E-ISSN: 2547 - 9431

BAGCILAR MEDICAL BULLETIN

Bağcılar Tıp Bülteni

Volume 8, Issue 2, June 2023

ORIGINAL RESEARCHES / ARAŞTIRMALAR

Periodical Publication of
Health Sciences University
Turkey, Bagcilar Training
and Research Hospital

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

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E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: June 2023
E-ISSN: 2547-9431
International scientific journal published quarterly.

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English Title: Bagcilar Medical Bulletin

Turkish title: Bağcılar Tıp Bülteni

Official abbreviation: Bagcilar Med Bull

E-ISSN: 2547-9431

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Dergi Adı (İngilizce): Bagcilar Medical Bulletin

Dergi Adı (Türkçe): Bağcılar Tıp Bülteni

Resmi Kısaltma: Bagcilar Med Bull

E-ISSN: 2547-9431

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The journal is published quarterly in March, June, September and December.

Original clinical and experimental articles,interesting case studies, and literature reviews made from relevant authors in their brancheswill be accepted for evaluation in BMB.

Bagcilar Medical Bulletin is indexed in **TÜBİTAK/ULAKBİM, EBSCO, Gale, Türk Medline, Turkey Citation Index, Index Copernicus, ProQuest, J-Gate** and **ScopeMed.**

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E-ISSN: 2547-9431

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Resmi Kısaltma: Bagcilar Med Bull

E-ISSN: 2547-9431

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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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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).

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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.

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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

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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

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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.

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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.)

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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.

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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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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.

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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.

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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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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.

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

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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.

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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.

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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

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•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.

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Ensure that the following items are present:

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-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

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

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

-Body text

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-Reference

-All tables (including title, description, footnotes)

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Peer- Review

Submission is considered on the conditions that papers are previously unpublished and are not offered simultaneously elsewhere; that authors have read and approved the content, and all authors have also declared all competing interests; and that the work complies with the ethical approval requirements and has been conducted under internationally accepted ethical standards. If ethical misconduct is suspected, the Editorial Board will act in accordance with the relevant international rules of publication ethics (i.e., COPE guidelines).

Editorial policies of the journal are conducted as stated in the rules recommended by the Council of Science Editors and reflected in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. Accordingly, authors, reviewers, and editors are expected to adhere to the best practice guidelines on ethical behavior contained in this statement.

Submitted manuscripts are subjected to double-blinded peer-review. The scientific board guiding the selection of the papers to be published in the journal consists of elected specialists of the journal and, if necessary, selected from national and international experts in the relevant field of research. All manuscripts are reviewed by the editor, section associate editors, and at least two external expert reviewers.

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For the experimental, clinical, and drug human studies, approval by the ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the Bagcilar Medical Bulletin together with the manuscript.

The approval of the ethics committee; a statement on the adherence to international guidelines mentioned above; and proof that the patient's informed consent is obtained should be indicated in the `Material and Method` section. These items are required for case reports whenever data/media could reveal the identity of the patient.

For persons under 18 years of age, please provide a consent form that includes both parents' signatures or of the person's legal guardian or supervisor.

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Fabrication: To publish data and findings/results that do not exist.

Duplication: Using data from another publication; this includes republishing an article in different languages.

Salamisation: Creating multiple publications by abnormally splitting the results of a study.

Data Manipulation/Falsification: Manipulating or deliberately distorting research data to give a false impression.

We disapprove of such unethical practices and of efforts to influence the review process with such practices as gifting authorship, inappropriate acknowledgements, and references in line with the COPE flowcharts.

Submitted manuscripts are subjected to automatic software evaluation for plagiarism and duplicate publication. Authors are obliged to acknowledge if they published study results in whole or in part in the form of abstracts.

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The publisher will take all appropriate measures to modify the article in question, in close cooperation with the editors, in cases of alleged or proven scientific misconduct, fraudulent publication, or plagiarism. This includes the prompt publication of an erratum, disclosure, or retraction of the affected work in the most severe case. Together with the editors, the publisher will take reasonable steps to detect and prevent the publication of articles in which research misconduct occurs and will under no circumstances promote or knowingly allow such abuse to occur.

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Reviewers offer objective judgments and evaluations. The reviewers express their views clearly with appropriate supporting arguments.

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Reviewers ought to identify a relevant published study that the authors have not cited. Reviewers also call to the editor's attention any substantial similarity or overlap between the manuscript and any other published paper of which they have personal knowledge.

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A submitted manuscript should be original, and the authors ensure that the manuscript has never been published previously. Research data should be represented literally in the article. A manuscript should include adequate detail and references to allow others to replicate the study.

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Authors should not submit the same study to multiple journals. Simultaneous submission of the same study to more than one journal is unacceptable and constitutes unethical behaviour.

Acknowledgement of Sources

Acknowledgement to the workof others must be given. Authors should cite publications of relevance to their own study. All of the sources for the author’s study should be noted.

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Authorship of a paper ought to be limited to those who have made a noteworthy contribution to the study. If others have participated in the research, they should be listed as contributors. Authorship also includes a corresponding author who is in communication with the editor of a journal. The corresponding author should ensure that all appropriate co-authors are included in a paper.

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All sources of financial support should be disclosed. All authors should disclose if a meaningful conflict of interest exists in the process of forming their study. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board of the Bagcilar Medical Bulletin. The ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors to disclose a potential conflict of interest. The journal's Editorial Board determines cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

Conditions that provide financial or personal benefit bring about a conflict of interest. The reliability of the scientific process and the published articles is directly related to the objective consideration of conflicts of interest during the planning, implementation, writing, evaluation, editing, and publication of scientific studies.

Financial relations are the most easily identified conflicts of interest, and it is inevitable that they will undermine the credibility of the journal, the authors, and the science. These conflicts can be caused by individual relations, academic competition, or intellectual approaches. The authors should refrain as much as possible from making agreements with sponsors in the opinion of gaining profit or any other advantage that restrict their ability to access all data of the study or analyze, interpret, prepare, and publish their articles. Editors should refrain from bringing together those who may have any relationship between them during the evaluation of the studies. The editors, who make the final decision about the articles, should not have any personal, professional, or financial ties with any of the issues they are going to decide. Authors should inform the editorial board concerning potential conflicts of interest to ensure that their articles will be evaluated within the framework of ethical principles through an independent assessment process.

If one of the editors is an author in any manuscript, the editor is excluded from the manuscript evaluation process. In order to prevent any conflict of interest, the article evaluation process is carried out as double-blinded. Because of the double-blinded evaluation process, except for the Editor-in-Chief, none of the editorial board members, international advisory board members, or reviewers is informed about the authors of the manuscript or institutions of the authors.

Our publication team works devotedly to ensure that the evaluation process is conducted impartially, considering all these situations.

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Appeal and complaint cases are handled within the scope of COPE guidelines by the Editorial Board of the journal. Appeals should be based on the scientific content of the manuscript. The final decision on the appeal and complaint is made by Editor in Chief. An Ombudsperson or the Ethical Editor is assigned to resolve cases that cannot be resolved internally. Authors should get in contact with the Editor in Chief regarding their appeals and complaints via e-mail at info@galenos.com.tr.

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.

MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3:171-178.

2. Ek sayı için: MEDLINE'da yer alan ve kısaltması MEDLINE'a göre yapılan dergi makalesi için: Sharan P, Sundar AS. Eating disorders in women. Indian J Psychiatry 2015:57(Suppl 2):286-295.

MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Maner F. Yeme bozukluklarının tedavisi. Anadolu Psikiyatri Dergisi 2009;10(Ek 1):55-56.

3. Baskıdaki makale için: 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).

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4. Kitaptan alıntılar:

Tek yazarlı kitaptan alıntı için:

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

Kitaptan bir bölüm için, editör(ler) varsa:

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.

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Eckel RH (editor). Treatment of obesity with drugs in the new millennium. In Obesity Mechanisms and Clinical Management. 1st ed., Philadelphia: Lippincott Williams & Wilkins, 2003:449-476.

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Bagcilar Med Bull 2023;8(2):113-126
DOI: 10.4274/BMB.galenos.2023.2023-03-021

The Role of DHEA, NGF, and ADAMTS5 Pathways in Osteoarthritis and Current Developments

Osteoartritte DHEA, NGF ve ADAMTS5 Yollarının Rolü ve Mevcut Gelişmeler

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Abstract

Degenerative joint disease is a condition that affects joints and is commonly referred to as osteoarthritis (OA). This form of arthritis is most prevalent among women and tends to become more frequent as people age. The pathogenesis of OA involves an imbalance of cytokines in favor of pro-inflammatory cytokines. However, the steroid hormone dehydroepiandrosterone (DHEA) exerts chondroprotective effects and regulates the balance of catabolic factors such as thrombospondin motif disintegrin and metalloproteinase (ADAMTS), thereby playing a role against OA. Pro-inflammatory cytokines induce aggrecanases, such as ADAMTS5, which degrade the extracellular matrix and contribute to OA. The molecule nerve growth factor (NGF), associated with pain in OA, is important for cartilage homeostasis, and DHEA can modulate pain by interfering with NGF receptors. This review covers the roles of DHEA, ADAMTS5, and NGF in the pathogenesis of OA, their relationship with pain pathways, and their use in current treatments. We also anticipate that these pathways will be crucial in developing new strategies to prevent and treat OA, and understanding their interactions may make it possible to enhanced the quality of life of patients with OA.

Keywords: ADAMTS5, DHEA, NGF, osteoarthritis

Öz

Dejeneratif eklem hastalığı, eklemleri etkileyen ve genellikle osteoartrit (OA) olarak adlandırılan bir durumdur. Bu artrit formu en çok kadınlar arasında görülür ve insanlar yaşlandıkça daha sık olma eğilimindedir. OA'nın patogenezi, sitokinlerin pro-enflamatuvar sitokinler lehine dengesizliğini içerir. Ancak steroid hormon dehidroepiandrosteron (DHEA) kondroprotektif etki gösterir ve trombospondin motif disintegrin ve metalloproteinaz (ADAMTS) gibi katabolik faktörlerin dengesini düzenleyerek OA'ya karşı rol oynar. Pro-enflamatuvar sitokinler, hücre dışı matrisi bozan ve OA'ya katkıda bulunan ADAMTS5 gibi agrekanazları indükler. OA'da ağrı ile ilişkili sinir büyüme faktörü (NGF) molekülü, kıkırdak homeostazı için önemlidir ve DHEA, NGF reseptörlerine müdahale ederek ağrıyı modüle edebilir. Bu derlemede OA patogenezinde DHEA, ADAMTS5 ve NGF'nin rolleri, ağrı yolakları ile ilişkileri ve güncel tedavilerdeki kullanımları ele alınmaktadır. Ayrıca, bu yolların OA'yı önlemek ve tedavi etmek için yeni stratejiler geliştirmede çok önemli olacağını ve etkileşimlerinin anlaşılmasının OA'lı hastaların yaşam kalitesini artırmayı mümkün kılacağını tahmin ediyoruz.

Anahtar kelimeler: ADAMTS5, DHEA, NGF, osteoartrit

Introduction

Worldwide, more than 250 million people are affected by osteoarthritis (OA), which is known as the most prevalent form of arthritis and characterized as a degenerative joint disease (1-3). Factors such as continued population growth and aging are the main causes of the increasing in the prevalence of OA which makes it considered as on of the

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Cite this article as: Sarı Ak D, Helvacı N, Alomari O, Yılmaz EB, Al-Jebaili MM, Kural A. The Role of DHEA, NGF, and ADAMTS5 Pathways in Osteoarthritis and Current Developments. Bagcilar Med Bull 2023;8(2):113-126

leading causes of disability among elderly (4,5). OA has a higher incidence in women and is a significant socio-economic burden in many countries globally (6). The disease is progressive and debilitating, causing pain and resulting in a loss of function, which can be so severe that it disrupts the patient's ability to get restful sleep. At the societal level, the annual cost of OA is estimated to exceed $303 billion due to medical costs and lost earnings (7). The economic impact of OA is expected to double by 2030 on a global scale (8), emphasizing the urgency for extensive research to comprehensively understand the contributing factors in the onset and advancement of the disease. Various factors contribute to women's susceptibility to OA, including thinner cartilage, joint instability, misalignment, and unequal mechanical loading (9). Recent studies have demonstrated that a sharp decrease in sex hormone levels during menopause can trigger OA development (10,11). Other risk factors for OA include trauma, genetics, high basal metabolic index, and structural abnormalities in the joint (12). Genetic factors have been found to be effective in primary generalized OA with Heberden's nodule, Bouchard's nodule, hip involvement, and knee involvement. This is particularly evident in Heberden's nodules and is carried by an autosomal gene that is dominant in females and recessive in males. Matched twin and family-risk studies have shown that the genetic contribution to OA may be around 50-65% (13). For instance, occupational activity in professional athletes such as football players can cause the development of OA (12). OA can affect both small joints, such as those in the hand, and larger joints such as the knee and hip (14). Although pain is the primary symptom, other symptoms may accompany OA, including joint swelling, locking, cramping, decreased range of motion, and morning stiffness that resolves within thirty minutes (15). Radiographic evaluation of the joint is the gold standard in diagnosis (16). Treatment options for OA vary depending on the severity of the disease and the individual's specific needs. Some of the available treatments include joint replacement surgery, autologous mesenchymal stem cell transplantation, and non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain (17,18). In those whose pain is not adequately controlled, first-line evidence-based analgesia, NSAIDs and acetaminophen (paracetamol) are used. Oral NSAIDs and the use of cyclooxygenase-II (COX-II) inhibitors, opiates, or intra-articular steroids are considered when first-line agents fail (13,19). Additionally, early interventions such as chondroitin sulfate and glucosamine may be recommended (17). Physical therapies can also be used to treat early-stage OA (17). Finally, a Mediterranean diet may decrease the prevalence of OA and improve patients' quality of life (20).

In the pathogenesis of OA, an important factor is the disruption of the balance between anti-inflammatory and pro-inflammatory cytokines, with pro-inflammatory cytokines often becoming more dominant. The induction of interleukin (IL)-1β results in aggrecanases such as a Disintegrin and Metalloproteinase with ThromboSpondin motifs (ADAMTS)-4 and ADAMTS5 leading to extracellular matrix (ECM) degradation. Moreover, matrix metalloproteinase (MMP) induction can cause hypertrophy, differentiation, and apoptosis in chondrocytes due to these events (21). Among the 19 members of ADAMTS enzymes with various functions, ADAMTS-5 is more notable in arthritis (22). Dehydroepiandrosterone (DHEA) is a steroid hormone produced by the adrenal gland cortex, which regulates the balance between catabolic factors such as ADAMTS in cartilage (23). DHEA shows chondroprotective effects and reduces oxidative stress, protecting against OA (24). Although the role of DHEA in modulating OA-related pain is not confirmed, studies suggest that DHEA can interfere with nerve growth factor (NGF) receptors (25). NGF is primarily expressed in synovial fibroblasts and is associated with pain. Patients with knee OA and hip OA have higher NGF expression, as studies have demonstrated (26). There is evidence from mouse models that NGF and other neurotrophins are overexpressed in symptomatic diseases and are themselves synthesized by joint connective tissue (19). In 2019, a study emphasized the role of NGF signaling in the calcification of human joint chondrocytes and the importance of NGF signaling in articular cartilage homeostasis (27). Although conventional OA treatments alleviate pain, they cannot reverse cartilage damage (28). Therefore, it is crucial to further explore new molecular targets. This article will explain how ADAMTS5, DHEA, and NGF contribute to OA disease and the mechanisms they mediate by summarizing articles published in the last 5 years.

In humans, DHEA is synthesized in the central nervous system (CNS), gonads, and adrenal cortex, and it has been found to have anti-inflammatory effects on various tissues, including the prevention of leukocyte recruitment. DHEA has been shown to interact with various nuclear receptors, such as estrogen receptors, as well as G protein-coupled receptors found in endothelial and neuronal cells (29). In a study conducted by Lazaridis et al. (30), specific antibodies were employed to target tropomyosin-related kinase A (TrkA) and p75 in coimmunoprecipitation assays and

Western blot analyses of precipitates. The study showed that DHEA can directly suppress the NGF receptors p75 and TrkA, and can eliminate both receptors from PC12 cells (30). Given this discovery, it is feasible that DHEA could potentially compete with NGF for its intended receptors, resulting in the inhibition of peripheral pain production. This is because NGF binding to these receptors located in peripheral nociceptors is responsible for initiating the downstream cascade of pain signals (25,31).

In addition, research has demonstrated that both DHEA and NGF can effectively prevent apoptosis in neuronal cells. Their antiapoptotic effects begin at the plasma membrane and involve the activation of similar prosurvival kinase cascades. They also regulate the transcription of the antiapoptotic protein B-cell lymphoma 2 (Bcl-2) through the activation of transcription factors nuclear factor kappa-B (NF-B) and cyclic AMP-responsive element binding protein. Researchers have hypothesized that NGF receptors may play a role in the antiapoptotic effects of DHEA, given the similarities observed in the signal transduction pathways triggered by both molecules (32).

DHEA Pathways in OA

DHEA is a hormone that is synthesized in the zona reticularis of the adrenal gland and serves as the precursor to all sex steroid hormones. Its levels are more closely linked to age than gender, with a marked decline in the elderly that is strongly linked to the development of age-related conditions (33,34). Numerous studies have emphasized the potential therapeutic benefits of DHEA in treating chronic degenerative joint diseases, including OA. Earlier studies have suggested that administering DHEA has a positive effect on cartilage preservation in animal models of OA, particularly in the early and mid-stages of the disease (35-37). In 2015, a study was conducted to investigate the modifying effect of DHEA in various stages of experimentally induced OA disease. The results showed that DHEA treatment significantly reduced cartilage lesions and delayed cartilage degeneration in four regions of the knee (38). These findings suggest that DHEA may play a role in the pathophysiology of OA. DHEA is produced by the zona reticularis part of adrenal gland (39). The inactive sulfate ester of DHEA is converted to sulfate DHEAS in the adrenal glands and liver (40). They are bound to albumin and together form the most abundant steroid hormones in the human circulation (41). Due to the aging-related decrease of DHEAS and DHEA levels, it has been suggested that the formation of aging-related diseases may be linked to a relative deficiency of these hormones (42,43). Therefore, it is important to consider the role of DHEA in the context of OA and explore its potential as a treatment option. Moreover, DHEA has been shown to have protective effects against various aging-related diseases such as dementia (44,45), osteoporosis (46), and atherosclerosis (47).

