (2). Although the pathogenesis of BMPM has not yet been fully elucidated yet, past surgical operations, endometriosis, and pelvic inflammatory disease (PID) are blamed for the pathogenesis (3,4). In this article, we aimed to present benign peritoneal mesothelioma, a rare lesion that mimics malignancy, which should be taken into account in the differential diagnosis of cystic lesions.

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Case Report

A 41-year-old female patient was admitted to the emergency service with the complaint of abdominal pain lasting for 4 days. The patient's clinical history indicates no relevant disease. However, she had a history of cholecystectomy 4 years ago and a tubal ligation operation 10 months ago. She was also hospitalized for PID 8 months ago and recovered after receiving treatment for the infection. In the first examination, tenderness was detected in the right lower quadrant of the abdomen. Abdominal ultrasonography (USG) revealed an increased size of the right ovary, decreased blood supply, and the presence of free fluid in the Douglas cavity. Findings observed in the USG were interpreted as ovarian torsion. In the abdominal computed tomography (CT), a 45x40 mm hypodense lesion was observed in the right lower quadrant (Figure 1). The obstetrician performed a diagnostic laparoscopic examination and the uterus and ovaries were observed naturally. However, the procedure was terminated to obtain a general surgical opinion due to the appearance of a mass on the intestine in the ileocecal region.

Magnetic resonance imaging (MRI) demonstrated a thick-walled, multicystic mass lesion with heterogeneous contrast enhancement in the paracecal region (Figure 2). The patient was operated on with a preliminary diagnosis of plastron appendicitis. Right hemicolectomy was performed due to a 3 cm mass observed in the ileocecal region during the operation. After the operation, 32 cm long right hemicolectomy material was sent to our pathology department. In the cecal region, a lesion of 4x4x2.5 cm with a multicystic appearance with a raised serosa was observed (Figure 3a). In the microscopic examination, numerous cystic structures of varying diameters, sometimes flat, some of them swollen and with large eosinophilic cytoplasm, some of them lined with cells in the appearance of hobnails, were observed. Eosinophilic amorphous material was present in the cystic spaces. The surrounding stroma of the cyst structures was composed of loose fibrovascular connective tissue (Figure 3b-d). In immunohistochemical studies, staining of Calretinin with PanCK was observed in these cells surrounding the cystic structures. No staining was observed with CD31, CD34, D2-40, ER, and Pax8 (Figure 3e, f). With the support of immunohistochemical studies, the case was diagnosed as benign multicystic peritoneal mesothelioma. No additional treatment was planned for the patient after diagnosis, close follow-up by

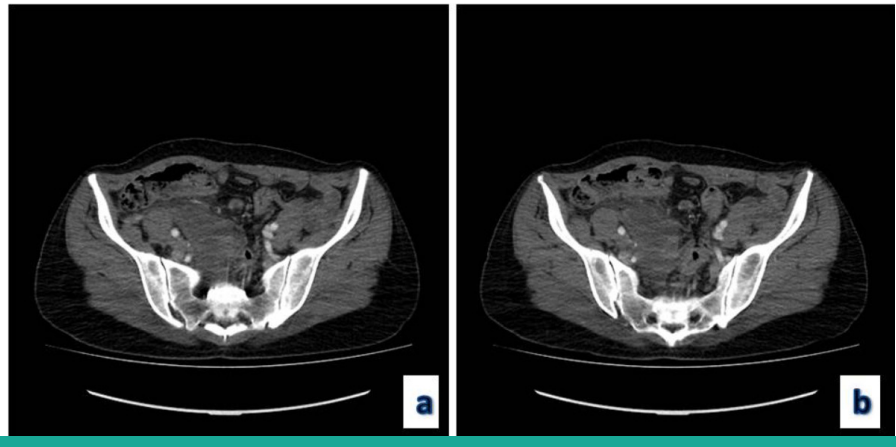

Figure 1a, b. Abdominal computed tomography images of the patient before the laparoscopy

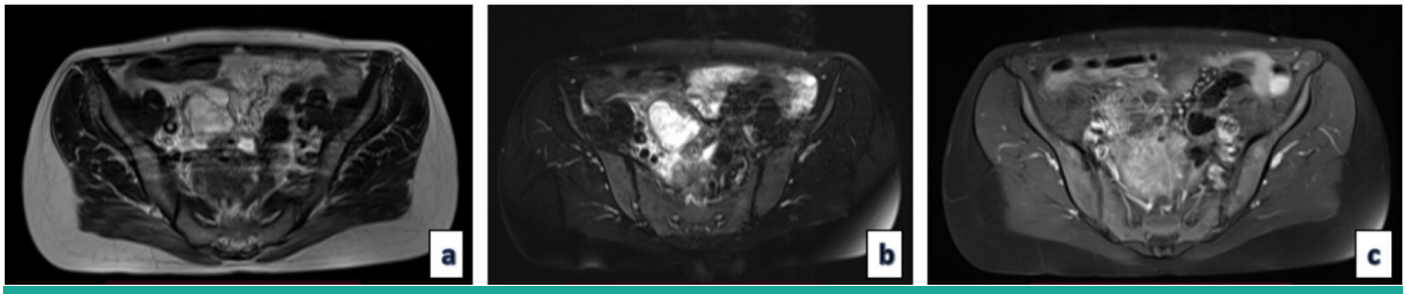

Figure 2. a) T2-weighted axial MR images showed a thick-walled, multicystic mass lesion in the paracecal region, **b)** no signal loss on fat-suppressed T2-weighted images, **c)** heterogeneous contrast enhancement on post-contrast images

MR: Magnetic resonance

general surgery was recommended and no recurrences were detected during the 36-month post-operative period.