DHEA's ability to positively influence chondrocyte/articular cartilage metabolism has been demonstrated in numerous animal- and cell-based studies, which supports its chondroprotective effects (36,37,48). Disruption to this role of DHEA could be considered as a predominant cause of OA related pathogenesis. Chondrocytes, a special cell type of the skeletal system, play a significant role in skeletal maturation and fracture healing, and endochondral ossification, a process that replaces the developing cartilage nidus by bone, may assist both fracture healing and skeletal maturation (49). Although there are few studies about the relationship between DHEA and chondrocytes, the literature suggests that DHEA can affect the overall performance of chondrocytes (49). By preventing the expression of matrix metalloproteinases enzymes known to catalyze cartilage degradation, DHEA has a chondroprotective impact on mature cartilage (36,37,48). Therefore, DHEA may be helpful in degenerative chronic conditions like OA. Moreover, there is evidence to suggest that Wnt/β-catenin pathway can be modulated by DHEA, which is critical for the maintenance of myogenic and cartilage homeostasis, with β-catenin levels playing a crucial role (50). A 2013 study examined the protective mechanism of DHEA in experimental models of OA and suggested that the chondroprotective effect of DHEA on the animals cartilage and chondrocytes may be due in part to its aromatase-mediated conversion to estrogens. This process may occur via the blocking of aromatase with letrozole (36). Therefore, it is understood that DHEA levels play a vital role in the mechanism of OA. In healthy cartilage, a robust collagen scaffold and high aggrecan content are necessary for its weight-bearing properties. However, massive loss of aggrecans, caused by aggrecanases, is the hallmark of most arthropathies, including OA (51). Aggrecanase-mediated degradation of aggrecan is an important event in the early stages of OA. While the mechanisms of action of DHEA in OA are not fully understood, data from *in vitro* studies and animal models suggest that its protective efficacy on osteoarthritic cartilage may be due to its role in the inhibition of pro-inflammatory pathways, leading to down-regulation of MMP enzymes that play a critical role in aggrecan loss in OA (37,52). Additionally, DHEA has been shown to have an anti-catabolic effect by suppressing MMPs and inducing tissue inhibitor of metalloproteinases (TIMPs), which

suggests that modulating the balance between MMPs and TIMPs is another protective mechanism of DHEA on OA (53).

Researchers conducted a study in 2003 to explore the impact of DHEA on the expression of catabolic enzymes in chondrocytes. The results demonstrated that DHEA treatment suppressed the expression and protein synthesis of MMP-1, a metalloproteinase associated with cartilage degradation, while increasing the expression and synthesis of TIMP-1, an inhibitor of MMP-1. Additionally, DHEA treatment decreased the expression of type I collagen, which is a marker of ECM senescence, and increased the expression of type II collagen, a marker for chondrogenesis (37). These findings suggest that DHEA may have chondroprotective effects in osteoarthritic chondrocytes.

In 2006, a follow-up study explored the influence of DHEA on chondrocytes obtained from neonatal rats that were exposed to catabolic stimulators, such as lipopolysaccharide (LPS) and *S*-nitroso-*N*-acetyl-l-penicillamine (SNAP). The study revealed that DHEA treatment did not impact the viability of healthy chondrocytes or interfere with their glycosaminoglycan (GAG) production capabilities (49). Furthermore, the administration of DHEA was shown to suppress the expression of prostaglandin E2 caused by LPS, MMP-13, MMP-1, and MMP-3, and also hinder the NO synthesis and GAG degradation induced by SNAP in chondrocytes (49). These results suggest that DHEA possesses anti-catabolic characteristics that address inflammation and degeneration, two crucial biological processes involved in the progression and development of OA (49). Taken together, these investigations indicate that DHEA can protect cartilage by impeding catabolic enzymes, stimulating the production of extracellular matrix, and halting inflammation and degeneration in chondrocytes. These results underscore the potential therapeutic advantages of DHEA in treating OA (53).

The pathophysiology of OA involves a complex interplay of various factors, including ECM-degrading enzymes. The MMP family has been extensively studied as an important catabolic factor in the development of OA. However, other enzymes, such as the urokinase plasminogen activator (uPA), the cysteine protease family, and the disintegrin and metalloproteinase with thrombospondin motifs family, have also been implicated in the pathogenesis of OA (54). uPA has been shown to regulate the extent of ECM degradation and is believed to play a role in the development of arthritis (54). Aggrecanases, particularly ADAMTS4 and ADAMTS5 from the ADAMTS family, are the most powerful enzymes that degrade aggrecan, a crucial constituent of the cartilage ECM (55-57). Meanwhile, cathepsins K, B, L, and S from the cysteine protease family are deemed the most significant enzymes in the progression of OA (58,59).

In healthy cartilage, it is necessary to achieve a balance between anabolic and catabolic processes to preserve homeostasis (51). However, if catabolic processes outweigh the chondrocytes' potential for regeneration, articular cartilage will degenerate. Therefore, targeting these catabolic enzymes, such as MMPs, ADAMTS, and cysteine proteases, could be a potential therapeutic approach for OA.

Several studies have investigated the association between ECM-degrading catabolic enzymes and OA. In 2014, a study investigated the impact of TIMP1, a glycoprotein, on MMPs and revealed that TIMP1 has the capacity to inhibit all MMPs by establishing complexes with high-affinity at one to one ratio (60). This discovery could potentially pave the way for novel OA treatment approaches.

Natural inhibitors of cysteine proteinase and uPA, such as cystatin C and plasminogen activator inhibitor-1 (PAI-1), respectively, have been identified (61,62). To better understand the chondroprotective function of DHEA, researchers conducted a study to investigate how DHEA affected these linked enzyme systems in the development of OA. According to *in vivo* conducted study, by regulating the metabolic balance of certain enzymes such as ADAMTS/TIMP-3 (63), uPA/PAI-1 (35), MMP-3/TIMP-1 (53), and cysteine proteinases/cystatin C, DHEA protects the cartilage from damage and degradation.

ADAMTS5 Interactions in OA

ADAMTS5 is a group of ADAMTS enzymes containing thrombospondin motifs and metalloproteinases. The ADAMTS family has 19 members in humans (64,65), with members 4 and 5 in the aggrecanases subgroup, which are responsible for tissue morphogenesis and pathophysiological remodeling (66). In arthritis, proteoglycan degradation is facilitated by ADAMTS4 and 5, leading to cartilage aggrecan degradation. Knee injuries increase the risk of post-traumatic OA, and while the relationship of subchondral bone and bone marrow lesions with OA is known, the response of the synovium to joint damage is not fully understood. A study conducted to determine changes in the synovium within the first 14 days of knee injury found that transcripts encoding ADAMTS4 increased in the synovium (67). In addition, the expression

of aquaporin 1 (AQP 1), a channel, increased in OA chondrocytes, and the downregulation of AQP 1 was found to decrease the expression of ADAMTS4, which suppresses IL-1β-induced ADAMTS4 (68). Therefore, the reduction of AQP 1 expression in OA can suppress ADAMTS4. OA is characterized by degenerative loss of articular cartilage in synovial joints, with changes in bone and synovium. The main culprit in aggrecan cleavage, an ECM component, is ADAMTS5 (69). In rats with medial meniscal tear, the OA group had a significant increase in ADAMTS5 at 4, 6, and 8 weeks compared to healthy controls and the placebo group, leading Elsadek et al. (70) to conclude that ADAMTS5 could serve as a serological marker in OA.

ADAMTS5, also known as aggrecanase 2, is a risk factor for degenerative disorders due to its overexpression, which is the main cause of joint destruction and matrix loss in OA (71). IL-1β induces ADAMTS5 expression in human chondrocytes, while WW domain-containing protein 2 (Wwp2) overexpression down-regulates it. Thus, Wwp2 is thought to regulate ADAMTS5 expression in articular cartilage (72). A recent study conducted in 2021 showed that ADAMTS5 is highly regulated in cartilage with OA and that miR-9-3p overexpression suppresses ADAMTS5 expression, leading to inhibition of IL-1β-induced apoptosis and ECM destruction. The study also found that MIR22HG inhibition reduced ECM degradation through the miR-9-3p/ADAMTS axis (73). A research study on the genetic variation of ADAMTS5 revealed that the polymorphism of rs2830585 contributes to the risk of OA in the knee. The study found that individuals with the TT genotype had a 1.95-fold higher risk of developing OA compared to those with the CC genotype, and the presence of the rs28305885T allele increased the risk of OA by 39% compared to individuals with the C allele (74). However, it was observed that the *ADAMTS5 rs226794* gene polymorphism was not associated with knee OA, and the G allele was not confirmed to be a risk factor for OA (75). In a study by Canbek et al. (64), the relationship between *OA* and *ADAMTS5* gene polymorphisms in Turkey was examined. As a result of the study, no significant difference was found in allele frequencies between the groups for the ADAMTS5 rs226794 and rs2830585 genotypes (64).

Age-related DNA damage is a known factor in the development of OA, as it can lead to cellular aging in joint tissue (76). To investigate the role of interferon genes (STING) in the pathogenesis of OA, a study was conducted in human and mouse cartilage. The study found that STING expression increased in OA patients and overexpression of STING led to increased expression of ADAMTS5. However, the use of lenti-sh-STING to destroy STING reversed the IL-1β-stimulated expression of ADAMTS5. Therefore, the study concluded that STING induces ECM degradation, contributing to the progression of OA (77).

Betulinic acid was found to reduce OA-like changes in a collagenase-injected mouse model by inhibiting the production of pro-inflammatory cytokines and the production of ADAMTS4 and 5 (78).

The TIMP family consists of four members, TIMP1-4, which are proteins with protease inhibitory effects. While TIMP3 is bound to the ECM, the others exist in a soluble form in the ECM. Selective inhibition of members of the ADAMTS family is achieved by TIMPs (79). A study carried out in 2016 aimed to identify the primary endogenous inhibitor of ADAMTS5 and ADAMTS4. The results revealed that TIMP-3 is the most significant inhibitor of ADAMTS4 and ADAMTS5 (80).

In a study investigating the effects of DHEA on the expression of aggrecanases and endogenous inhibitors of aggrecanases in a rabbit model of OA, cartilage treated with DHEA was found to have higher expression of TIMP-3 and lower expression of ADAMTS4 and ADAMTS5 compared to the control group, as determined by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis. The results suggest that intra-articular administration of DHEA can decrease the gene expression of aggrecanases and increase the expression of the endogenous inhibitor TIMP-3, leading to a reduction in aggrecanase activity. This suggests that DHEA may be a beneficial treatment for OA by affecting the balance between aggrecanases and TIMP-3 (63).

NGF Pathways in OA

Musculoskeletal conditions such as OA and back pain remain prevalent and cause substantial distress and societal costs, despite considerable therapeutic progress in recent decades (81). To meet the pressing medical need for effective pain relief in these conditions, there is a demand for novel approaches and targeted therapies (81). NGF inhibitors offer a promising alternative to traditional drugs, which often pose risks of adverse effects on organs such as the gastrointestinal tract, heart, or kidneys (81). Although OA can manifest in various functional impairments, pain remains the principal symptom, and thus, pain management represents a key aspect of clinical care for OA patients (82).

NGF, the first growth factor to be identified, was discovered by Rita Levi-Montalcini in 1952. Subsequent studies in

the 1950s with Stanley Cohen showed that this factor regulated the growth and development of the nervous system (83). NGF belongs to a family of neurotrophic factors that includes brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 (84). Neurotrophins signal through tyrosine receptor kinases (Trk), also known as tropomyosin receptor kinases, including TrkA, TrkB, and TrkC. Among the neurotrophins, TrkA shows significant NGF specificity and binds to NT-3 as well (85).

Initially, NGF was identified as a soluble signaling protein produced by tumor tissue that promoted the survival and proliferation of sensory neurons (84). However, in the 1990s, it was discovered that NGF also contributes to tissue damage, discomfort, and pain in adults (83). NGF is released by immune cells involved in the inflammatory response to peripheral damage. Besides immune cells, non-immune cells such as endothelial cells, pericytes, chondrocytes, and synoviocytes may also produce NGF (83,86,87). Previous research has suggested that NGF does not immediately cause pain but rather contributes to pain by inducing peripheral and potentially central nerve sprouting (88). In an original study published by Testa et al. (89) in 2019, researchers investigated the relationship between NGF and pain by creating transgenic mice with the human *661C>T NGF* gene mutation. The study found that the nociception of heterozygous NGFR100W/wt mice was impaired (89). Recent studies have demonstrated that targeted inhibition of NGF is highly effective in animal models of many acute and chronic pain conditions while being notably free of side effects (90). Interestingly, research suggests that inflammation-induced NGF expression is seen in OA (84).

The Role of DHEA, NGF, and ADAMTS5 in the Treatment of OA and Current Treatments

Currently, there is no cure for OA. However, there are several forms of treatment available that can be grouped into the categories of reducing modifiable risk factors, intra-articular therapy, physical modalities, alternative therapies, and surgical treatments. In the early stages of OA, the primary goal of treatment is to alleviate stiffness and pain. As the disease progresses, the focus of treatment shifts towards maintaining physical function and preventing further damage (15).

OA is typically managed with first-line treatments such as NSAIDs and acetaminophen. However, if these options fail or are not appropriate, stronger medications like weak opioids and narcotic analgesics may be considered. Steroid injections into the affected joint can also be used for the management of inflammatory flares, although their effectiveness is limited and temporary. Intra-articular administration of hyaluronic acid and other viscosupplements can provide longer-lasting treatment, but their short-term efficacy is questionable and results are inconsistent (91-94). Conservative treatment approaches for OA primarily aim to alleviate symptoms, while arthroplasty is usually recommended for individuals with moderate to severe OA. For young patients seeking to preserve their knee function, osteotomy around the knee may be considered as an alternative surgical procedure, as it focuses on "knee preservation" (28). The effectiveness of these interventions may vary based on the severity of the condition (95). The effectiveness of OA treatment can be limited due to various factors, such as an individual's response to medications like NSAIDs and acetaminophen. Although these drugs can offer pain relief, their prolonged use can lead to serious negative effects and must be used with caution under medical supervision (96). While corticosteroid therapy can significantly improve outcomes in the short term, its regular use may promote cartilage deterioration, joint damage, or tissue atrophy (96). Unlike traditional treatments, in a study conducted in Turkey, autologous conditioned serum (ACS) treatment was tried. For this purpose, they performed bilateral knee injections. The results showed that the use of ACS resulted in significant improvement in pain severity and knee community scoring (97).

Additionally, lifestyle changes like weight loss and exercise can slow disease progression and reduce symptoms, but may not fully alleviate advanced stage symptoms (98). Surgeries, such as joint replacement, can provide significant function improvement and relief of pain, but they are invasive and carry risks like aseptic loosening, stiffness, prosthesis failure, instability, infection, and misalignment (99). OA treatment often involves a gradual process of multiple approaches, and it may not completely eliminate symptoms or restore function.

NGF

Studies using various OA models have demonstrated that anti-NGF drugs can effectively reduce pain-related behaviors, however, preclinical testing of NGF antibodies and TrkA inhibitors in OA models have lagged behind clinical trials (100). Utilizing preclinical models is important in understanding the mechanisms behind the analgesic relief provided by inhibiting the NGF/TrkA pathway in OA, as well as identifying the reasons and risk factors for rapid progression of the disease, which is often observed in clinical trials (100). Despite the lack of human use approval, anti-

NGF monoclonal antibodies (mAbs) are being developed as potential therapies for pain management in various conditions (101). Tanezumab (Pfizer in collaboration with Eli Lilly), fulranumab (Amgen), and fasinumab (Regeneron Pharmaceuticals in partnership with Sanofi) are currently humanized mAbs that have been developed to target free NGF as treatments (101). Clinical trials using NGF inhibition have been conducted in patients with hip and knee OA, which have shown that anti-NGF antibodies significantly reduce pain and improve function (102). A recent study by Ohashi et al. (26) 2021 aimed to investigate the relationship between pain, central sensitization, and synovial NGF expression in patients with hip OA who had undergone total hip replacements. The study found that in hip OA patients, synovial NGF expression is linked to both pain intensity and central sensitization, which supports the association between NGF molecule and pain (26). These findings demonstrate the potential for NGF inhibition as a promising therapeutic approach for OA pain management. In a 2019 study by Dakin et al. (103), 342 patients were given fasinumab, an anti-NGF monoclonal antibody drug, over a 36-week period to assess its efficacy and safety in OA. Results showed that fasinumab produced statistically significant and clinically meaningful pain reductions in comparison to placebo at all four dosages from baseline to week 16 (103).

The phase 3 study by Berenbaum et al. (104) in 2020 demonstrated significant pain relief, physical function improvement, and positive physician global assessment scores in patients with moderate-to-severe OA who had not responded to or could not tolerate standard-of-care analgesics after receiving subcutaneous tanezumab at a dose of 5 mg every 8 weeks. It is noteworthy that tanezumab is the most extensively researched anti-NGF drug and the most advanced agent, making it the likeliest candidate for regulatory approval among the anti-NGF drugs studied in OA (105). In 2019, Krupka et al. (106) published an original article evaluating the effectiveness and safety of GZ389988A, TrkA inhibitor, in participants with painful knee OA. Several pre-clinical OA models have demonstrated reduced pain behavior with TrkA inhibition, as TrkA is one of the receptors for NGF. This approach focuses on antagonizing both TrkA and p75NTR, the two NGF receptors, to decrease NGF-induced pain (105).

In a study by Krupka et al. (106) in 2019, 104 participants with moderate to severe knee OA pain were administered a single intra-articular injection of either GZ389988A, a TrkA inhibitor, or a placebo. The authors found that the injection of the TrkA inhibitor resulted in a sustained reduction in pain and a quantifiable functional improvement compared to the placebo. Additionally, the TrkA inhibitor demonstrated an acceptable safety profile (106). In 2020, Ishiguro et al. (107) conducted a study to evaluate the efficacy, safety, and tolerability of ONO-4474, a Pan-Tropomyosin Receptor Kinase inhibitor, in Japanese patients with knee OA. The study demonstrated that the drug effectively reduced pain in individuals with knee OA, supporting the association between blocking Trk and pain reduction in patients with OA, and further supporting the relationship between NGF molecule and pain (107). In contrast, a 2019 study by another research team investigated the efficacy of ASP7962, another TrkA inhibitor, in treating pain in knee OA. Despite a suitable study design, the oral small-molecule TrkA inhibitor did not improve pain in individuals with knee OA, and the authors confirmed the reliability of their results because of the significant improvement in pain observed between naproxen and placebo in the same study (108). According to the authors of the study, the discrepancy in results between their findings and other studies showing pain reduction after TrkA inhibitor administration may be due to the possibility that a higher dose of ASP7962 could have a stronger pharmacological effect, but this would need to be balanced against an increased risk of toxicity (108). Furthermore, the authors suggest that the slightly higher baseline pain levels in the ASP7962 group compared to the placebo group may have hindered the drug's ability to achieve a statistically significant effect (108). While the effectiveness of DHEA in reducing OA-related discomfort has not yet been confirmed, recent research suggests a potential relationship between DHEA's pharmacological actions and pain generation in OA (Figure 1). Given the lack of effective pharmaceutical options for treating OA, understanding the molecular pathways underlying DHEA's pain-relieving effects may pave the way for the development of novel anti-OA medications (25).

DHEA

In 2004, a study was conducted on a rabbit model to investigate the effects of DHEA treatment. Based on gross morphological examination and histological analysis, the results indicated that the femoral condyles that received DHEA treatment exhibited lower levels of cartilage damage compared to the untreated condyles (52). Additional evaluation to the overall structure of the cartilage, Safranin O staining, and thickness showed reduced damage in the DHEA group in comparison to the placebo group. The findings were further corroborated by the RT-PCR

based analysis of gene expression. These analysis has demonstrated a reduction in MMP-1/3 mRNA and IL-1 expression. Furthermore, TIMP-1 mRNA levels increase has also been detected in a treated knee joint cartilage with DHEA. These results indicate that DHEA may impede the catabolic degradation of MMPs in the OA process *in vivo* (109).

In 2015, a study using a rabbit model of OA examined the modifying effects of DHEA on the structure. The results demonstrated that DHEA treatment was capable of halting the advancement of pre-existing cartilage degeneration in various areas of the knee joint at different stages of OA, with certain variations possibly linked to the severity of the disease (38). In particular, in moderate OA, DHEA administration was found to prevent deterioration in both compartments of the knee. However, in advanced OA, DHEA was found to be effective only in inhibiting the deterioration of the lateral knee compartment. This site-specific and time dependent efficacy suggests that DHEA's structure-modifying effects against OA may vary depending on the location and stage of the disease. The multitargeted protective features of DHEA are illustrated in Figure 2. These findings suggest that understanding the molecular pathways of DHEA's protective effects on OA may lead to the development of new anti-OA medications, as there are currently no effective pharmaceuticals for treating OA.

ADAMTS5

Current treatments for OA are mainly aimed at relieving symptoms, such as the use of intra-articular drugs like NSAIDs and hyaluronic acid. Surgical options are considered for patients with end-stage OA. Disease-modifying osteoarthritis drugs (DMOADs) have the potential to alter the course of the disease by preventing structural changes in the joint and improving symptoms. One promising DMOAD is the anti-ADAMTS5 Nanobody M6495, which belongs to the proteinase inhibitor family (110). In an *ex vivo* cartilage model, M6495 demonstrated high affinity for the ADAMTS5 target and did not bind to ADAMTS4. In addition, it was observed that M6495 was able to completely inhibit the enzymatic activity of its target in a concentration-dependent manner (111).

A study conducted on rats with OA, bone marrow mesenchymal stem cell-derived exosomes were found to significantly reduce the upregulation of the IL-1β derived ADAMTS5 proteolytic enzyme, which researchers hypothesized was due to exosomes protecting chondrocytes

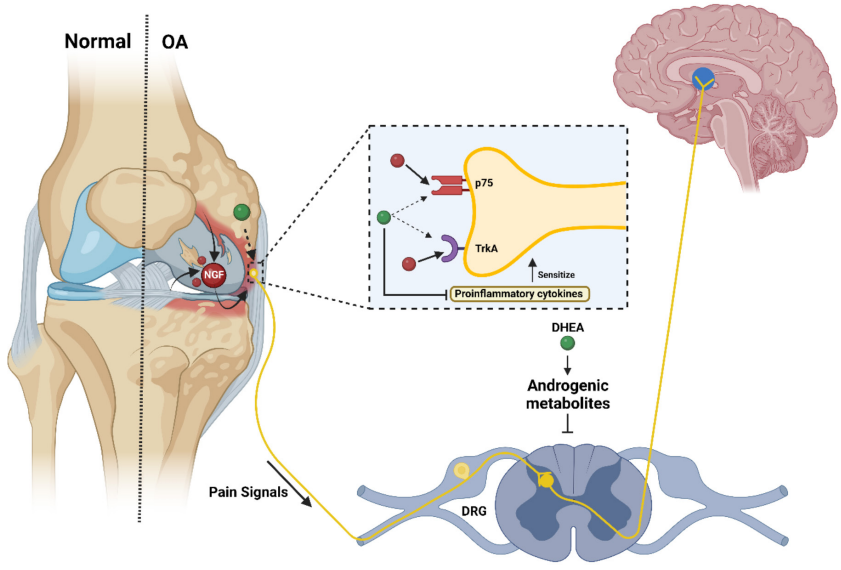

Figure 1. Interaction between DHEA and NGF-mediated pain pathwyas in osteoarthritis. This figure illustrates the intricate interaction between DHEA and NGF-mediated pain pathways in osteoarthritis. Nociceptor cells located in the peripheral regions of the body sense pain signals, which then travel to the dorsal horn of the spinal cord. The signal is then transmitted to the brain via the central terminals of the afferent nociceptors, which connect with second-order neurons in the dorsal horn. DHEA has the potential to reduce pro-inflammatory cytokines and block inhibitory mechanisms in the peripheral nervous system by suppressing NGF-mediated pain signaling, thereby preventing the transmission of pain signals from nociceptors in the joint capsule. Moreover, DHEA may be converted into androgen centrally, which can help to decrease the transmission of pain signals in the posterior horn of the spinal cord

DHEA: Dehydroepiandrosterone, NGF: Nerve growth factor, DRG: Dorsal root ganglion, OA: Osteoarthritis, TrkA: Tropomyosin-related kinase A

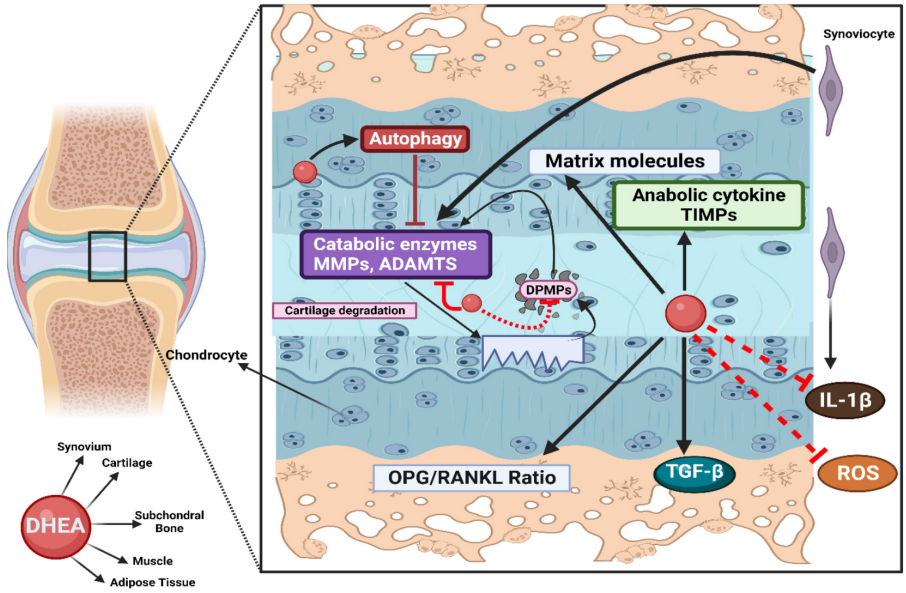

Figure 2. DHEA's multitargeted protective features are important for the various tissues affected by OA and the whole-joint pathology. This figure illustrates the multifaceted protective effects of DHEA on various tissues affected by OA and the overall joint pathology. DHEA influences the metabolic processes of different tissues involved in OA, including synovium, subchondral bone, cartilage, muscle, and fat. DHEA's potential mechanisms for preventing OA include: Reducing the release of damage-associated molecular patterns (DAMPs) and decreasing the production of catabolic enzymes, suppressing synovial inflammation by inhibiting IL-1β, enhancing chondrocyte autophagy, balancing the ratio of osteoprotegerin (OPG) and receptor activator of nuclear factor-kappa B ligand (RANKL) in subchondral bone, regulation of the signaling pathways of TGF-β in subchondral bone and cartilage, as well as the reduction of inflammation and oxidative stress in the near joint muscle

DHEA: Dehydroepiandrosterone, OA: Osteoarthritis

from IL-1β induced damage. The protective effect was also observed to be dose-dependent (112). Another potential therapeutic agent is hyperoside, a bioactive flavonoid with anti-inflammatory properties that has been shown to reduce ADAMTS5 expression and have anti-arthritic effects (113).

Aptamers are single-stranded DNA or RNAs with 3-dimensional structures that enable them to selectively bind to specific molecular targets (114). Recently, two new DNA aptamer inhibitors, apt 21 and apt 25, were developed, both of which demonstrated high binding affinity and specificity towards ADAMTS5. These aptamers exclusively inhibit ADAMTS5 activity and do not bind to ADAMTS4, making them potential candidates for the treatment of OA (115). A study conducted on rats with knee OA caused by monosodium iodoacetate (MIA) investigated the therapeutic potential of fibroblast growth factor-2 (FGF-2). The researchers overexpressed FGF-2 via rAAV-mediated gene transfer and found that inhibiting toll-like receptor 4 (TLR4) signaling and activating TIMP-1 downregulated ADAMTS5 mRNA and MMP13, markers of knee joint degradation. These results suggest that FGF-2 may have therapeutic benefits for MIA-induced knee OA (116).

In another study, Jia et al. (117) isolated and used murine primary chondrocytes to investigate the effect of cell-free fat extract (CEFFE) on ADAMTS5 expression. The researchers found that when primary chondrocytes were co-cultured with inflammation factors, ADAMTS5 expression increased, while treatment with CEFFE led to a reduction in ADAMTS5 expression. These findings suggest that CEFFE may be a promising therapeutic strategy for the treatment of OA (117).

In a study conducted in 2022, miR-17 was found to be expressed highly in the middle and superficial regions of articular cartilage and was observed to protect against the destruction of cartilage caused by destabilization of the medial meniscus by targeting pathological catabolic factors, including ADAMTS5. In the context of OA, miR-17 downregulation has been observed, which results in an increase in catabolic factors like ADAMTS5. The targeting of these genes by miR-17 suppresses the function of these catabolic factors and helps in maintaining cartilage homeostasis. Therefore, miR-17 could be a potential therapeutic target for the treatment of OA (118).

In a separate study conducted in 2022, researchers utilized IL-1β-treated chondrocytes as a cellular OA *in vitro* model

to assess the inhibitory impact of microRNA-613 (miR-613) on ADAMTS5. The researchers discovered the strong inhibitory effect of miR-613 on ADAMTS5 in this model, and the expression of ADAMTS5 was inversely correlated with the expression of miR-613. These results suggest that miR-613 may be a potential therapeutic target for OA by inhibiting ADAMTS5 expression in chondrocytes (119).

Conclusion

OA is a common condition that affects the joints and can cause pain and disability. Several molecules have been identified as being involved in the pathogenesis of OA, including:

- Pro-inflammatory cytokines such as TNF-α IL-1, which can promote the breakdown of cartilage and stimulate the formation of osteophytes (bone spurs).
- MMPs, enzymes that break down the ECM of cartilage.
- Reactive oxygen species, which can cause damage to cells and contribute to the development of OA.
- Aggrecanases, enzymes that break down the proteoglycan aggrecan, a major component of cartilage.
- Proteolytic enzymes such as ADAMTS4 and ADAMTS5 that can break down the ECM of cartilage.
- Cytokines (IL-1, IL-6, TNF-α) that are involved in promoting inflammation and pain in OA.

In treating OA, various methods such as therapy, medication, and in some cases, joint replacement surgery may be recommended to alleviate pain, improve joint function, and slow down the progression of the disease. Our review has predominantly focused on recent studies that aim to understand the role of DHEA, NGF, and ADAMTS5 in the pathophysiology of OA. These molecules play a significant role in distinct aspects of OA, such as cartilage breakdown, inflammation, and bone remodeling.

Currently, anti-NGF monoclonal antibodies are not a substitute for commonly used medications like NSAIDs. While ongoing research is exploring the effectiveness of targeting NGF as a treatment strategy for OA, there are no approved treatments that specifically target this molecule. On the other hand, targeting ADAMTS5 has shown promise as a treatment strategy for OA. Several ADAMTS5 inhibitors are currently under development, which specifically target the enzyme and inhibit its activity. As a result, these inhibitors slow down the destruction of cartilage. Additionally, it's worth noting that ADAMTS5 inhibitors are still in pre-clinical and clinical trial phases and not yet available on the market. Meanwhile, DHEA supplements have been suggested as a possible treatment for OA, but their effectiveness remains uncertain due to limited evidence, requiring more research to determine their efficacy in treating the condition. DHEA therapy is not commonly utilized for OA treatment as it lacks FDA approval for that indication, and further studies are necessary to evaluate its safety and effectiveness. The investigation of the molecular mechanisms underlying OA is still ongoing, and new molecules are continuously being discovered.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Drafting Manuscript: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K., Critical Revision of Manuscript: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K., Final Approval and Accountability: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K., Writing: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K.

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

Bagcilar Med Bull 2023;8(2):127-134
DOI: 10.4274/BMB.galenos.2023.2022-11-096

Predictive Value of Nesfatin-1, Galectin-3, Ghrelin, and Leptin Expressions in Patients with Metabolic Syndrome who Underwent Coronary Artery Bypass Graft (CABG) Surgery

Koroner Arter Bypass Grefti (CABG) Ameliyatı Yapılan Metabolik Sendromlu Hastalarda Nesfatin-1, Galektin-3, Ghrelin ve Leptin Ekspresyonlarının Prediktif Değeri

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Abstract

Objective: This study aims to investigate the expression of Nesfatin-1, Galectin-3, Ghrelin, and Leptin in mediastinal adipose tissue and their relationship with postoperative complications in patients with and without metabolic syndrome who underwent on-pump coronary artery bypass graft (CABG) surgery.

Method: Fifty patients who underwent CABG surgery and who were in sinus rhythm were included in the study. The patients were divided into two groups according to whether they had metabolic syndrome or not. All patients' age, gender, weight, height, postoperative intensive care unit length of stay, total hospital stay, and post-operative complications (Low cardiac output synd. Inotropy-IABP requirement, insulin-dependent diabetes mellitus, arrhythmia, kidney failure, respiratory failure) were recorded. In the histopathological evaluation, the expression density of Nesfatin-1, Galectin-3, Ghrelin, and Leptin in the the adipose tissue samples were mainly examined.

Results: There was no statistically significant difference between the expression of Galectin-3, Ghrelin, and Leptin with post-operative complications, length of stay in the intensive care unit, and body mass index in patients with and without metabolic syndrome. However, there is a significant difference between Nesfatin-1 expression and the risk of

Öz

Amaç: Bu çalışmanın amacı, on-pump koroner arter bypass grefti (CABG) ameliyatı yapılan metabolik sendromu olan ve olmayan hastalarda mediastinal yağ dokusunda Nesfatin-1, Galectin-3, Ghrelin ve Leptin ekspresyonlarını ve postoperatif komplikasyonlarla ilişkisini araştırmaktır.

Yöntem: Çalışmaya CABG cerrahisi uygulanan ve sinüs ritminde olan 50 hasta dahil edilmiştir. Hastalar metabolik sendromu olanlar ve olmayanlar olarak iki gruba ayrıldı. Tüm hastaların yaşı, cinsiyeti, kilosu, boyu, postoperatif yoğun bakım yatış süreleri, total hastane yatış süreleri ve post-operatif komplikasyonlar (düşük debi send. İnotropi-IABP ihtiyacı, insüline bağımlı diabetes mellitus, aritmi, böbrek yetmezliği, solunum yetmezliği) kayıt altına alınmıştır. Histopatolojik değerlendirmede incelenen mediastinal yağ doku örneklerinde adiposit ve lenfosit nükleusunda Nesfatin-1, Galectin-3, Grehelin and Leptin ekspresyonu yoğunluğu değerlendirilmiştir.

Bulgular: Galectin-3, Ghrelin and Leptin ekspresyonu istatistiksel olarak metabolik sendromu olan ve olmayan hastalarda, post-operatif komplikasyonlar, yoğun bakım yatış süresi, vücut kitle indeksi ile anlamlı bir fark bulunmamaktadır (p>0,05). Bununla birlikte Nefsatin-1 ekspresyonu ile post-operatif komplikasyonlar, yoğun bakım yatış süresi ve metabolik sendrom riski ile anlamlı bir fark bulunmaktadır (sırasıyla, p=0,026, p=0,030, p=0,047).

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Cite this article as: Altun E, Dolapoğlu A, Solmaz Avcıkurt A, Avcı E. Predictive Value of Nesfatin-1, Galectin-3, Ghrelin, and Leptin Expressions in Patients with Metabolic Syndrome who Underwent Coronary Artery Bypass Graft (CABG) Surgery. Bagcilar Med Bull 2023;8(2):127-134

Abstract

postoperative complications, length of stay in intensive care unit and metabolic syndrome (respectively p=0.026, p=0.030, p=0.047).