Discussion

A benign peritoneal mesothelial cyst is extremely rare. Multiple peritoneal cysts were first described by Plaut in 1928, and in 1979 it was confirmed that they were of mesothelial origin (5,6). Although it is not related to asbestos, the etiology is not fully known. However, previous surgery, endometriosis, and PID have been reported in the pathogenesis (3,4). Chronic inflammation and previous surgery are thought to trigger the migration of mesothelial cells. The history of previous surgery and PID in our case support this. However, it has been suggested that this disease has a neoplastic etiology since patients without a history of chronic inflammation and surgical operation have also been reported in the literature (7,8). The appearance of the lesion after previous surgery varies between 6 months and 20 years (8). Patients are mostly diagnosed incidentally on imaging or during laparotomy performed for different reasons. When clinically present, it triggers symptoms such as abdominal pain, distention, intestinal obstruction, nausea, and vomiting, depending on the location of the lesion (5,9).

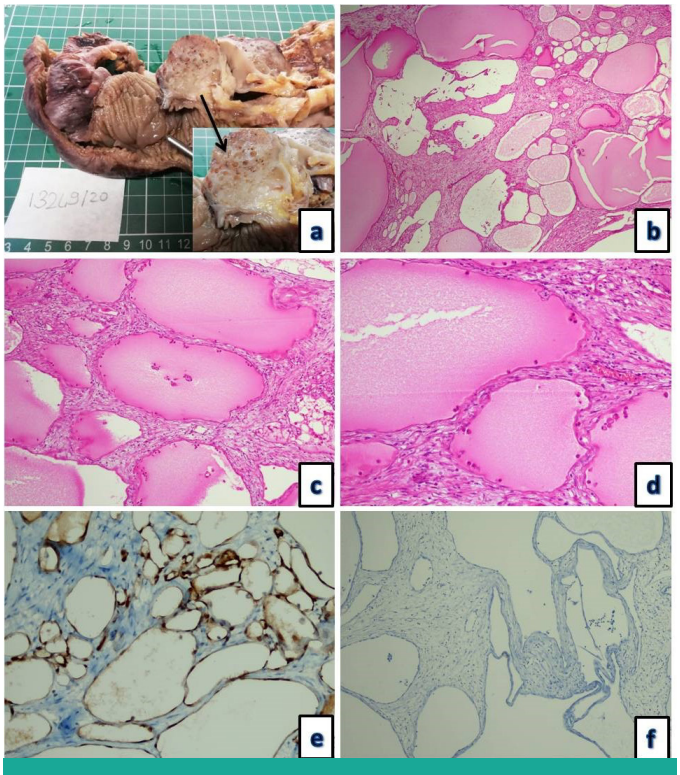

Figure 3. Multicystic lesion in the cecum on the surgical specimen **(a)**. Variable-sized cysts lined by flattened mesothelial cells and filled with amorphous eosinophilic material (**b**: HEx40, **c**: HEx100, **d**: HEx200). Immunohistochemical staining shows calretinin in the lining cells (**e**: Calretinin x100) and the negative staining of D2-40 (**f**: D2-40x100)

In pre-operative imaging, these lesions can often mimic different lesions, such as ovarian malignancy and cystic lymphangioma. On ultrasonographic examination, it typically presents as grape-like, multilocular, thin-walled cysts containing fluid and multiseptated anechoic cysts. In magnetic resonance imaging, it is observed as multilocular, thin-walled septal, fluid density masses (10). Lymphangioma, malignant peritoneal mesothelioma, and cystic adenomatoid tumor should be considered in the differential diagnosis (11). On MRI, BMPM exhibits low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, reflecting high fluid content (10). In our case, the initial CT could not distinguish between ovarian cystic neoplasia. Usually, it is not possible to distinguish other cystic lesions with USG, CT, and MRI. Therefore, the diagnosis is often made postoperatively (10,11).

Although there is no consensus yet on treatment, complete resection is the recommended first step (12). Complete surgical excision helps to prevent the risk of malignant transformation and recurrence, yet more aggressive approaches can also be recommended since half of the cases suffer from recurrence. After cytoreductive surgery, hyperthermic intraperitoneal chemotherapy can be preferred to reduce the risk of recurrence and malignant transformation. Hormonal treatments such as antiestrogen and gonadotropin analogs are also recommended. Recurrence has been reported frequently, ranging from 27% to 75% (11). The risk of malignant transformation is much less common. Only 2 cases have been reported in the literature so far (13).