Conclusion: Nesfatin-1 plays a role in glucose homeostasis as a negative regulator of glucose levels. In this study, it is thought that patients with low body mass index and high Nefsatin-1 expression may have a better postoperative clinical course.

Keywords: Adipose tissue, Galectin-3, Ghrelin, Leptin, metabolic syndrome, Nesfatin-1, open-heart surgery

Öz

Sonuç: Nesfatin-1, glikoz seviyelerinin negatif düzenleyicisi olarak glikoz homeostazında rol oynar. Bu çalışmada düşük vücut kitle indeksi ve Nefsatin-1 ekspresyonu yüksek olan hastaların daha iyi bir post-operative klinik seyir gösterebileceği düşünülmüştür.

Anahtar kelimeler: Açık kalp cerrahisi, Galektin-3, Ghrelin, Leptin, metabolik sendrom, Nesfatin-1, yağ dokusu

Introduction

Although there are many new innovations in coronary artery bypass graft (CABG) surgeries, patients may experience many physical, psychological, and social problems following surgery. In studies, patients undergoing CABG surgery have been reported to experience mild symptoms such as pain, wound infections, leg edema, numbness in the arms, constipation, nausea, vomiting, anorexia, sleep disturbance, fatigue, weakness, cognitive problems as well as life-threatening complications such as arrhythmia, low cardiac output syndrome and respiratory-renal failure (1).

Studies have shown that obesity and metabolic syndrome are very common and strong risk factors for operative mortality in patients undergoing CABG surgery. Interventions that may contribute to reducing the prevalence of metabolic syndrome in patients with coronary artery disease (CAD) can significantly improve survival in these patients (2,3). On the other hand, body mass index (BMI) has been shown to be an independent predictor of post-CABG pulmonary complications, although not mortality after CABG (4).

According to the definition of the World Health Organization (WHO), metabolic syndrome is characterized by a combination of metabolic abnormalities such as central (abdominal) obesity, low high-density lipoprotein, high triglycerides, high blood pressure, and hyperglycemia (5). It is known that the mortality and morbidity risk of CABG surgery is high in patients with obesity and/or metabolic syndrome. Accordingly, the multiple risk factors that drive patients with CAD to open-heart surgery are collectively found in metabolic syndrome.

In recent years, many obesity genes have been identified. The expression of Nesfatin-1 (nucleobindin-2 NUCB2/Nesfatin-1), an anorexigenic peptide, decreases with fasting (6). Studies have reported that Nesfatin-1 can cross the blood-brain barrier and be expressed in various peripheral tissues, indicating that Nesfatin-1 exhibits a wide range of physiological activities (7). Nesfatin-1 has been proven to be a new moderator in appetite, energy and glucose homeostasis, and insulin secretion, with important implications for the etiology of metabolic diseases including diabetes and obesity (8). Leptin and ghrelin, on the other hand, are two hormones that are considered to have a major impact on energy balance. Leptin is a mediator in the long-term regulation of energy balance by suppressing food intake and thereby inducing weight loss. Ghrelin release increases appetite and acts as an eating initiation signal (9). The net effect of leptin is to reduce food intake and increase energy expenditure. Galectin-3 is a lectin that plays an important regulatory role in cardiac fibrosis and remodeling, mechanisms that contribute significantly to the development and progression of heart failure. Galectin-3 has been found to increase in patients with acute decompensated and unstable heart failure (10).

Within this scope, this study aims to investigate the expression of Nesfatin-1, Galectin-3, Ghrelin, and Leptin in mediastinal adipose tissue and its association with postoperative complications in patients with and without metabolic syndrome who underwent CABG.

Materials and Methods

In this prospective study, 50 patients who presented to the cardiovascular surgery clinic, were diagnosed with CAD after coronary angiography, were between the ages of 53-85, underwent adult CABG surgery, and were in sinus rhythm were included. Patients who used immunosuppressive drugs and had a history of oncological and hematological diseases were excluded.

Surgical technique: All CABG surgeries were performed under general anesthesia with standard median sternotomy. Cardiopulmonary bypass was used in all operations with crossclamped aorta under cardioplegic arrest and moderate hypothermia. Multidose cold blood cardioplegia was administered intermittently through the aortic root in all patients and retrogradely

through the coronary sinus for myocardial protection. CABG was performed using conventional techniques, and complete revascularization was achieved in all the patients. In the presence of total occlusion of coronary vessels, endarterectomy was performed. After surgery, the patients were transferred to the intensive care unit. The patients were then extubated providing they breathed spontaneously, achieved adequate blood gases, and had stable hemodynamics.

Adipose tissue sampling: Following sternotomy, the anterior mediastinum was exposed and pre-pericardial adipose tissue was dissected to create better exposure and then the pericardium was opened. This mediastinal adipose tissue material that was removed during other routine procedures was fixed in 10% formaldehyde solution for 48 hours. The samples were turned into paraffin blocks after fixation and conventional tissue processing protocols. Histopathological evaluation was performed on hematoxyline-eosin stained slides. Sections of 3 µm thick were taken from the prepared blocks on a slide using a microtome (Leica 2245, Nussloch, Germany). Hydrogen peroxide receptor blockade was performed after all samples were washed with phosphate-buffered solution (PBS) in immunohistochemical procedures. The samples were then incubated by primary anti-Leptin (Rabbit polyclonal, Human specific, Abcam), anti-Ghrelin (Mouse monoclonal, Human specific, Abcam), anti-Galectin-3 (Mouse monoclonal, Human specific, Abcam), and anti-NUCB2/Nesfatin-1 antibodies (Mouse monoclonal, Human specific, Abcam). This was followed by washing in PBS and incubation with universal secondary antibody. Paraffin blocks were taken for immunohistochemical staining. The preparations obtained in the immunohistochemical studies were examined under the light microscope (Nikon, Eclipse Ci, Tokyo, Japan) by the pathologist in a blinded manner.

Nesfatin-1, galectin-3, leptin and ghrelin immunoreactivity was localized in nucleus of the cells. To assign an objective score, a histogram profile of each image, i.e., the number of pixels of a given intensity value relative to a given intensity value, was created using the standard program feature of Nis Elements 4.30 (Nikon, Imaging Software, Tokyo, Japan). It is noteworthy that we excluded the pixel intensity values corresponding to non-specific staining. The image analysis system that was used to acquire and analyze images consisted of a PC with hardware and software, a spot insight camera, and an optical microscope. This necessitates preliminary software procedures including spatial calibration (on a micron scale) and color segmentation adjustments for quantification. The brown staining intensity of the nucleus indicated the presence of Nesfatin-1, Galectin-3, Ghrelin, and Leptin expression. The positivity ratio was estimated. That is, the number of pixels shows the expression level of the detected antigen and may also be expressed as a percentage of the total number of image pixels. <80 pixels reflects: Weak (1+), 80-200 pixels reflects: Moderate (2+) or >200 pixels reflects: strong (3+). A score of 1 was considered negative, while the scores of 2 and 3 were positive (11).

The length of stay in the intensive care unit, total hospital stay, and post-operative complications (Low Cardiac Output syndrome, Insulin-Dependent DM, Arrhythmia, Kidney Failure, Respiratory Failure) of all patients were recorded.

BMI was calculated for each patient according to WHO categorization. All patients included in the study were evaluated consistently with the International Diabetes Foundation 2005 Metabolic Syndrome (MetS) diagnostic criteria (5). Accordingly, the patients included in the study were divided into two groups: MetS (-) and MetS (+).

Statistical Analysis

Before the study, "Power analysis" was performed to determine the number of subjects to be used in the study. To find a significant difference between the group means, the required minimum number of subjects in each group was determined as 8 (type 1 error =0.05, power of the test =0.80). G*Power version 3.1.9.4 was used for power analysis. SPSS v.24.0 package program (SPSS Inc, Chicago, Illinois, USA) was used in the statistical analysis of the data obtained from the study. In statistical analysis, the Mann-Whitney U test was used to compare metric or categorical variables between patients and controls. p-values of <0.05 were considered statistically significant.

Ethics committee approval: In this study, the investigation protocol was in accordance with the Helsinki Committee requirement and approved by the Ethical Committee of Balıkesir University (decision no: 2017/47).

Results

Descriptive data about the patients have given in Table 1. When evaluated in terms of nefsatin-1 expression, 32 patients were observed as nefsatin-1 positive (Figure 1a, 1b). The results showed that there was a statistically significant difference between Nefsatin-1 positive and negative patients according to postoperative status, BMI,

metabolic syndrome, and length of hospital stay ($p<0.05$). Patients with high nefsatin-1 expression stayed in the intensive care unit shorter (Table 2) and had less metabolic syndrome (Table 3). It was observed that 68.4% of patients with a BMI of 25 and below showed high expression of Nefsatin-1 (Table 3). While 40.6% of Nefsatin-1 positive patients did not have a post-operative complication, at least one complication was observed in 88.9% of Nefsatin-1 negative patients (Table 4).

Considering Leptin, Ghrelin, and Galectin-3 expressions, there was no statistically significant difference in terms of postoperative status, BMI, metabolic syndrome, and hospital stay ($p>0.05$).

On the other hand, considering the operative conditions of the CABG patients such as CPB time, X-clamp time, and endarterectomy bypass count, there was no statistically significant difference in terms of Nefsatin-1, Leptin, Ghrelin, and Galectin-3 expressions ($p>0.05$) (Table 5).

Discussion

In this study, immunohistochemical expression of Nesfatin-1, Galectin-3, Ghrelin, and Leptin was investigated in pericardial adipose tissue and inflammatory cells that infiltrate the adipose tissue in patients undergoing CABG. Additionally, its relationship with the postoperative status, BMI, metabolic syndrome, and length of hospital stay was examined. Increased nefsatin-1 expression was associated with fewer post-operative complications, shorter intensive care unit length of stay, and lower metabolic syndrome risk. Patients with low BMI and high Nefsatin expression had a better post-operative clinical course.

Ghrelin is a 28 amino acid polypeptide hormone released from the fundus of the stomach. Clinical studies have reported that ghrelin has potentially beneficial cardiovascular effects such as reduction of mean arterial

Table 1. Descriptive information and postoperative conditions of the patients

	n	%
Gender		
Male	36	72
Female	14	28
Body mass index (BMI)		
BMI above 25	31	62
BMI below 25	19	38
Post-operative status		
Insulin dependent diabetes mellitus	16	32
Arrhythmia	11	22
Renal failure	1	2
Respiratory failure	1	2
Atrial fibrillation	2	4
Low cardiac output syndrome	9	18
Mortality	1	2
None	16	32
Length of stay in hospital (days)		
Length of stay in intensive care	3.1±1	
Total length of stay	9.2±3	
Metabolic syndrome (MetS)		
MetS (-)	32	64
MetS (+)	18	36

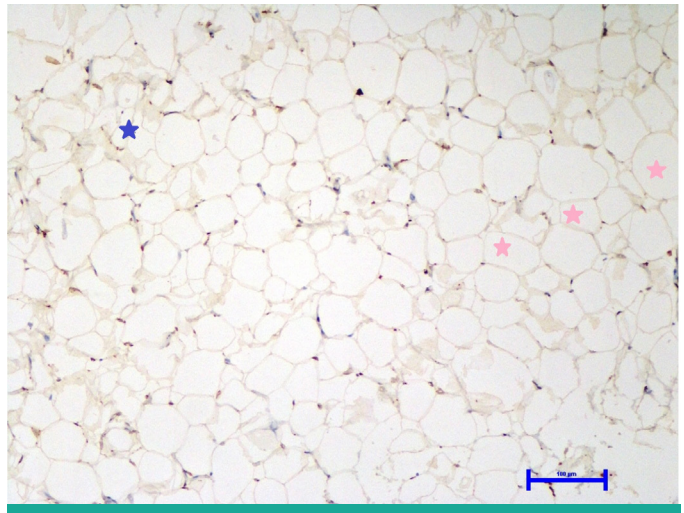

Figure 1a. Low Nesfatin expression in pericardial adipose tissue (pink stars) and inflammatory cells (blue stars), (Nesfatin-1 antibody, 100x)

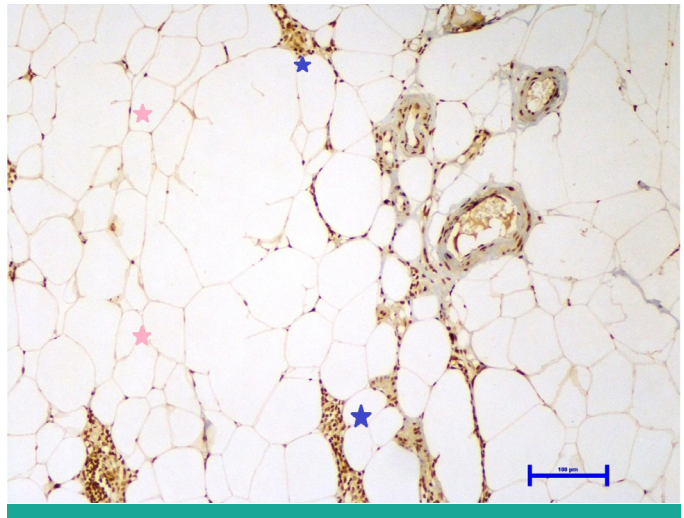

Figure 1b. High Nefsatin expression in adipocytes and inflammatory cells (Nesfatin-1 antibody, 100x)

blood pressure, increase in myocardial contractility, protection of endothelial cells, and improvement of energy metabolism of myocardial cells (12). Clinical studies have shown that the administration of exogenous ghrelin results in improvement in coronary flow, heart rate, dilatation of peripheral blood vessels, narrowing of the coronary arteries, and ventricular and endothelial function. Exogenous ghrelin administration has also been reported to reduce muscle wasting in heart failure, improve exercise capacity, inhibit cardiomyocyte apoptosis, inhibit sympathetic nerve activity, and protect against heart failure induced by myocardial infarction (12).

Table 2. Comparison of Nesfatin-1, Leptin, Ghrelin and Galectin-3 expressions in terms of length of stay in intensive care and hospital

	Length of stay in intensive care (mean/SD)	Total length of stay (mean/SD)
Nefsatin-1 positive	**2.6 days*/1.4**	8.4 days/3.4
Nefsatin-1 negative	4.1 days/1.4	10.8 days/3.5
Leptin positive	2.9 days/1.4	8.8 days/3.3
Leptin negative	3.3 days/1.3	9.6 days/3.3
Ghrelin positive	3.1 days/1.3	9.1 days/3.4
Ghrelin negative	3.2 days/1.4	9.7 days/3.4
Galectin-3 positive	3 days/1.5	8.5 days/3.7
Galectin-3 negative	3.1 days/1.4	9.3 days/3.4

*Statistically significant, SD: Standard deviation

Table 3. Comparison of Nefsatin-1 expression positive patients in terms of metabolic syndrome and comparison of Nefsatin-1 expression and BMI in patients

	Nefsatin-1	
	Positive	**Negative**
BMI above 25	19 (61.3%)	12 (38.7%)
BMI below 25	**13 (68.4%)***	6 (31.6%)
MetS (-)	**20 (76.9%)***	6 (23.1%)
MetS (+)	12 (50%)	12 (50%)

*Statistically significant, BMI: Body mass index, MetS: Metabolic syndrome

Table 4. Comparison of Nefsatin-1 expression and post-operative complication of the patients

	Post-operative complication	
	Yes	**No**
Nefsatin-1 positive	19 (59.4%)	**13 (40.6%)***
Nefsatin-1 negative	**16 (88.9%)***	2 (11.1%)

*Statistically significant

Table 5. Comparison of Nesfatin-1, Leptin, Ghrelin, and Galectin-3 expressions in terms of operative conditions of the coronary artery bypass graft patients

	Operative conditions										
	All patients	**Metabolic syndrome n (%)**		**Nefsatin -1 n (%)**		**Leptin n (%)**		**Ghrelin n (%)**		**Galectin-3 n (%)**	
	Average	MetS (-) 32 (64%)	MetS (+) 18 (36%)	Positive 32 (64%)	Negative 18 (36%)	Positive 20 (40%)	Negative 30 (60%)	Positive 41 (82%)	Negative 9 (18%)	Positive 4 (8%)	Negative 46 (92%)
CPB time	52.4	52.8	52.6	51.4	51.1	56.5	49.1	53.4	52.2	51.1	53.2
X-clamp time	33	32.9	33.4	32.3	34.4	31	30.8	33.2	32.3	33.2	33.6
Endarterectomy	5 patient	3 patient	2 patient	1 patient	4 patient	3 patient	2 patient	4 patient	1 patient	1 patient	4 patient
By-pass count	2.6	2.6	2.6	2.6	2.5	2.5	2.4	2.6	2.4	2.4	2.6

Leptin, a major regulator of fat and energy storage in mammals, on the other hand, acts on hypothalamic receptors to increase energy expenditure and decrease food intake. Plasma leptin levels are closely associated with fat mass and decrease with weight reduction (13).

Galectin-3 is a carbohydrate-binding protein with a molecular weight of 29-35 kDa, depending on the type. It is similar to Bcl-2 protein, which has an anti-apoptotic role in cells. Due to its structural similarity with Bcl-2, galectin-3 has also been reported to have anti-apoptotic properties (4). Galectin-3 is a pro-inflammatory protein and plays a role in T-cell mediated inflammation. Studies have shown that Galectin-3 plays a role in the emergence of acute coronary syndromes such as myocardial infarction. Therefore, an increased galectin-3 amount may be a determinant in the prognosis and diagnosis of the disease, since increased inflammation in acute coronary syndromes adversely affects the prognosis (14,15).

Nesfatin-1 is very commonly expressed in peripheral tissues, including the adipose tissue, pancreas, kidney, liver, and gut. Nesfatin-1 has important metabolic functions such as gastrointestinal function, glucose homeostasis, water intake, temperature regulation, water intake, and sleep (16). Nesfatin-1 is an anorexigenic factor. Satiety triggers are drug targets of weight loss to reduce obesity-related diseases. Nesfatin-1 is thought to be post-translationally processed into the bioactive Nesfatin-1 peptide, which induces satiety, induces weight loss, and thus improves insulin sensitivity (16). Studies have shown that chronic intracerebroventricular injection of Nesfatin-1 reduces body weight in rats, while animals gain body weight following intracerebroventricular injection of antisense morpholino oligonucleotide against the gene encoding Nesfatin-1 (17). Yang et al. (18) found that Nesfatin-1 knockout mice exhibited low insulin secretion and late-onset blood glucose elevation as well as elevated blood glucose in the glucose tolerance test, revealing the role of pancreatic β-cell-produced nesfatin-1 for the automatic maintenance of insulin secretion by pancreatic β-cells. In their study, Ravussin et al. (16) showed that following a high-fat diet, loss of Nesfatin-1 exacerbated metabolic inflammation in adipose tissue macrophages in an NFkB-dependent manner without inducing classical M1 or alternative M2-like macrophage polarization. They also found that deletion of Nesfatin-1 did not affect food intake or adiposity and instead caused insulin resistance in mice fed a high-fat diet (16).

Slow coronary flow (SCF) is an important coronary angiographic phenomenon characterized by delayed progression of angiographic contrast agent in coronary arteries in the absence of obstructive CAD. A study showed that serum Nesfatin-1 level was lower in the SCF group than in the normal coronary flow group. Nesfatin-1 may play a role in the pathogenesis of the SCF phenomenon by mechanisms such as inflammation and endothelial dysfunction (19). In a study, myocardial infarction was induced in rats by subcutaneous injection of isoproterenol, and then the intraperitoneal administration of Nesfatin-1 revealed a significant cardioprotective activity by reducing cardiac troponin-T and pro-inflammatory cytokine levels, and thus the protective effect of Nesfatin-1 against isoproterenol-induced MI was demonstrated (20).

Recent studies have revealed that Nesfatin-1 expression in peripheral tissues including the heart, spinal cord, pancreas, islets, stomach and adipose tissue has crucial physiological roles in body weight and also contributes to the pathophysiology of insulin resistance and associated metabolic problems such as obesity and diabetes (8,21,22).

The anorexigenic and anti-hyperglycemic properties of Nesfatin-1 significantly affect both food intake and glucose metabolism in the body's metabolic regulation (8). Studies examining the relationship between obesity and Nesfatin-1 have shown that plasma Nesfatin-1 levels are associated with BMI, body weight, and fat mass. Peripheral administration of Nesfatin-1 has been proven to have an antihyperglycemic effect on glucose metabolism (23). Nesfatin-1 has a role in glucose homeostasis as a negative regulator of glucose levels and is also important in energy expenditure by increasing thermogenesis (24). Nesfatin-1 is thought to be a pioneer in the diagnosis and treatment of diseases such as metabolic syndrome, obesity, diabetes, and cardiovascular disease (23). Although there exist several studies on the issue, additional studies on Nesfatin-1 in the management of metabolic diseases, especially for type-2 diabetes and obesity, are needed.

In most people, the body weight is maintained in a balanced state and can remain the same for many years. To have a stable weight, there must also be a balance of energy. Energy intake should equal energy expenditure. However, when the energy balance is disturbed, as in obesity, constant weight problems may emerge. The obese and overweight population has been increasing rapidly as one of the important consequences of a high-energy diet that is rich in fat. An increasing number of people, including children, are becoming obese (25). Obesity adversely affects cardiac

hemodynamics, structure, and function. Furthermore, it causes systolic and especially diastolic left ventricular dysfunction. Therefore, it is not surprising that obesity significantly increases the prevalence of heart failure (9). Studies have shown that the most effective treatment is provided by a combination of diet and exercise (26). Since diet and exercise have important effects on energy homeostasis, the use of therapeutic drugs alone does not seem sufficient to treat obesity.

Conclusion

Recent years have witnessed a huge increase in our knowledge of the effects of Nesfatin-1 and the mechanisms underlying them. Finally, the therapeutic potential of Nesfatin-1 in these diseases should be further explored to encourage further studies. On the other hand in this study, we aimed to show the importance of Nesfatin-1 in CABG patients. Further studies can research biochemical or epigenetic changes. Identification of the as yet unknown Nesfatin-1 receptor will enable us to better explore the effects underlying its different actions, which will be a major step forward in understanding the physiology of Nesfatin-1.

Ethics

Ethics Committee Approval: In this study, the investigation protocol was in accordance with the Helsinki Committee requirement and approved by the Ethical Committee of Balıkesir University (decision no: 2017/47).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.A., A.S.A., E.Av., Design: E.A., A.S.A., E.Av., Data Collection or Processing: E.A., A.D., Analysis or Interpretation: E.A., A.D., Drafting Manuscript: E.A., A.S.A., E.Av., Final Approval and Accountability: E.A., A.S.A., E.Av., A.D., Technical or Material Support: E.A., A.D., E.Av., Supervision: E.A., A.D., Writing: E.A., A.S.A., A.D., E.Av.

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

Financial Disclosure: This study was supported by the Scientific Research Projects Unit of Balıkesir University (BAP 2017/202).

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ORIGINAL RESEARCH

Bagcilar Med Bull 2023;8(2):135-139
DOI: 10.4274/BMB.galenos.2023.2022-11-101

Analysis of Ovarian Pathology in Children: Ten-years Experience

Çocuklarda Over Patolojilerinin Analizi: On Yıllık Deneyim

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Abstract

Objective: In this study, we aimed to analyze whether laparoscopy is a feasible and safe surgical option for ovarian pathologies in children.

Method: Our study included 43 patients who were followed up and treated for ovarian pathology in our clinic between January 1, 2012, and January 1, 2022. The clinical information and data for the patients were reviewed retrospectively. The patients were divided into 2 groups: Laparoscopy and the laparotomy group. Demographic data of the patients, complaints at presentation, localization of the mass, laboratory hormone levels and surgical findings, histopathological diagnoses, treatment methods, and treatment results were evaluated.

Results: In the study, 43 female patients with a mean age of 9.6 years (1 month-15 years) were evaluated. It was the most common on the right side (58%). The most common symptom was abdominal pain (70%). Thirteen (30%) patients had acute abdomen findings. For surgical intervention, laparoscopy was performed in 22 (51%) patients and laparotomy was performed in 19 (44%) patients. Unilateral oophorectomy or salpingo-oophorectomy was performed in 28 (65%) of the patients as surgical treatment. Twenty-three (53%) of the ovarian pathologies were neoplastic, and 20 (47%) patients were non-neoplastic. Pathological diagnoses of ovarian pathologies 19 (44%) patients had ovarian torsion and 14 (33%) patients had teratoma. The operation time was shorter in the laparoscopy group ($p<0.05$). Tumor size was smaller in the laparoscopy group and larger in the conventional laparotomy surgery group ($p<0.05$). There was no significant difference between the laparoscopy group and the laparotomy surgery group in terms of age, tumor size, malignancy status, the presence of neoplastic mass, laterality, and tumor markers ($p>0.05$). While 42 of 43 patients survived, one patient with immature teratoma died from tumor-associated metastasis.

Öz

Amaç: Bu çalışmada, çocuklarda over patolojilerinde laparoskopinin uygulanabilir ve güvenli bir cerrahi seçenek olup olmadığını incelemeyi amaçladık.

Yöntem: Çalışmamıza 1 Ocak 2012-1 Ocak 2022 tarihleri arasında kliniğimizde over patolojisi nedeniyle takip ve tedavi edilen 43 hasta dahil edildi. Hastaların klinik bilgileri ve verileri retrospektif olarak incelendi. Hastalar laparoskopi ve açık grup olarak 2 gruba ayrıldı. Hastaların demografik verileri, başvuru yakınmaları, kitlenin lokalizasyonu, laboratuvar hormon düzeyleri ve cerrahi bulguları, histopatolojik tanıları, tedavi yöntemleri ve tedavi sonuçları değerlendirildi.

Bulgular: Çalışmada yaş ortalaması 9,6 (1 ay-15 yaş) olan 43 kadın hasta değerlendirildi. En sık sağda (%58) görüldü. En sık semptom karın ağrısıydı (%70). On üç (%30) hastada akut karın bulguları vardı. Cerrahi girişim için 22 (%51) hastaya laparoskopi ve 19 (%44) hastaya laparotomi uygulandı. Hastaların 28'ine (%65) cerrahi tedavi olarak unilateral ooferektomi veya salpingo-ooferektomi uygulandı. Over patolojilerinin 23'ü (%53) neoplastik, 20 (%47) hasta neoplastik değildi. Over patolojilerinin patolojik tanıları 19 (%44) hastada over torsiyonu, 14 (%33) hastada teratom vardı. Ameliyat süresi laparoskopi grubunda daha kısaydı ($p<0,05$). Tümör boyutu laparoskopi grubunda daha küçük, konvansiyonel açık cerrahi grubunda daha büyüktü ($p<0,05$). Laparoskopi grubu ile laparatomi grubu arasında yaş, tümör boyutu, malignite durumu, neoplastik kitle varlığı ve tümör belirteçleri açısından anlamlı fark yoktu ($p>0,05$). Kırk üç hastanın 42'si hayatta kalırken, immatür teratomlu bir hasta tümör ilişkili metastaz nedeniyle kaybedildi.

Sonuç: Over patolojilerinin büyük çoğunluğu benign olmasına rağmen malign kitleler oluşabileceğinden cerrahi mümkün olduğunca erken yapılmalıdır. İyi huylu olduğu düşünülen lezyonlarda mümkün olduğunca

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Cite this article as: Arslan S, Basuguy E, Aydoğdu B, Özçelik Otçu SM, Salık F, Okur MH. Analysis of Ovarian Pathology in Children: Ten-years Experience. Bagcilar Med Bull 2023;8(2):135-139

Abstract

Conclusion: Although the majority of ovarian pathologies are benign, since malignant masses may occur, surgery should be performed as early as possible. In lesions that are thought to be benign, ovarian-sparing surgery should be performed as much as possible. Laparoscopy is a feasible and safe surgical option for ovarian pathologies even, in malignant patients.

Keywords: Children, laparoscopy, ovary, pathology

Öz

yumurtalık koruyucu cerrahi yapılmalıdır. Laparoskopi, malign hastalarda bile over patolojileri için uygulanabilir ve güvenli bir cerrahi seçenektir.

Anahtar kelimeler: Çocuklar, laparoskopi, over, patoloji

Introduction

Ovarian pathologies can be cystic, complex, or solid. Ovarian cysts may be physiological, secondary to polycystic ovarian syndrome or infections. Most neoplasms in puberty or adolescence are benign. Many of these may be in the form of cystadenomas, mature teratomas, and serous cystadenomas. Malignant ovarian tumors are rare in children (1,2).

Ovarian pathologies are detected more frequently with the widespread use of imaging methods. While asymptomatic cases can be detected by routine ultrasonography, most of them are detected with complications. Adnexal masses are evaluated according to age, clinical symptoms, size, and complexity of the mass (3).

Detection of these pathologies in children, early intervention, and, if possible, the preservation of the ovary are important for future fertility. Since the ovarian pedicle is long in children, ovarian pathologies tend to be more torsioned compared to adults (1,2).

Ovarian pathologies can be treated with laparotomy surgery as well as frequently with laparoscopy. In this study, we aimed to analyze whether laparoscopy is a feasible and safe surgical option for ovarian pathologies in children.

Materials and Methods

In our study, 43 patients who were followed up and treated for ovarian pathology in our clinic between January 1, 2012 and January 1, 2022 were included in the study. The ethics committee of the study was accepted by the Dicle University Local Ethics Committee (ethics committee date: 14.04.2022, number: 127). Consent was obtained from all the patients included in the study.

Ultrasonography was performed primarily in symptomatic patients. Computed tomography examination was also performed in patients with an ovarian mass. In addition, complete blood count, biochemistry and alpha-fetoprotein (AFP), beta HCG, and Ca-125 levels were checked.

Regardless of the diagnosis of the patients in the preoperative period, laparoscopy was planned for patients with low tumor size (<8 cm), and laparotomy surgery was planned for patients with high tumor size (>8 cm). In only 2 patients, laparoscopy was terminated and converted to laparotomy surgery. Laparoscopy was started with 11.5 thoracoport-assisted single incision laparoscopic (SILS), starting from the umbilical incision. While 50% of the laparoscopy group was completed with SILS, additional ports were needed in the other half and additional ports were entered.

The clinical information and data for the patients were reviewed retrospectively. Demographic data of the patients, complaints at presentation, localization of the mass, laboratory hormone levels and surgical findings, histopathological diagnoses, treatment methods, and treatment results were evaluated.

Inclusion Criteria

Patients whose data were correct and consistent in retrospective patient file scanning were included in our study.

Exclusion Criteria

Patients with incomplete and inconsistent data in retrospective patient file screening were excluded from the study. In addition, patients who were noted as ovarian pathology on ultrasound but who had duplication cysts and mesenteric cysts during surgery were excluded from the study.

Statistical Analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics and frequency, was performed for all items. Continuous data are expressed as

mean ± standard deviation. The continuous variables were investigated using Shapiro-Wilk test to determine whether the data had a normal distribution. Continuous, normally distributed variables were compared using Student's t-test. Non-parametric tests were chosen when the data did not fit the normal distribution. The categorical variables were assessed by the chi-square test or Fisher's Exact test, as needed. Analyses were performed using SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). All p-values were two-sided and p≤0.05 was considered statistically significant.

Results

A total of 43 female patients were evaluated in the study, and the mean age was 9.6 years (1 month-15 years). Twenty-five (58%) of the ovarian masses were on the right side and 18 (42%) were on the left side. No bilateral ovarian mass was found. Thirty (70%) patients had abdominal pain, and 13 (30%) had abdominal distension. As physical examination findings, 30 (70%) patients had abdominal tenderness and a palpable mass. Thirteen (30%) patients had acute abdomen findings. In our study, AFP beta HCG, CEA, and Ca-125 were measured, and among these markers, AFP was increased in one of the 5 patients with malignant ovarian tumors, beta HCG in one, and Ca-125 in one. Of the ovarian pathologies, 23 (53%) were neoplastic, 20 (47%) patients were non-neoplastic, with 18 having ovarian torsion and 2 having cystic components. Unilateral oophorectomy or salpingo-oophorectomy was performed in 28 (65%) of the patients as surgical treatment. Ovarian sparing surgery was performed in 7 patients (16%). The ovaries of four (9%) patients were autoamputee. Four (9%) patients underwent ovarian detorsion. Pathological diagnoses of ovarian pathologies were primary ovarian torsion in 18 (42%) patients, mature teratoma in 14 (32%) patients, serous cyst adenoma in three (7%) patients, dysgerminoma (malignant) in two (5%) patients, yolk sac (malignant) in one (2%), dystrophic calcification in one (2%) patient, hematoma in one (2%) patient, mature adipose tissue in one (2%) patient, immature teratoma in one (2%) patient (malignant), and adenocarcinoma in one (20%) patient (malignant) (Table 1).

Laparoscopy was performed in 22 (51%) patients and laparotomy was performed in 19 (44%) patients for surgical intervention in patients with ovarian pathology. Two (5%) patients were started with laparoscopy and converted to laparotomy. The operation time was shorter in the laparoscopy group (p<0.05). Tumor size was smaller in the laparoscopy group compared to laparotomy (p<0.05). Tumor size was 5.7±3.4 in the laparoscopy group and 10.7±47.2 in the laparotomy group which was statistically significant (p<0.05).

There was no significant difference between the laparoscopy group and the conventional laparotomy surgery group in terms of age, malignancy status, the presence of neoplastic mass, laterality, and tumor markers (p>0.05) (Table 2).

While 42 of 43 patients were alive in our study, one patient with immature teratoma had metastasized. Although chemotherapy procedures were initiated, she died during the treatment phase due to malignant tumor metastasis.

Table 1. Patient characteristics

		n=43	%
Side	Right	25	58.
	Left	18	42.
Symptoms	Abdominal pain	30	70
	Distension	13	30
Findings	Tenderness	30	70
	Acute abdomen	13	30
Surgical approach	Laparoscopy	22	51
	Laparotomy	19	44
	Converted to laparotomy	2	5
Surgical procedure	Oopherectomy/salpingo-oophorectomy	28	65
	Ovarian-sparing surgery	7	16
	Autoamputed ovary	4	9
	Ovarian detorsion	4	9
Neoplasia	Neoplastic	23	53
	Non-neoplastic	20	47
Neoplastic	Benign	18	78
	Malignant	5.	22
Non-neoplastic	Ovarian torsion	18.	90
	Cystic component	2.	10
Histopathological diagnosis	Ovarian torsion	18	42
	Mature teratoma	14	32
	Immature teratoma	1	2
	Serous cyst adenoma	3	7
	Disgerminoma	2	5
	Yolk sac	1	2
	Dystrophic calcification	1	2
	Hematoma	1	2
	Adenocarcinoma	1	2
	Mature adipose tissue	1	2
Mortality	No	42	98
	Yes	1	2

Table 2. Comparison of laparoscopy and laparotomy surgery group

	Laparoscopy (n=22)	Laparotomy (n=21)	p-value
Age (year)	8.4±5.2	10.6±4.3	>0.05
Operation time (min)	55.6±18.2	75.2±21.8	**<0.05**
Tumour size (cm)	5.75±3.43	10.70±47.2	**<0.05**
Right	12	13	>0.05
Left	9	9	
Neoplastic	10	13	>0.05
Non-neoplastic	12	8	
Malignant	2	3	>0.05
Benign	10	8	
Oopherectomy	14	14	>0.05
Ovarian sparing surgery	3	4	
High AFP	3	2	>0.05
High B-hCG	0	1	>0.05
High CEA	0	0	>0.05
High Ca-125	1	0	>0.05
Mortality	0	1	>0.05

AFP: Alpha-fetoprotein

Discussion

While benign pathologies are common in children and adolescents, malignant adnexal masses are less common in this age group. In our study, more benign pathologies were observed. Abdominal pain is seen in 57-69% of patients with ovarian pathologies. In our study, similar to the literature, abdominal pain was observed in 70% of the patients. Ovarian torsion is more common on the right side. Therefore, patients mostly present with right lower quadrant pain and are confused with acute appendicitis (2-6).