Conclusion

Because the preoperative diagnosis of BMPM is challenging via clinical findings and imaging methods, its diagnosis is commonly made by postoperative pathological examination. Although the risk of malignant transformation is low, recurrence is seen in almost half of the cases. It should be taken into account in the differential diagnosis from other cystic lesions in the pathological examination, and these cases should be followed up closely after the operation.

Ethics

Informed Consent: The patient was informed about her published histopathological and radiological images and her written consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.Ö., Concept: Ç.Ö., H.G., O.O., Design: Ç.Ö., H.G., O.O., Data Collection or Processing: Ç.Ö., H.G., O.O., Analysis or Interpretation: Ç.Ö., O.O., T.B.Ş., Literature Search: Ç.Ö., T.B.Ş., Writing: Ç.Ö., T.B.Ş.

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CASE REPORT

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Bartter Type 4a Syndrome Diagnosed in a 30-week-old Preterm Neonate

Otuz Haftalık Prematüre Yenidoğanda Bartter Tip 4a Sendromu

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Abstract

Bartter syndrome is an uncommon autosomal recessive, salt-losing renal tubular disease. Its defining features are numerous electrolyte abnormalities, including low potassium and chloride levels, metabolic alkalosis, and low or normal blood pressure. We reported a case of neonatal Bartter syndrome presenting with severe hypokalemia, hypochloremic metabolic alkalosis, polyuria, and renal failure in a 28-week premature born to consanguineous parents. She was successfully treated with oral indomethacin and potassium supplements. Genetic tests were resulted in Bartter syndrome Type 4a with mutations in the *BSND* gene.

Keywords: Bartter syndrome, *BSND* gene, neonate, preterm

Öz

Bartter sendromu, otozomal resesif geçişli, tuz kaybettiren nadir bir renal tübüler hastalıktır. Düşük potasyum ve klorür seviyeleri, metabolik alkaloz ve düşük/normal kan basıncı gibi çeşitli elektrolit anormallikleri ile tanımlanır. Akraba anne-babadan 28 haftalık prematüre bir bebekte şiddetli hipokalemi, hipokloremik metabolik alkaloz, poliüri ve böbrek yetmezliği ile başvuran bir neonatal Bartter sendromu olgusunu bildirdik. Oral indometasin ve potasyum takviyeleri ile başarılı bir şekilde tedavi edildi. Genetik testler, *BSND* genindeki mutasyonlarla birlikte Bartter sendromu Tip 4a ile sonuçlandı.

Anahtar kelimeler: Bartter sendromu, *BSND* geni, preterm, yenidoğan

Introduction

One in a million people have Bartter syndrome, a rare autosomal recessive renal tubular disease of the thick ascending loop of Henle that causes salt loss. Five different types have been identified based on genetics. The neonatal form is characterized by polyhydramnios, preterm rupture of membranes, and preterm labor leading to prematurity. In the newborn period, patients often present with polyuria, dehydration, failure to thrive, growth retardation, and dysmorphic facies. Hypercalciuria and nephrocalcinosis are also typical in some forms. Bartter syndrome type IV is a neonatal Bartter syndrome with sensorineural deafness and dysmorphic facies including a triangular face, large eyes, and protruding ears. The *BSND* gene, which encodes the Barttin protein, is associated with this type. Barttin is a basic beta subunit of the ClC-Ka and ClC-Kb chloride channels localized in the renal tubules and inner ear (1).

We report a case of Bartter syndrome Type IVa with pathogenic change in the *BSND* gene, which was diagnosed early due to prenatal and postnatal complications.

Case Report

A 28-week-old female newborn born to a 21-year-old mother was admitted to our emergency delivery service. The infant was born via section because of massive polyhydramnios and breech presentation. On physical examination, the weight of the preterm neonate was 965 g, height 39 cm,