Tumor markers may increase in malignant germ cell tumors and epithelial tumors. It is used in the follow-up of patients. These hormones are usually normal in ovarian cysts. However, these values should not be neglected in malignant tumors. AFP, beta HCG, Ca-125, CA-19.9, and CEA values should be checked in patients with suspected malignancy (2). In our study, in 5 patients with malignant ovarian tumors, AFP increased in one, beta HCG in one, and Ca-125 in one.

In the study of Xac et al. (5), the mean size of benign masses was 7.3 cm, and the mean size of malignant tumors was 14 cm. In our study, the mean size of benign neoplastic tumors was 8.4 cm, and the mean size of malignant ovarian tumors was 10.6 cm.

The main goal of ovarian masses and torsions should be to perform ovarian-sparing surgery in the early period. Banlı-Cesur et al. (2) in the study, 24% of ovarian masses were treated with oophorectomy. Oophorectomy was performed in 52% of them due to ovarian torsion (2). In a study, 85-100% of patients were treated with oophorectomy (7-9). In our study, 28 (65%) patients underwent unilateral oophorectomy or salpingo-oophorectomy as surgical treatment. Ovarian sparing surgery was performed in 7 (16%) patients. Although our main goal in surgery is surgery to protect the ovary, irreversible ovarian damage has occurred due to the high number of patients with late diagnoses due to the socio-economic status in our region. Therefore, our oophorectomy rate is higher than in the literature.

There is a rare association between malignant lesions and ovarian torsion. This rate varies between 1-6%. Ovarian torsion is mostly associated with germ-cell tumors (10-13). It was determined as 2.7% in one study. Malignant ovarian tumors were seen in 4 (3.5%) of 114 patients (2,7). In our study, 5 malignant ovarian tumors were seen. One of them (20%) presented with ovarian torsion.

The rate of neoplastic ovarian cysts in the literature ranges between 50-70% (8-13). In our study, 23 (54%) of 43 patients were neoplastic. Of these, 18 (78%) were benign and 5 (22%) were malignant.

In studies conducted in adults, ovarian cancers are mostly of epithelial origin. In children, ovarian tumors are usually germ-cell tumors. Mature teratomas from germ cell tumors are common in children because they are slow

and frequently growing tumors (1). In our study, mature teratoma was observed at a rate of 32%. While 42 of 43 patients were alive in our study, the patient with immature teratoma died due to malignant tumor metastasis during the treatment process.

In the study of Xac et al. (5), 61% of ovarian masses were switched to laparoscopy, 25% to laparotomy, and 6.8% to laparoscopy from laparotomy. In our study, laparoscopy was performed in 51%, laparotomy was performed in 44%, and laparoscopy was started in 2 of our patients and switched to laparotomy. Our laparoscopy rate is lower than in the literature. We think that the reason is due to the large solid mass measurements. Regardless of the diagnosis of the patients in the preoperative period, laparoscopy was planned for patients with low tumor size, and laparotomy surgery was planned for patients with high tumor size. Laparoscopy was started with 11.5 thoracoport-assisted SILS, starting from the umbilical incision. While 50% of the laparoscopy group was completed with SILS, additional ports were needed in the other half and additional ports were entered. In the SILS group, the surgical scar was only in the navel, that is, it was the scarless method. Therefore, the patients were quite satisfied in this respect. In our study, when malignant patients and benign patients were compared according to the type of surgery performed (laparoscopy vs traditional laparotomy surgery), no difference was observed. From this point of view, we believe that laparoscopy can be safely performed even on malignant patients.

Conclusion

Although the majority of ovarian pathologies are benign, since malignant masses may occur, surgery should be performed as early as possible. In lesions that are thought to be benign, ovarian-sparing surgery should be performed as much as possible. Laparoscopy is a feasible and safe surgical option for ovarian pathologies, even in malignant patients.

Ethics

Ethics Committee Approval: The ethics committee of the study was accepted by the Dicle University Local Ethics Committee (ethics committee date: 14.04.2022, number: 127).

Informed Consent: Consent was obtained from all patients included in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: S.A., M.H.O., Design: S.A., S.M.Ö.O., F.S., M.H.O., Data Collection or Processing: E.B., B.A., S.M.Ö.O., F.S., M.H.O., Analysis or Interpretation: E.B., B.A., S.M.Ö.O., F.S., Literature Search: E.B., B.A., Writing: S.A., E.B., B.A., S.M.Ö.O., F.S., M.H.O.

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

Bagcilar Med Bull 2023;8(2):140-149
DOI: 10.4274/BMB.galenos.2023.2023-01-02

Multi-database Based Study of the Pharmacological Mechanisms of Resveratrol in the Treatment of Early Hepatocellular Carcinoma

Erken Hepatoselüler Karsinom Tedavisinde Resveratrolün Farmakolojik Mekanizmalarına İlişkin Çoklu Veritabanı Temelli Çalışma

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Abstract

Objective: To analyze the main target genes, key pathways and their mechanisms of action of resveratrol in the treatment of early hepatocellular carcinoma based on multiple databases using a network pharmacology approach.

Method: The targets of resveratrol was obtained from the Swiss Target Prediction database; the targets of early hepatocellular carcinoma were obtained from the GeneCards, OMIM and DisGent databases. The compound-target-disease network was constructed using Cytoscape software; the protein interaction network was constructed using STRING database; GO function and KEGG pathway enrichment analysis were performed in R language.

Results: Sixty-nine potential targets for resveratrol were obtained through the Swiss Target Prediction database. Searching and de-duplicating the disease database yielded 9682 disease targets for early hepatocellular carcinoma. Seven hundred and fifty four entries were obtained from GO functional enrichment analysis and 99 statistically significant pathways were obtained from KEGG enrichment analysis.

Conclusion: The mechanism of action of resveratrol for early hepatocellular carcinoma is a multi-target, multi-pathway interaction. The receptors may be related to SRC, CYP3A4, PIK3CA, CYP1A1, RELA, ESR1 and other targets, and the major signalling pathways may be related to Ovarian steroidogenesis, steroid hormone biosynthesis, chemical carcinogenesis-receptor activation, endocrine resistance, chemical carcinogenesis-DNA adducts, nitrogen metabolism, hepatocellular carcinoma, etc. It provides a theoretical basis for the next in-depth experimental study.

Keywords: Bioinformatics, early hepatocellular carcinoma, multi-database, pharmacological mechanism, resveratrol

Öz

Amaç: Resveratrolün erken hepatoselüler karsinomun tedavisinde ana hedef genlerini, anahtar yolaklarını ve bunların etki mekanizmalarını bir ağ farmakolojisi yaklaşımı kullanarak çoklu veritabanlarına dayalı olarak analiz etmektir.

Yöntem: Resveratrolün hedefleri, İsviçre Hedef Tahmini veritabanından elde edildi; erken hepatoselüler karsinomun hedefleri GeneCards, OMIM ve DisGent veritabanlarından elde edildi. Bileşik hedef hastalık ağı, Cytoscape yazılımı kullanılarak oluşturuldu; protein etkileşim ağı, STRING veritabanı kullanılarak oluşturuldu; GO işlevi ve KEGG yolağı zenginleştirme analizi, R dilinde gerçekleştirildi.

Bulgular: İsviçre Hedef Tahmini veritabanından resveratrol için altmış dokuz potansiyel hedef elde edildi. Hastalık veritabanının taranması ve kopyalanması, erken hepatoselüler karsinom için 9682 hastalık hedefi ortaya koydu. GO fonksiyonel zenginleştirme analizinden 754 giriş elde edildi ve KEGG zenginleştirme analizinden istatistiksel olarak anlamlı 99 yolak elde edildi.

Sonuç: Resveratrolün erken hepatoselüler karsinom için etki mekanizması, çok hedefli, çok yolaklı bir etkileşimdir. Reseptörler, SRC, CYP3A4, PIK3CA, CYP1A1, RELA, ESR1 ve diğer hedeflerle ilişkili olabilir ve ana sinyal yolakları, hepatoselüler karsinoma yolağı, PD-L1 ekspresyonu ve PD-1 kontrol noktası yolağı ile ilişkili olabilir. Kolin metabolizma yolağı, merkezi cabon metabolizma yolağı ve diğer yolaklar. Bir sonraki derinlemesine deneysel çalışma için teorik bir temel sağlar.

Anahtar kelimeler: Biyoinformatik, çoklu veritabanı, erken hepatoselüler karsinom, farmakolojik mekanizma, resveratrol

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Cite this article as: Si W. Multi-database Based Study of the Pharmacological Mechanisms of Resveratrol in the Treatment of Early Hepatocellular Carcinoma. Bagcilar Med Bull 2023;8(2):140-149

Introduction

Resveratrol is a compound found in grape skins, red wine, peanuts and certain berries. It has antioxidant properties that may help protect against cell damage and disease (1). Resveratrol has also been studied for its potential anti-aging and anti-inflammatory effects. In addition, research suggests that resveratrol may help protect against heart disease, improve cognitive function and physical performance, and have anti-cancer properties (2).

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer. It is a fast-growing cancer that starts in the cells of the liver and can spread to other organs. Risk factors for HCC include HBV or C infection, cirrhosis of the liver, excessive alcohol consumption, smoking, obesity and diabetes (3). Symptoms can include abdominal pain, weight loss and jaundice. Diagnosis is made using imaging tests such as computed tomography or magnetic resonance imaging scans, liver function tests and a biopsy. Treatment options include surgery, ablation therapy (destroying tumour cells with heat or cold), radiotherapy (using high-energy X-rays) and chemotherapy (drugs to kill cancer cells). According to statistics, more than 572,000 people are affected each year. The incidence rate has been increasing over time, particularly in parts of Africa, Asia, Eastern Europe and South America (4). In some countries, such as China and Japan, HCC accounts for nearly 40% of all cancers reported each year. The highest incidence rates occur in regions where chronic hepatitis B (HBV) infection is most prevalent. It is estimated that 90-95% of HCC cases are due to HBV or hepatitis C (HCV) (5). The mortality rate for HCC varies widely by geographical region. Worldwide, more than 400,000 people are estimated to die from this form of cancer each year (6). This makes HCC one of the leading causes of cancer death worldwide. In some countries with a high prevalence of HBV/HCV infection, such as China and India, HCC accounts for nearly 80% of all liver cancer deaths (7). Treatment options for HCC depend on several factors, including stage at diagnosis, tumour size and location in the liver, as well as the patient's age and general health. Surgery is often the first-line treatment for early-stage tumours (8,9). However, this option may not always be feasible due to comorbid conditions or other factors. For more advanced stages or tumours that are not suitable for surgery, other treatments such as radiotherapy, systemic chemotherapy or targeted therapies may be used alone or in combination with surgery. Other newer treatments such as transarterial chemoembolization, radiofrequency ablation, stereotactic body radiation therapy, cryoablation and microwave ablation have also been used with varying success in certain cases where surgical resection is not possible or feasible (10). In addition, clinical trials are underway to test new approaches that aim to improve both outcomes and patient safety, while providing a better quality of life after treatment.

In this study, the potential targets of resveratrol for the treatment of early stage HCC were investigated using a network pharmacology approach based on multiple databases and related biological information and pathways. This study has laid the foundation for further research into the pharmacological mechanism of resveratro in the treatment of early HCC.

Materials and Methods

Target Screening of Resveratrol

The structure of resveratrol was searched in PubChem, database (11) (https://pubchem.ncbi.nlm.nih.gov/) using the keyword "resveratrol", and then the obtained structure information was searched in the Swiss Target Prediction database (12) (http://www.swisstargetprediction.ch/) to obtain the target information of resveratrol.

Disease Target Acquisition

The search term "Early Hepatocellular Carcinoma", "human" as the retrieval object, through the Genecards database (13) (https://www.genecards.org/),OMIM database (14) (https://www.omim.org/),DisGeNET database (15) (https://www.disgenet.org) obtain disease targets.

Acquisition of Intersectional Targets

Venny (https: //bioinfogp.cnb.csic.es/tools/venny/) software was used to create VEEN plots of compounds and diseases and to obtain intersection targets. Using intersecting targets as potential targets for resveratrol in early HCC (16).

Compound-target-disease Network Construction

Prepare compound gene "network" files and Type files, import the relevant files using Cytoscape software, and draw a "compound-target-disease" network map.

Protein Interaction (PPI) Network Construction and Network Topology Analysis

Using string (17) (https://string-db.org/) platform, import the intersecting targets, set the object as "homo sapiens"

with the highest confidence level of 0.900, hide the free gene nodes, and obtain the PPI relationship. The results were imported into Cytoscape software, and the network topology parameters were obtained by selecting "network analyzer" and analyzing the degree, betweenness centrality (BC) and closeness centrality (CC) of PPI network nodes. The degree value, BC and CC of the PPI network nodes were calculated. The top ten targets of degree value was used as key targets.

GO and KEGG Enrichment Analysis

Use bioinformatics open source software to install and run clusterProfiler (18), André et al. (19) packages in R language (3.5.1) for GO and KEGG enrichment analysis. And through the microscopic letter platform to visual display (https://www.bioinformatics.com.cn/). The enrichment analysis was performed to annotate resveratrol in terms of biological process (BP), cellular component (CC) and molecular function (MF) for the treatment of early hepatocellular carcinoma. The top 10 GO entries for BP, CCo and MF were filtered according to p-value size and plotted in bubble plots. cnetplot is part of the Gene-Concept Network, which describes the connections between genes and biological pathways as a network, allowing visualisation of the genes involved in these entries and the interacting genes between entries. Cnetplot is used to show the top 10 KEGG pathway interacting genes and Emapplot shows the overlap between the enriched pathways. Finally, the "compound-target-disease-KEGG pathway" network was mapped based on the relevant information.

Results

Natural Drug Active Ingredients, Diseases and Intersecting Targets

The Swiss target prediction database was searched and 69 resveratrol-related targets (Probability >0) were identified. By searching the GeneCards, OMIM and DisGENET databases, 9713 disease targets were screened, and 9451 targets were obtained after removing duplicate items. Using Venny software to intersect the TCM targets with the disease targets, 59 intersecting targets were obtained, which are the potential targets for resveratrol in the treatment of early HCC (Figure 1).

"Compound-component-target" Network Construction

The potential targets for resveratrol in early HCC were summarised and the information was mapped into a network using Cytoscape software. The network diagram had 61 nodes and 118 edges (Figure 2).

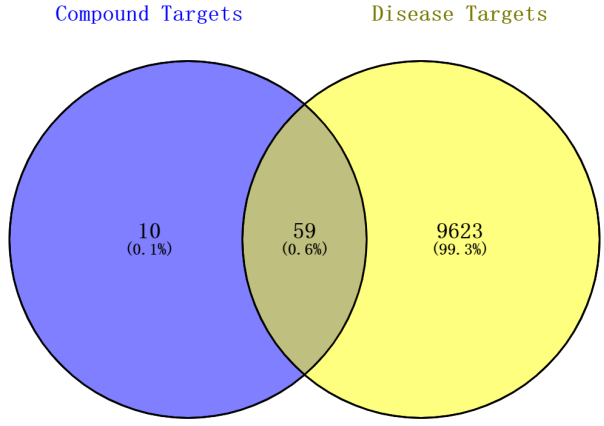


Figure 1. Intersection of drug targets and disease targets

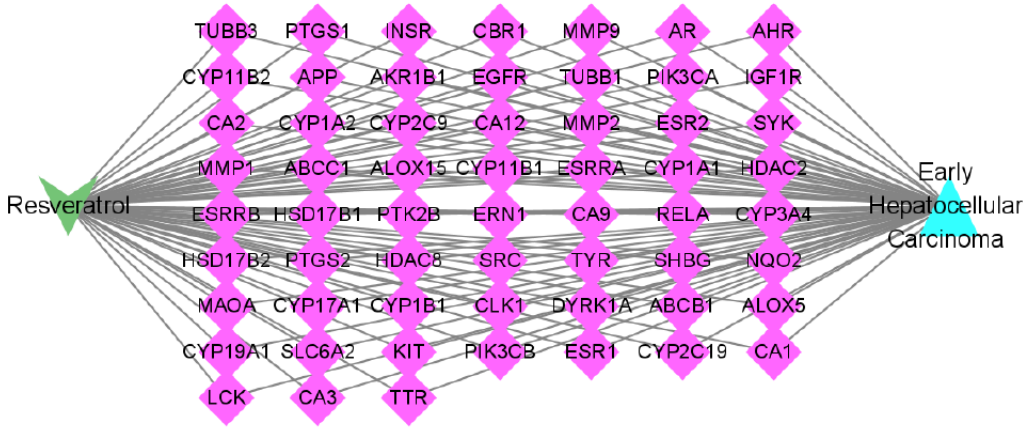


Figure 2. "Chinese herbal medicine-ingredient-target-disease" network diagram
(green represents compounds; purple represents targets: blue represents diseases)

PPI Network Construction and Network Topology Analysis

The topology of the PPI network was analysed using Cytoscape software and consisted of 8 nodes and 11 edges (Figure 3). The degree values of the compounds were analysed using the "network analyzer" plug-in. The key targets were sorted by degree size and listed in a table (Table 1). The SRC target had the highest degree value of 14.