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body temperature 36 °C, heart rate 144/min, respiratory rate 44/min, and arterial blood pressure 60/35 mmHg. In physical appearance; triangular faces, protruding ears, and drooping mouths were visible. Her pH of 7.55, pCO_2 22 mmHg, and HCO_3 20.9 was found in cord blood gases. Complete blood count, biochemical parameters, and bleeding profile were normal. The patient was intubated because of respiratory distress. Her urine output was 4 cc/kg/hr on the first day of her life. Hyponatremia, hypokalaemia, hypochloremia, and hypocalcemia were found in blood tests along with renal failure. Hyponatremia, hypokalaemia, hypochloremia, and hypocalcemia were found in blood tests along with renal failure on the fourth day of the neonate's fourth day of life (Na: 129 mmol/L, K: 2,6 mmol/L, Cl: 87 mmol/L, serum urea 136 and serum creatinine 1.4 mg/dL). In total parenteral nutrition, the amount of intravenous fluid, sodium, and potassium was high. The urinary ultrasound was normal. Although urea and creatinine values decreased following sepsis, polyuria and potassium loss continued due to tubulopathy, and insufficient weight gain was observed, indomethacin was prescribed. As the weight loss of the patient whose polyuria continued, the amount of intravenous fluid increased. Despite this, the patient reached birth weight on the day of the 30th. The glomerular filtration rate was calculated as 13 mL/kg/1.73 m^2. Since the decrease in sodium and potassium continued (Na 123; K: 2.31 mmol/L), oral sodium saline and oral potassium were added to the diet of the patient who tolerated enteral nutrition. A 35 mg/kg dose of $MgSO_4$ was started on the 54th day of her life when hypomagnesemia became evident (magnesium: 1.04 mg/dL). Sodium excretion fraction was 12% and urine output was up to 7.7 cc/kg/hr. Urine density was 1007, protein creatinine ratio was 1.07, and calcium creatinine ratio was 0.92. Despite 11 meq/kg sodium administration, the simultaneously measured sodium level was only increased to 139 mmol/L, while the potassium level was only 2.69 mmol/L even though 40 meq/L potassium replacement was given. Gene analysis was sent from the patient who was suspected of having Bartter's syndrome due to polyuria and excessive loss of sodium and potassium in the urine. We obtained blood samples, pedigree, and informed consent from the parents. DNA was isolated according to the manufacturer's recommendations (QIAamp DNA blood Maxi kit, Qiagen, Hilden, Germany). The coding exon regions and +/-20 exon-intron junction regions of the genes included in the panel test (*BSND, CASR, CLCNKA, CLCNKB KCNJ1, SLC12A1, SLC12A3*) were investigated. We used the GRCh37/hg19 genome as a reference. We used databases [HGMD®, ClinVar, OMMM®, dbSNP (v151), gnomAD (v2.1.1)] and in silico prediction tools (MutatonTaster, SIFT, PolyPhen-2...) to filter and evaluate variants. Variants with minor allele frequencies below 1% (gnomAD) were evaluated and classified according to the ACMG Variant Classification Manual1.

We detected a homozygous c.1A>T (p.M1?) variant due to loss of function in the *BSND* gene (NM_057176.3, BARTTIN CLCNK-TYPE ACCESSORY SUBUNIT BETA, * 606412) (Figure 1). Heterozygosity for the same mutation was found in the parents (Figure 2). Her polyuria decreased

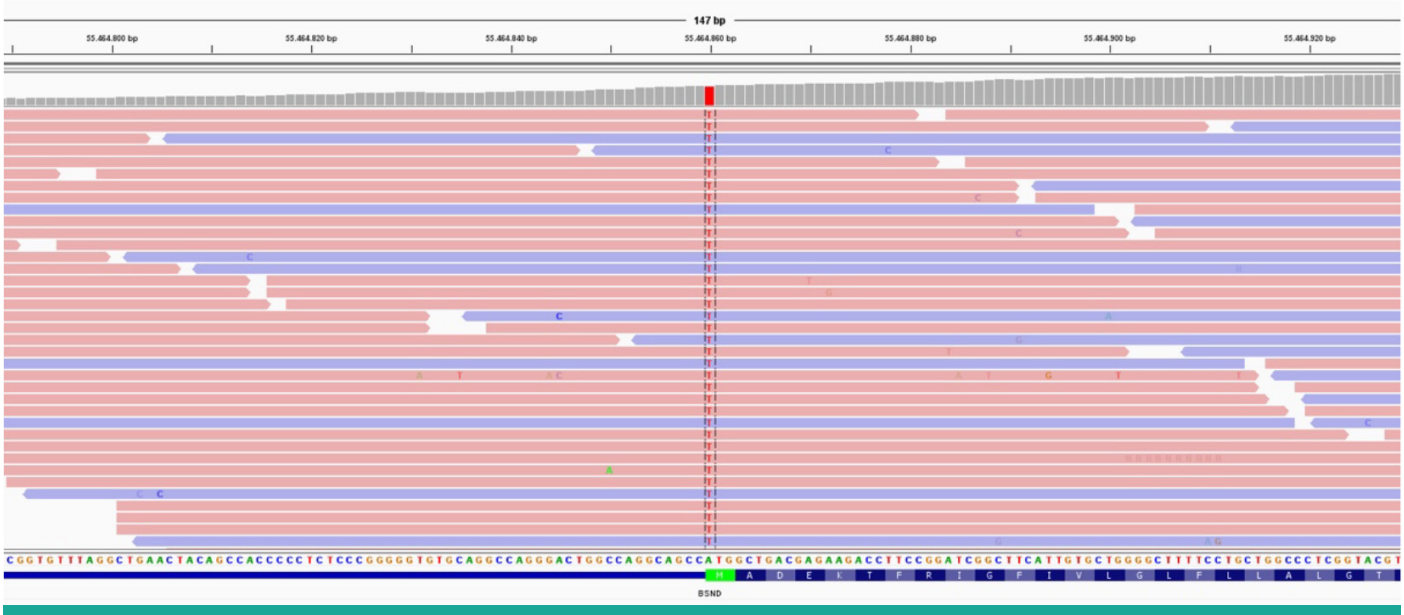

Figure 1. IGV illustration of the NGS result of patient genome

with indomethacin treatment after sepsis, she started to gain weight and was in the fourth stage of chronic kidney disease.