GO and KEGG Enrichment Analysis

A total of 646 statistically significant pathways ($p<0.05$) were involved in the GO enrichment analysis (Figure 4), including 24 statistically significant BP entries, mainly related to olefinic compound metabolic process, cellular hormone metabolic process, Arachidonic acid metabolic process, icosanoid metabolic process, etc.; there were 178 statistically significant CC entries, mainly related to membrane raft, membrane microdomain, membrane region, membrane region, etc. Cytoplasmic side of plasma membrane, etc.; 84 statistically significant MF entries, mainly related to steroid hydroxylase activity, heme binding, tetrapyrrole binding, monooxygenase. KEGG enrichment analysis yielded 99 statistically significant pathways, mainly includes ovarian steroidogenesis, steroid hormone biosynthesis, chemical carcinogenesis-receptor activation, endocrine resistance, chemical carcinogenesis-DNA adducts, nitrogen metabolism, HCC, etc. And the top ten KEGG enrichment analyses are shown in Figure 5. The information on the top ten pathways analysed by KEGG enrichment is shown in Table 2. STAT3, VEGFA, HSP90AA1, FGF2, IL2, MET, BCL2L1, RORC et al. and multiple pathways all have an action relationship with each other, further suggesting the above as key targets. The Cnetplot diagram and Emapplot Diagram are shown in Figure 6.

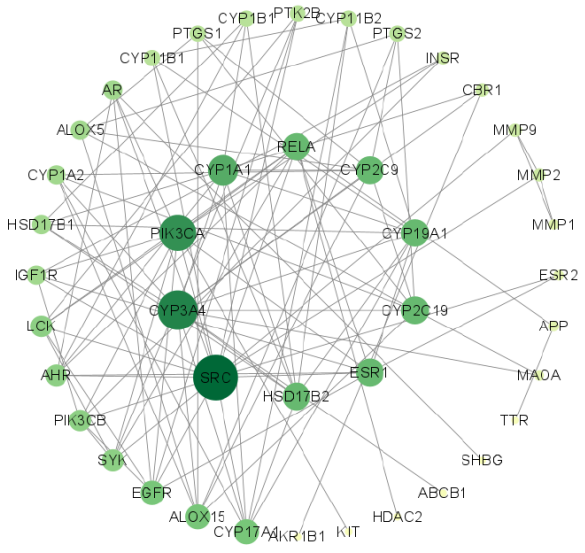


Figure 3. Topology analysis of the PPI network
PPI: Protein interaction

Discussion

The molecular mechanisms by which resveratrol exerts its anticancer effects are complex and involve various pathways. Resveratrol has been found to treat tumours by activating sirtuin family proteins (SIRT1-7), which are involved in regulating cellular stress responses, DNA repair and cell death. Resveratrol has been shown to induce cell cycle arrest, apoptosis and autophagy in cancer cells. In addition, resveratrol has been shown to inhibit angiogenesis, reduce blood supply to tumour cells, inhibit metastasis and regulate several pathways such as NF-kB and PI3K/Akt/mTOR to treat tumours (20).

Table 1. Table of key target information

Name	Degree	BC	CC
SRC	14	0.249149377	0.431578947
CYP3A4	12	0.217415796	0.39047619
PIK3CA	11	0.10011896	0.38317757
CYP1A1	9	0.267417115	0.436170213
RELA	8	0.168627213	0.401960784
ESR1	8	0.246560377	0.445652174
CYP2C9	8	0.116902386	0.344537815
CYP2C19	8	0.020897213	0.303703704
HSD17B2	8	0.018156214	0.362831858
CYP19A1	8	0.229654384	0.431578947

BC: Betweenness centrality, CC: Closeness centrality

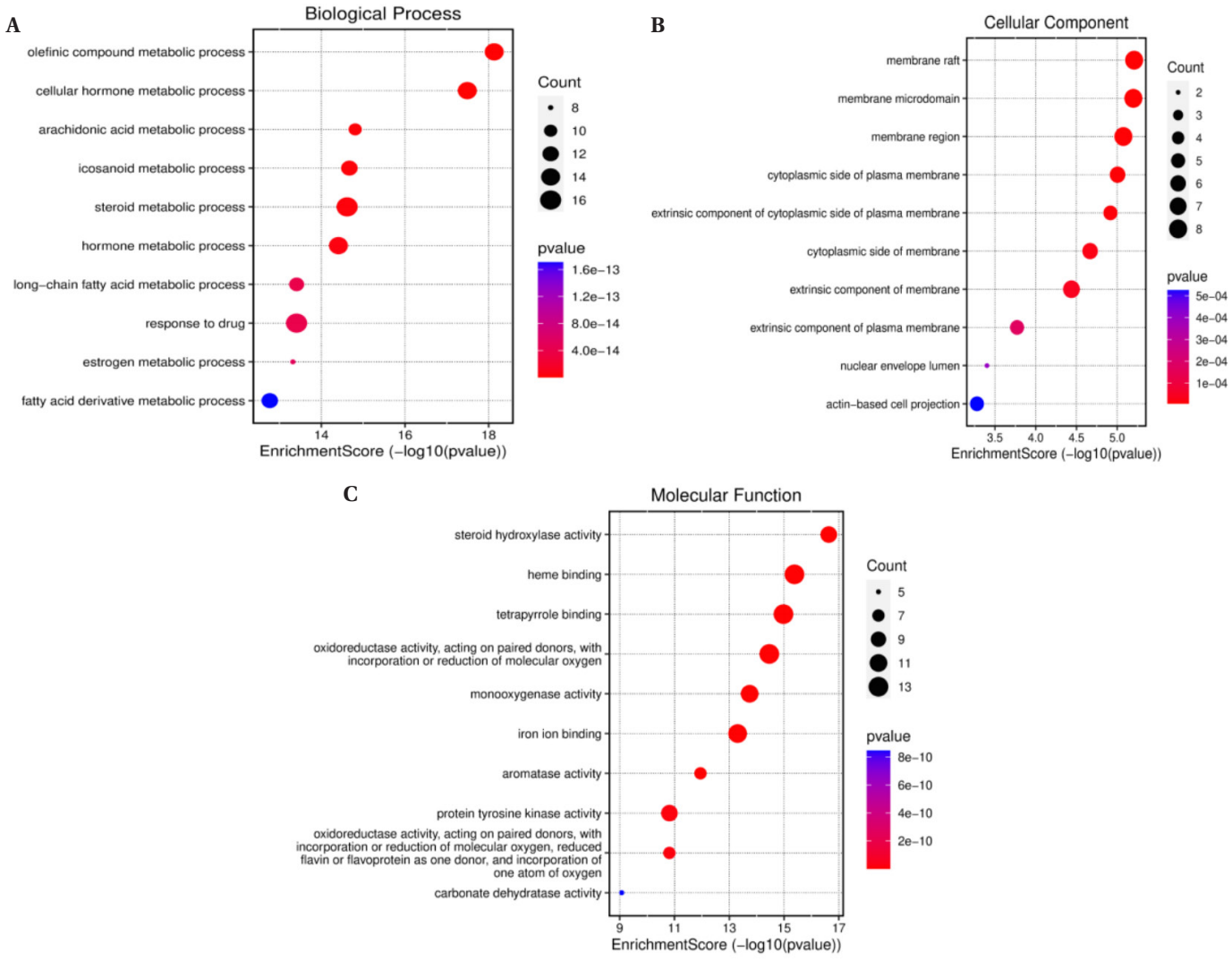


Figure 4. A) Bubble diagram of GO-BP enrichment analysis; **B)** Bubble diagram of GO-CC enrichment analysis; **C)** bubble diagram of GO-MF enrichment analysis

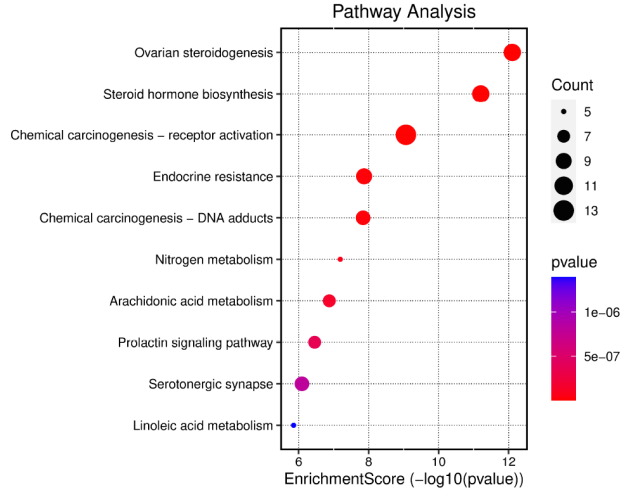


Figure 5. Bubble diagram of top ten KEGG enrichment analysis

Table 2. Top ten KEGG enrichment analysis data table

ID	Description	GeneRatio	p-value	Count
hsa04913	Ovarian steroidogenesis	10/55	7.85885E-13	10
hsa00140	Steroid hormone biosynthesis	10/55	6.25835E-12	10
hsa05207	Chemical carcinogenesis-receptor activation	13/55	8.60283E-10	13
hsa01522	Endocrine resistance	9/55	1.35159E-08	9
hsa05204	Chemical carcinogenesis-DNA adducts	8/55	1.44305E-08	8
hsa00910	Nitrogen metabolism	5/55	6.47215E-08	5
hsa00590	Arachidonic acid metabolism	7/55	1.33399E-07	7
hsa04917	Prolactin signaling pathway	7/55	3.50005E-07	7
hsa04726	Serotonergic synapse	8/55	8.06724E-07	8
hsa00591	Linoleic acid metabolism	5/55	1.39526E-06	5

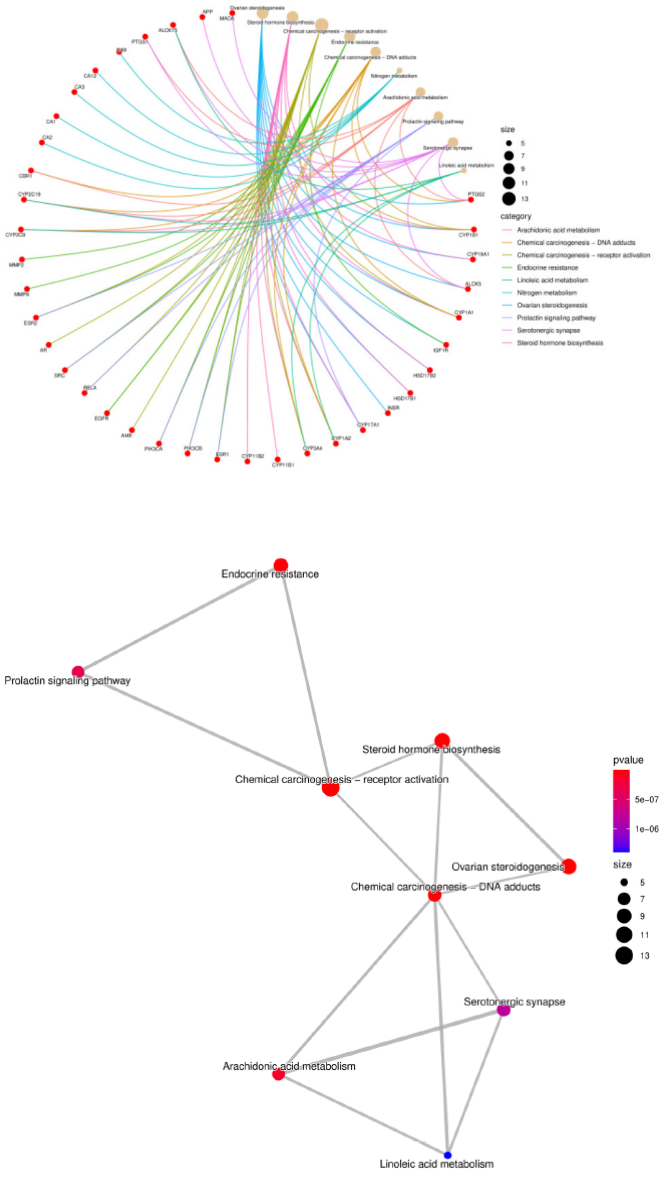


Figure 6. Cnetplot diagram and Emapplot diagram

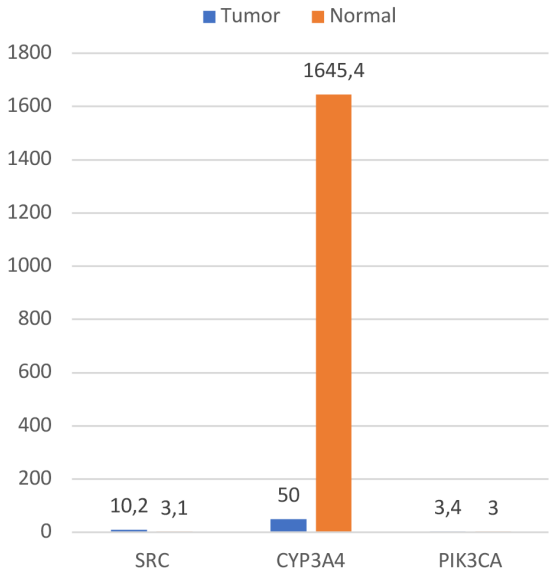
In this study, a network pharmacology approach was used to analyse 59 potential targets of resveratrol for the treatment of early hepatocellular carcinoma. The PPI analysis of the intersecting targets identified 10 key targets, namely SRC, CYP3A4, PIK3CA, CYP1A1, RELA, ESR1, CYP2C9, CYP2C19, HSD17B2 and CYP19A1. Three of these targets had a degree of more than ten, namely SRC, CYP3A4 and PIK3CA. PIK3CA.

SRC is a protein-coding gene. Diseases associated with SRC include thrombocytopenia, colorectal cancer and hepatocellular carcinoma (21). Pathways related to it include signaling downstream of RAS mutants and negative regulation of FGFR1 signaling. Gene ontology (GO) annotations associated with this gene include transferase activity, transfer of phosphorus-containing motifs and protein tyrosine kinase activity (22,23).

CYP3A4 is a protein coding gene. Diseases associated with CYP3A4 include vitamin D-dependent rickets, type 3 and acetaminophen metabolism. Among its related pathways are Imipramine/desipramine pathway, pharmacokinetics and metapathway biotransformation phase I and II (24,25). GO annotations related to this gene include enzyme binding and iron ion binding (26).

PIK3CA is a protein coding gene. Diseases associated with PIK3CA include megalencephaly-capillary malformation-polymicrogyria syndrome and congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (27). Among its related pathways are Downstream signaling of activated FGFR2 and translation insulin regulation of translation. GO annotations related to this gene include transferase activity, transferring phosphorus-containing groups and protein serine/threonine kinase activity (28). The expression of the three genes *SRC*, *CYP3A4* and *PIK3CA* in *HCC* is shown in Figure 9.

Resveratrol can have a direct therapeutic effect on early HCC (Figure 8) as well as a therapeutic effect on early HCC through the regulation of related gene expression and related metabolism (Figures 9-11).



	SRC	CYP3A4	PIK3CA
Tumor	10,2	50	3,4
Normal	3,1	1645,4	3

Figure 7. The expression of the three genes SRC, CYP3A4 and PIK3CA in hepatocellular carcinoma

Conclusion

This study predicted the key targets and pathways of action of resveratrol in the treatment of early HCC based on multiple databases and using a network pharmacology approach. The mechanism of action of resveratrol for Early HCC was found to be a multi-target, multi-pathway interaction. The key targets of resveratrol for Early HCC were found to be SRC, CYP3A4, PIK3CA, CYP1A1, RELA and others. Related KEGG pathways are HCC pathway, PD-L1 expression and PD-1 checkpoint pathway, choline metabolism pathway, central carbon metabolism pathway, etc. It provides a theoretical basis for the next in-depth experimental study.

Ethics

Ethics Committee Approval: This is a description of the article. The data in my article comes from multiple network databases (such as BioGPS Database, Oncomine database, Kaplan-Meier Plotter, Database, etc.). And the article does not involve any real patients or experimental animals. There is therefore no need to submit an application to the Ethics Committee.

Informed Consent: N/A.

Peer-review: Internally and externally peer-reviewed.