Discussion

Bartter syndrome is a group of diseases characterized by metabolic alkalosis, hypercalciuria, and salt wasting. As antenatal Bartter syndrome (Type 1, 2, and 4) maternal polyhydramnios neonatal salt loss and recurrent episodes of severe dehydration are more severe than classical Bartter syndrome (Type 3) Type 4 Bartter syndrome, which was seen in the patient we presented as a case report, is a prenatal or postnatal manifestation of autosomal recessive inherited sensorineural hearing loss with a mutation in *BSND* gene, but not with nephrocalcinosis. The thick ascending limb of the loop of Henle and the descending convoluted tubule are affected, resulting in sodium chloride and potassium loss. The five different types of Bartter syndrome can be broken down into different disease genes (2). The *BSND* gene is localized in the 1p32.3 region, weighing 35197 Da. BSND codes for Barttin protein, which functions as an accessory subunit of the chloride channels of the kidney and inner ear and modulates the stability of channels (3). The homozygous loss-of-function mutation identified in this study is located in exon 1 encoding the transmembrane domain. The position is strongly maintained (phyloP100way =8.12 greater than 7.2). The variant is not found in gnomAD genomes. This variant has been previously described in the literature with Bartter syndrome patients (4). Our variant is the same, mutations of 5 patients of Turkish origin in this publication (F314, F591, F730, F786, F791). *BSND* gene mutation was originally described as a severe form of antenatal BS4. Renal failure has been found mainly in patients with mutations that lead to complete protein loss (5-7). Polyhydramnios and preterm delivery are typical features of *BSND* gene mutations in patients (8,9). However, variants caused by mild and late-onset phenotypes have also been reported in later studies.

This variability in renal outcome may be explained by the residual function of some mutated proteins or other factors. Despite the highly variable renal clinic, hearing loss is usually present at the time of diagnosis. The auditory brainstem response test performed on the patient was normal, but our patient should be followed up for hearing loss (7). *BSND* gene mutations or deletions involving the *ClCNKB* and *ClCNKA* genes have been reported to be associated with chronic renal failure, a rare complication for other types of Bartter syndrome (4,10,11). Calcium reabsorption occurs mostly by passive paracellular transport in the proximal tubules and loop of the thick ascending limb of Henle. The loss of the transepithelial voltage gradient, which permits calcium reabsorption in the loop of Henle, leads to hypercalciuria in Bartter syndrome. The TRPV5 channel, which is triggered by parathormone, is used by transcellular transport to reabsorb a minimal amount of filtered calcium in the distal tubule (12). In some studies, it has been shown that prostaglandins decrease calcium reabsorption in the distal tubule and increase calcium reabsorption directly by inhibition of prostaglandin E2 (13,14). Management of Bartter syndrome

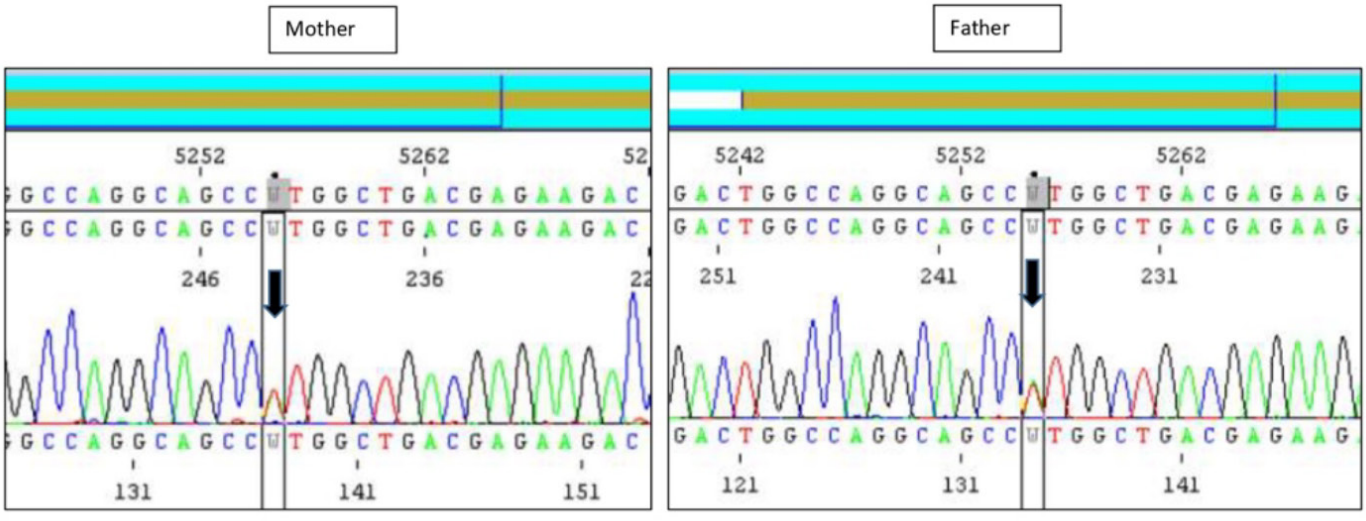

Figure 2. Representative chromatogram sequencing of the mutation is shown fort the unaffected parents. Arrows indicate the nucleotide change in the sequence

is to prevent dehydration and maintain nutritional status to treat electrolyte disorders. Despite electrolyte and fluid replacement therapy, polyuria and electrolyte imbalance persisted and we started indomethacin.

As a result, in newborns with polyhydramnios, alkalosis, hyponatremia, hypokalemia, and tubulopathies involving the ascending loop of the loop Henle such as Bartter's syndrome should be considered in the differential diagnosis. In patients with renal insufficiency, type 4 Bartter syndrome should be considered genetically and diagnosed and supported in treatment.

Ethics

Informed Consent: Written informed consent received from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H., Concept: Ç.C.G., Ö.K., Design: Ç.C.G., Ö.K., Data Collection or Processing: Ç.C.G., Ö.K., Analysis or Interpretation: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H., Drafting Manuscript: Ç.C.G., Ö.K., Final Approval and Accountability: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H., Supervision: E.C., Ş.H., Writing: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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CASE REPORT

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A Very Rare Reason for Hyperandrogenism: Adrenal Tumor Case

Hiperandrojenizmin Çok Nadir Bir Nedeni: Adrenal Tümör Olgusu

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Abstract

Adrenal tumors are very rare causes of hyperandrogenism. Androgen-secreting adrenal tumors are usually malignant; however, benign tumors have also been described in women. Adrenocortical carcinoma is very rare with incidence of 1 2 million per year. The androgen secreting type of adrenocortical carcinoma can be presented with hirsutism, acne, alopecia and virilization symptoms such as cliteromegaly. This case was presented with hyperandrogenism and virilization symptoms and it was diagnosed as having a very rare cause, namely androgen secreting adrenal tumor. Because the symptoms are related to gynecological complaints such as menstrual irregularities and cliteromegaly, these patients would first need to apply to their gynecologists, who may play an important role in the early diagnoses of these rare diseases.

Keywords: Adrenal, adrenocortical carcinoma, adrenal tumor, andreogen excess, virilization

Öz

Adrenal tümörler hiperandrojenizmin çok nadir nedenleridir. Androjen salgılayan adrenal tümörler genellikle maligndirler, ancak kadınlarda benign tümörler de tanımlanmıştır. Adrenokortikal karsinom 1-2/milyon/yıl sıklığı ile çok nadirdir. Androjen salgılayan tipteki adrenokortikal karsinomlar hirsutizm, akne, alopesi ve kliteromegali gibi virilizasyon semptomları ile prezente olabilir. Bu olgu hiperandrojenizm ve virilizasyon bulguları ile başvurdu ve çok nadir bir neden olan androjen salgılayan adrenal tümör olarak teşhis edildi. Semptomlar adet düzensizliği ve klitoris büyüklüğü gibi jinekolojik şikayetlerle ilişkili olduğu için bu hastalar öncelikle jinekologlarına başvurabilirler. Jinekologlar bu nadir hastalıkların erken teşhisinde önemli bir rol oynayabilir.

Anahtar kelimeler: Adrenal, adrenal tümör, androjen fazlalığı, adrenokortikal karsinom, virilizasyon

Introduction

Hyperandrogenemia is an increased level of androgens in the blood and it can be presented by symptoms such as hirsutism, acne, androgenic alopecia, and virilization symptoms such as cliteromegaly. Polycystic ovarian syndrome (PCOS) is the main reason for hyperandrogenism in premenopausal women. The diagnosis of PCOS is made through the exclusion of other reasons for hyperandrogenism, such as non-classic congenital adrenal hyperplasia (NCCAH), hyperprolactinemia, Cushing's syndrome, and virilization tumors (1).

Androgen secreting tumors are very rare causes of hyperandrogenism originating from the adrenals. These tumors are generally malignant even though benign adrenal tumors also occur. In the studies published in the last 20 years, the rate of adrenocortical tumors was found to be 0.1% in patients investigated for clinical hyperandrogenemia (2). Adrenocortical carcinoma (ACC) is very rare, with incidences numbering 12 million per year (3). Approximately 60-80% of ACC is hormonally active. Of these, 30% are associated with glucocorticoids only, 20% with androgen-only hypersecretions, and less than 10% with hyperaldosteronism and feminization (4).

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17OH progesterone, androstenedione, DHEAS, and testosterone values occur at an increased level in most patients with ACC who secrete sex steroids (5). For all ACC cases, surgery with adrenalectomy is the treatment. Prognoses depend on the stage of the tumor and the feasibility of radical surgery (6).

Case Report

A 24 year old female patient presented with the complaint of not having had a menstrual period for eight months and an increase in hirsutism. She stated that her periods were regular prior to her complaints and she did not have any complaints of hirsutism. In ultrasonography, her uterus and ovaries were bilaterally normal. On examination, intense hirsutism (especially in the lower abdomen and chin) and cliteromegaly were present. Hormone test results of the patient showed hyperandrogenism and the other hormone results and tumor markers were normal (Table 1).

Hemogram, liver and kidney function blood test results were normal. Because the patient's androgens were very high, an upper abdominal ultrasound was requested to investigate possible adrenal tumor. A hyperechoic mass of 66×58 mm was observed in the right adrenal lodge. In a contrast-enhanced upper abdominal MRI, a tumoral lesion, which appeared to have pushed the right kidney inferiorly at the level of the right adrenal gland, had a size of 77×61 mm at its widest point (Figure 1). The lesion also appeared to have a well-contoured, distinctly heterogeneous internal structure, with local cystic necrotic areas being observed in T2 examinations. Intense heterogeneous contrast enhancements in the post-contrast examinations on T1 images (Figure 2) were observed. In the patient who was referred to the endocrinology department, catecholamine metabolites, adrenaline, noradrenaline, dopamine, metanephrine, normetanephrine, renin plasma activity, and aldosterone levels were measured in her 24hour urine. No pathological value was detected.

Whole body positron emission tomography (PET) was taken with the preliminary diagnosis of ACC. In the right adrenal gland, a mass lesion of 59×61×58 mm in size that is slightly heterogeneous increased the fluorodeoxyglucose (FDG) (12.45 mCi F18 FDG) uptake with smooth borders, with heterogeneous density being observed. Faintly circumscribed, locally hypodense, cystic necrotic foci is also observed. In this lesion, which was minimally hypermetabolic on PET examination, malignancies with low FDG affinity could not be excluded.

The patient underwent general surgery for a right adrenalectomy. Pathology results were evaluated as cortical adenomas. Focal necrosis was present with no significant capsular invasion. The patient's clear cell rate was less than 5%, and atypical mitosis was not observed. Her Weis score was reported as 3.

In the checks performed one month after the operation, androgen levels were found to be normal. Written informed consent was obtained from the patient.

Table 1. Hormone and tumor marker test results

Test	Result	Reference range
Beta HCG	0.1	0.15 IU/L
FSH	10.2	3.312.5 IU/L follicular phase
LH	4.36	2.412.6 IU/L follicular phase
Estradiol	22.73	26.7156 pg/mL follicular phase
Progesterone	4.11	0.21.5 ng/mL follicular phase
TSH	1.03	0.275.4 mU/L
Prolactin	35.1	4.7923.3 ng/mL
17OHprogesterone	13.2	0.150.7 ng/mL
Free testosterone	15	0.293.18 pg/mL
Total testosterone	4.69	0.0350.513 ng/mL
DHEAS	>1.000	148407 µg/dL
Cortisol	12.43	6.219.4 µg/dL
CA 199	7.5	033 U/mL
CEA	0.4	05 ng/mL non-smokers
CEA 125	14.4	035 U/mL

HCG: Human chorionic gonadotropin, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone

Discussion

Hirsutism is usually a symptom of hyperandrogenism. The causes of hirsutism in 7080% of cases can be attributed to PCOS, 520% to idiopathic hirsutism, 4.2% to non-classical congenital adrenal hyperplasia and 0.2% of cases of hirsutism can be attributed to androgen-secreting tumors. In addition, Cushing's syndrome, acromegaly, hypothyroidism and rare incidences of hyperprolactinemia are also included in the differential diagnosis (7).

Figure 1. Adrenal tumor indicated by star. Tumor has well-contoured, distinctly heterogeneous internal structure. Local cystic necrotic areas were observed in T2 examinations

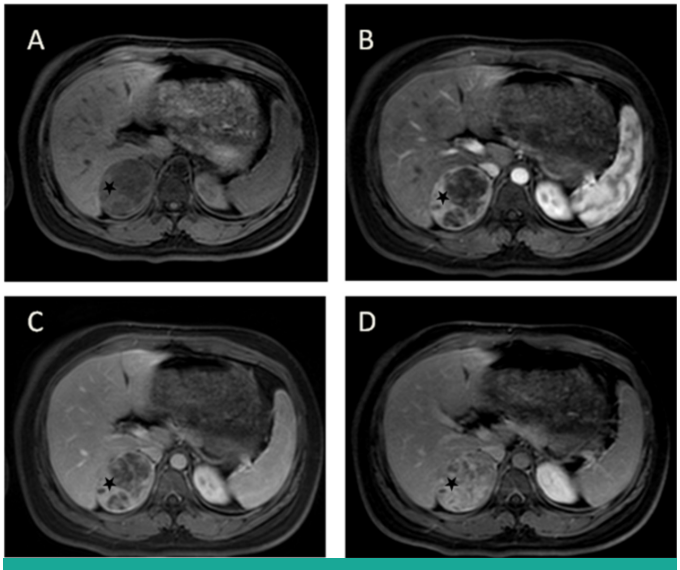

Figure 2. On pre contrast axial fat sat T1 A images, the lesion is hypointense, and on post contrast series (B-D), the lesion is observed to increase in contrast. The adrenal tumor is indicated by a star

If there is menstrual irregularity with hirsutism, there is usually an underlying endocrine disorder. Cases of hirsutism with a normal menstrual cycle are usually PCOS or idiopathic hirsutism and are unlikely to be serious.

Androgen-secreting adrenal tumors present with rapidly developing virilization, hirsutism, oligo-amenorrhea and androgenic alopecia (2).

Our case also presented with the complaints of hirsutism and secondary amenorrhea, which progressed rapidly in the last six months. In the examination, intense hirsutism and cliteromegaly were detected. The fact that the patient had regular menstrual cycles and did not have a complaint of hirsutism in addition to the presence of new virilization findings and the rapid exacerbation of her current complaints led us to conduct further research with the preliminary diagnosis of an androgen-secreting tumor.

Serum androgen levels were checked in patients presenting with hirsutism. In addition, if there is oligo-amenorrhea, pregnancy is excluded and ovarian and thyroid functions as well as prolactin levels are checked.

The most useful laboratory test in the evaluation of hirsutism is the total testosterone level. The upper limit of testosterone in women is between 0.45 and 0.6 ng/mL. Patients with mild androgen elevation, such as PCOS and NCCAH, have testosterone values above normal limits, but still below normal male levels. Women with testosterone values greater than three times the upper limit usually have evidence of virilization and androgen-secreting tumors, which should be investigated (8). In our patient, this value was 4.69, which is approximately ten times the upper limit.

DHEAS measurements are helpful in the investigation of adrenal hyperandrogenism. DHEAS may be elevated in both PCOS and adrenal tumors (9). In patients with a DHEAS value higher than 700 µg/dL, adrenal tumors should be excluded (7). In our patient, the DHEAS value was reported as >1.000.

17OHP measurements are important to rule out NC-CAH. In patients with 17OHP values of 210 ng/mL, the diagnosis of NC-CAH is made by performing the ACTH stimulation test (10). 17OHP is among the tests that should be investigated in ACC cases. In our case, a high value of 13.2 ng/mL was found.

It is recommended to investigate the symptoms and signs of pheochromocytoma, hyperaldosteronism, hyperandrogenism, and hypercortisolism in all patients with an adrenal mass (11). Laboratory studies were also

conducted in our patient. According to the results, it was determined that this adrenal mass secreted only androgens.

Among only androgen-secreting tumors, 75% were classified as adrenocortical cancer in histopathological examinations, while the others were adenomas (2).

Computed tomography and magnetic resonance imaging are important in diagnosis and surgical planning. FFDG PET is recommended for the evaluation of local recurrence and distant metastasis in ACC (5). In line with the clinical findings and hormonal changes in our patient, an adrenal tumor was suspected, and an adrenal mass was observed in the ultrasound. This was evaluated with magnetic resonance and FDG PET. No signs of metastasis or spread were detected.

In all ACC cases, surgical adrenalectomy is the treatment modality. Adjuvant Mitotane therapy is administered according to a post-operative evaluation and guidelines (6).

The Weiss score is very important in pathological evaluations. It includes nine criteria, such as proliferation, nuclear abnormality and tumor spread. A score of ≥3 is considered malignant. Tumors with a Weiss score of 23 may have ambiguous behavior (12). The Weiss score was evaluated as 3 in our patient.

Conclusion

Adrenal tumors are a very rare cause of hyperandrogenism with androgen-secreting tumors usually being malignant. Adrenocortical cancers are rare endocrine malignancies and have a poor prognosis. They can be detected incidentally or during investigations into the effects of the mass or hormonal disorders. 60% of ACCs are hormonally active and 20% of these are androgen-secreting tumors only. These patients may present in gynecology outpatient clinics with hirsutism, menstrual irregularity and virilization findings such as cliteromegaly. By making the differential diagnosis of hyperandrogenism, an early diagnosis can be made by a gynecologist. Early diagnoses positively affect the prognosis and surveillance of such patients. In addition, surgery is recommended for all androgen-secreting tumors.

Ethics

Informed Consent: Written informed consent was obtained from patient.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: N.K.A., Design: N.K.A., Data Collection or Processing: N.K.A., G.G.P, Analysis or Interpretation: N.K.A., H.G., Drafting Manuscript: N.K.A., Critical Revisation of Manuscript: N.K.A., H.G., G.G.P., Final Approval and Accountability: N.K.A., H.G., G.G.P., Writing: N.K.A., H.G., G.G.P.

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ERRATUM

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DOI: 10.4274/BMB.galenos.2022.2022-10-081 upon request from the author "[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Obstetric and Gynecology, İstanbul, Turkey" expression in the first page, author institutions section has been corrected as "University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey".

ERRATUM

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