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

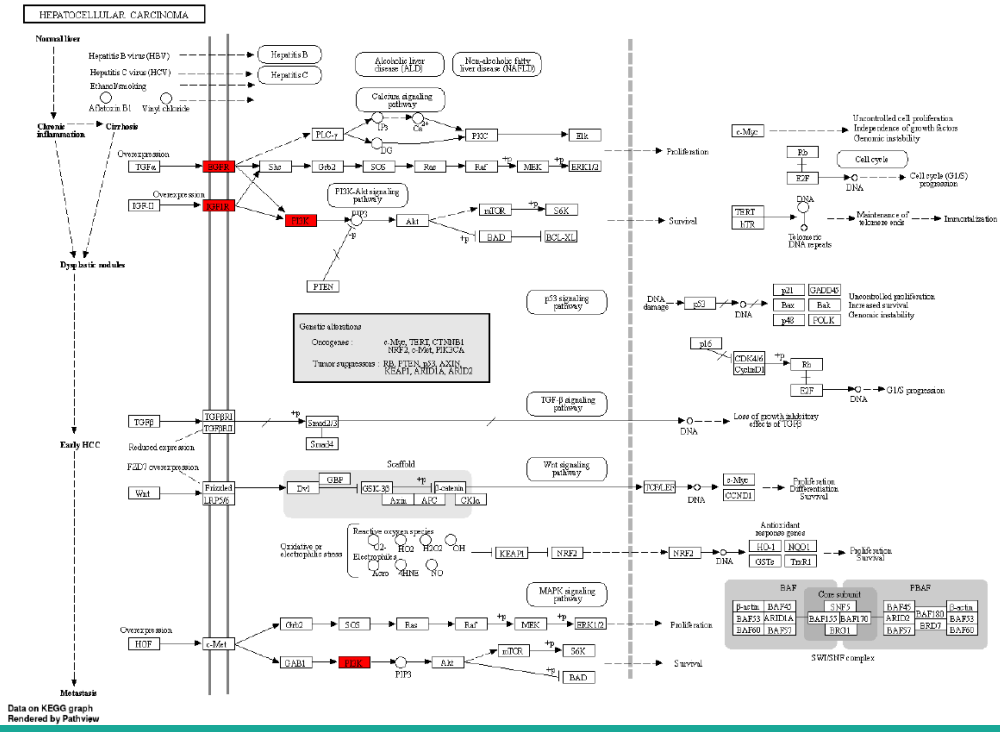


Figure 8. Resveratrol pathway for early-stage hepatocellular carcinoma

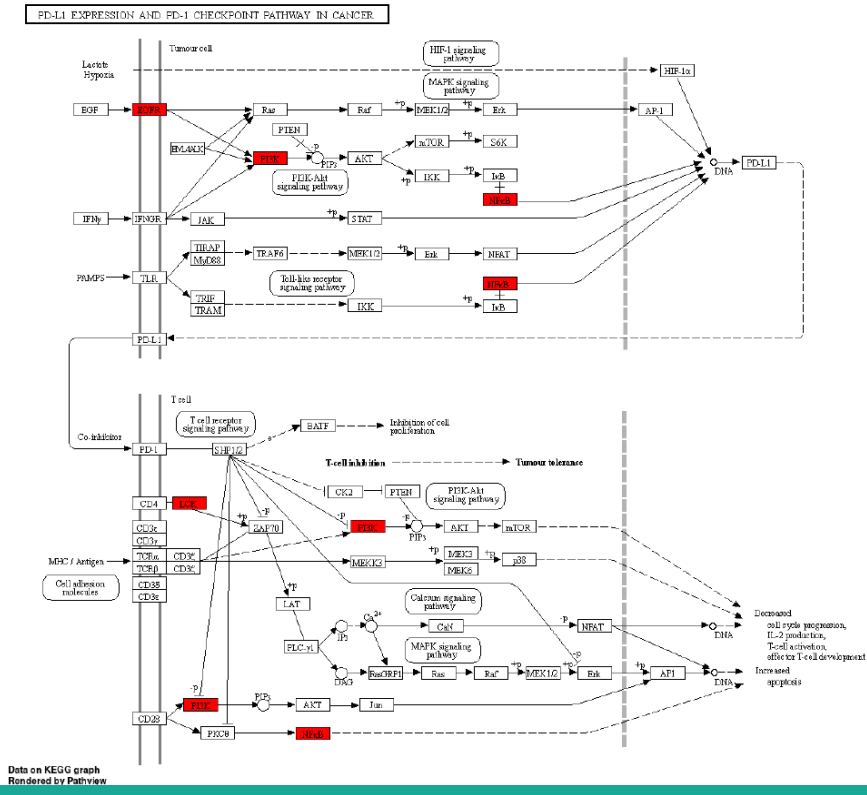


Figure 9. PD-L1 expression and PD-1 checkpoint pathway in cancer

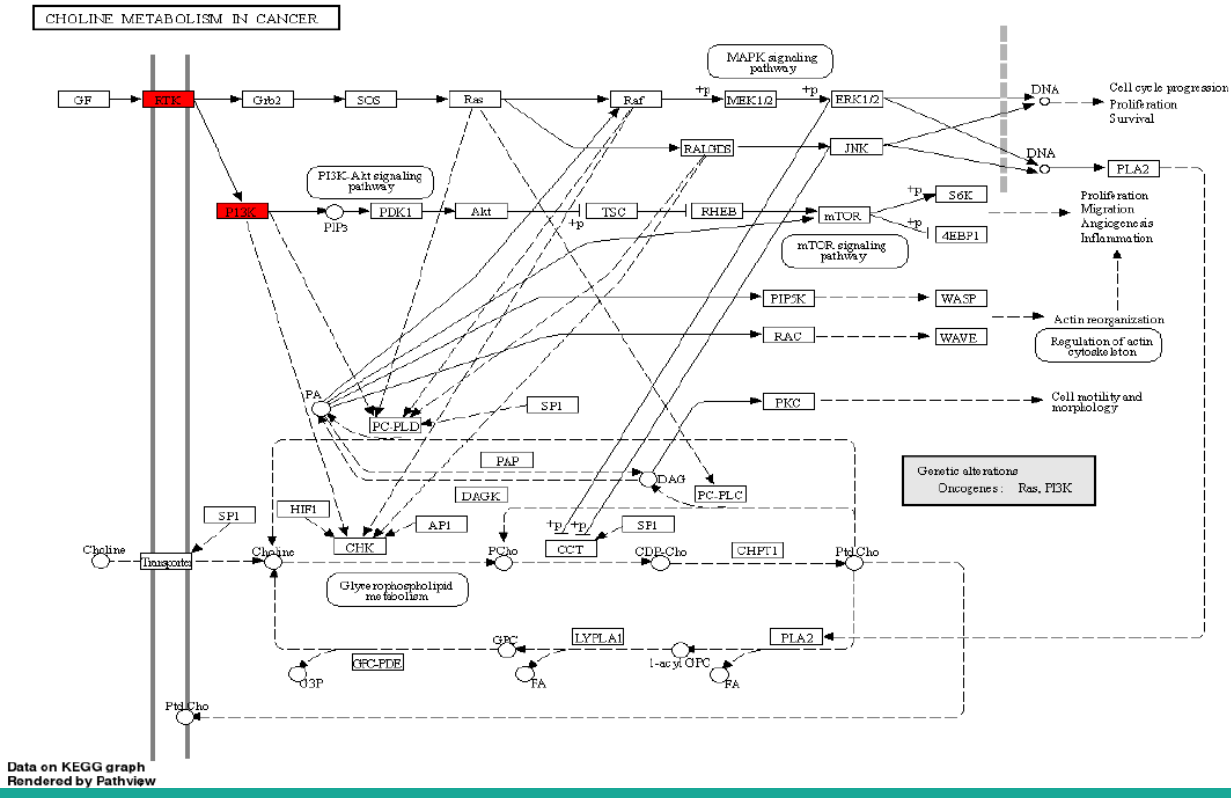


Figure 10. Choline metabolism in cancer

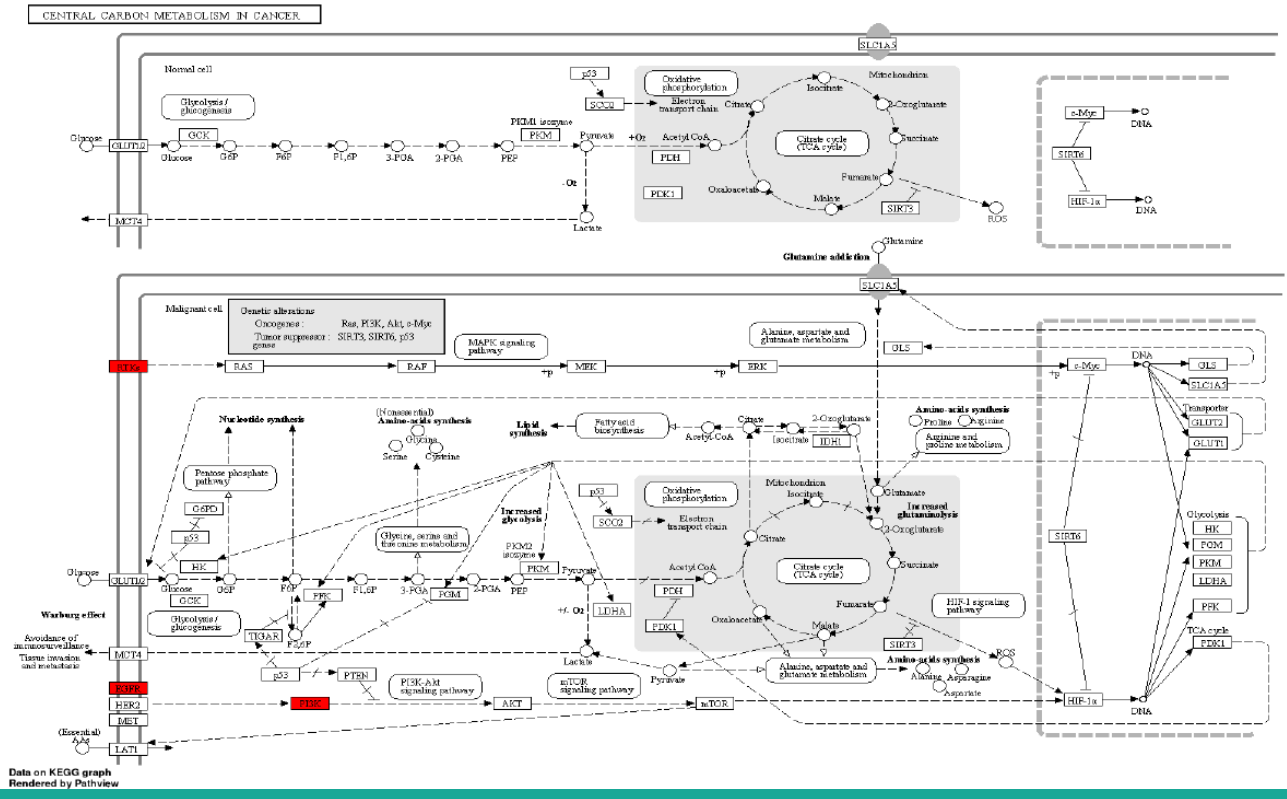


Figure 11. Central cabon metabolism in cancer

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ORIGINAL RESEARCH

Bagcilar Med Bull 2023;8(2):150-154
DOI: 10.4274/BMB.galenos.2023.2022-12-102

Comparing the Efficacy of GnRH Agonists on the Castration Levels of Metastatic Prostate Cancer; Leuprolide Acetate 22.5 mg vs. Goserelin Acetate 10.8 mg

Metastatik Prostat Kanseri Tedavisinde Kullanılan Leuprolide Asetat 22,5 mg ile Goseraline Asetat 10,8 mg İlaçlarının Karşılaştırılması

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Abstract

Objective: We aimed to evaluate the effects of leuprolide 22.5 mg and goserelin 10.8 mg on castration levels in patients with metastatic prostate cancer.

Method: We evaluated 50 metastatic prostate cancer patients between 01.06.2012-01.06.2014, retrospectively. Of the patients, 25 received leuprolide 22.5 mg and 25 received goserelin 10.8 mg. Patients were followed up for 2 years and testosterone, prostate specific antigen (PSA) values were checked in every 3-months periods.

Results: The mean age of the patients were 64.48±8.18 and 65.52±7.93 years in leuprolide 22.5 mg and goserelin 10.8 mg groups, respectively (p=0.466). The mean Gleason score of the patients in both groups were similar (7.80±0.95 vs 7.84±1.17, p=0.949). Two (8%) patients treated with leuprolide and three (12%) patients treated with goserelin had testosterone levels above castration during follow-up. There were no statistically significant differences between the two groups in terms of reaching castration levels (p=0.641). There were no statistically significant differences between the drugs in the duration of exceeding from the castration levels (16.5 months vs. 13 months, p=0.4). In both groups, patients with low Gleason score (<9), single organ metastasis at the time of diagnosis, and PSA values of 2.5 ng/mL and below remained castrated for a longer period of time.

Öz

Amaç: Çalısmamızda metastatik prostat kanseri tedavisinde kullanılan leuprolide acetate 22,5 mg ile goseraline acetate 10,8 mg ilaçlarının kastrasyona etkilerini karşılaştırmayı amaçladık.

Yöntem: Kliniğimizde 01.06.2012 ile 01.06.2014 tarihleri arasında metastatik prostat kanseri tanısıyla löprolide 22,5 mg ve goserelin 10,8 mg tedavisi almış hastalar retrospektif olarak değerlendirildi. Her grupta 25 kişi yer aldı. Birinci gruptaki hastalara löprolid 22,5 mg, ikinci gruptaki hastalara goserelin 10,8 mg tedavisi başlandı. Hastalar 2 yıl süre ile takip edildi. Testosteron, prostat spesifik antijen (PSA) değerleri üç aylık sürelerle kontrol edilerek kastrasyona olan etkileri karşılaştırıldı.

Bulgular: Her iki gruptaki hastaların ortalama yaşları 64,48±8,18 ve 65,52±7,93 (p=0,466) idi. Löprolid ile tedavi edilen hastaların ortalama Gleason skoru 7,80±0,95 goserelin ile tedavi edilen hastaların ortalama Gleason skoru 7,84±1,17 olarak saptandı (p=0,949). Löprolid ile tedavi edilen iki hastada (%8), Goserelin ile tedavi edilen üç (%12) hastada takipleri sırasında testosteron seviyeleri kastrasyon seviyesinin üzerinde bulundu. İki grup arasında istatistiksel olarak anlamlı fark yoktu (p=0,641).

Sonuç: Her iki grupta da kastre düzeyin üzerine çıkan hastalar karşılaştırıldığında anlamlı bir fark saptanmadı. Ancak tanı anında Gleason skoru daha düşük olan (<9), tek organ metastazı saptanmış, PSA değerleri daha düşük (<2,5 ng/mL) olan hastalar kullandıkları ilaçtan bağımsız olarak daha uzun süre kastre seviyede kalmıştır.

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Cite this article as: Çil G, Yağcı F. Comparing the Efficacy of GnRH Agonists on the Castration Levels of Metastatic Prostate Cancer; Leuprolide Acetate 22.5 mg vs. Goserelin Acetate 10.8 mg. Bagcilar Med Bull 2023;8(2):150-154

Abstract

Conclusion: Both leuprolide 22.5 mg and goserelin 10.8 mg are effective in achieving castration levels among metastatic prostate cancer patients. However, patients with low Gleason score (<9), single organ metastasis at the time of diagnosis and PSA values of 2.5 ng/mL and below remained castrated for a longer period of time.

Keywords: Castration, GnRH agonist, goserelin, leuprolide, LHRH agonist, prostate cancer, testosterone

Öz

Anahtar kelimeler: Goserelin, GnRH agonisti, kastrasyon, leuprolide, LHRH agonisti, prostat kanseri, testosteron

Introduction

Prostate cancer is the most common cancer in men (1). It is the second leading cause of death from malignant tumors after lung cancer (1). The majority (75%) of newly diagnosed cases are localized prostate cancer, and their overall survival rates are very high (2). On the other hand, the overall survival rate of metastatic prostate cancer ranges from 25% to 30% at 5 years (2). Prostate cancer cells are highly sensitive to the manipulation of the androgens and castration is causing prostate cancer cell death (3). In 80-85% of men with metastatic prostate cancer, androgen suppression can provide an average of 12-33 months of progression-free survival (4). Medical and surgical methods are used to suppress androgens in advanced prostate cancer (4). Bilateral orchiectomy can be performed for surgical castration (5). Luteinizing hormone-releasing hormone (LHRH) analogs, LHRH antagonists, steroids and non-steroidal antiandrogens can be used to achieve medical castration (4). LHRH analogs can be used in depot form for 1, 3 and 6 months (5) and it aims to keep testosterone levels below the level of castration (<50 ng/dL) (6). In our study, we aimed to compare the effects of leuprolide 22.5 mg and goserelin 10.8 mg, which are used as gonadotropin-releasing hormone (GnRH) agonists in metastatic prostate cancer for two years.

Materials and Methods

We evaluated 50 patients who were diagnosed with metastatic prostatic cancer in our clinic between 01.06.2012-01.06.2014, retrospectively. There were 25 metastatic prostatic cancer patients in each group. Leuprolide 22.5 mg was given to the patients in the first group, and goserelin 10.8 mg to the patients in the second group. Non-metastatic patients, those who had previously received hormone therapy, and orchiectomized patients were excluded from the study. Patients were followed up for 2 years and serum testosterone and prostate specific antigen (PSA) levels were evaluated once in every three months. Castrated serum testosterone level was defined as ≤50 ng/dL. Patients provided their written informed consent and the study was approved by the institutional review board (June 09, 2014-subject 197).

Statistical Analysis

Chi-square and Student's t-test were used as needed. Analyses were performed using the SPSS 10.0 statistical program. $p<0.05$ was accepted as statistically significant.

Results

The mean age of the patients was similar in leuprolide and goseroline groups (64.48±8.18 and 65.52±7.93, p=0.466). The mean Gleason score of the patients in the leuprolide and goseroline groups were (7.80±0.95 vs. 7.84±1.17, respectively (p=0.949). The castration level was exceeded in 2 (8%) and 3 (12%) patients in leuprolide and goseroline groups respectively and the rates were similar in groups (p=0.641). Twelve patients (48%) in the leuprolide group and 9 patients (36%) in the goserelin group and had single organ metastases whereas 13 (52%) patients in the leuprolide group and 16 (64%) patients in the goserelin group and had multiple organ metastases (p=0.395) (Table 1). Mean testosterone levels were 0.28 ng/mL at the third month in the goserelin treatment group, and 0.26 ng/mL in the leuprolide treatment group (p=0.592). The castration level was exceeded in an average of 13 months in patients receiving goserelin treatment, and in an average of 16.5 months in patients receiving leuprolide treatment. There were no statistically significant differences between the two groups (p=0.4). The mean PSA values at the third month were 5.2 ng/mL in the goserelin group, and 3.87 ng/mL in the leuprolide group (p=0.376).

At the end of the 2-year follow-up, 5 (10%) patients in both groups had testosterone levels above the castration level. The mean Gleason score of these patients was 9.0±1.0 and that of 45 patients who remained at the castrated level was 7.68±0.99 (p=0.078). The mean PSA values in the

2-year follow-up were significantly higher among patients whose testosterone levels were above the castration level (5.26±4.89 vs. 2.36±8.31, p=0.021), (Table 2). The percentage of prostate cancer patients who had multiple organ metastases at the time of diagnosis was higher among patients whose testosterone levels were above the castration level (80% vs. 55.5%, p=0.298).

Discussion

In our study, testosterone levels were found higher than castration level in a total of 3 patients (median at 13 months) in the goserelin 10.8 mg treatment group, and in 2 patients in the group using leuprolide 22.5 mg treatment (median at 16.5 months). There were no significant differences between the two groups in terms of the time period of exceeding castration levels. We have observed that testosterone levels rise above the castration level earlier in patients with higher PSA value, multiple organ metastases and a Gleason score of 9 and above, regardless of the GnRH agonist used.

Even if the PSA levels are very low, there is a risk of prostate cancer (7% can be detected when PSA is <0.5 ng/mL). Gleason scoring is used when evaluating pathological preparations and is an important prognostic indicator. A Gleason score of 8-10 was used for poorly differentiated, 5-7 for moderately differentiated and 2-4 for well-differentiated cancer (7). Despite early diagnosis and progress in treatment, approximately 25% of patients progressed to metastatic disease.

A high Gleason scores is associated with more aggressive metastatic prostate cancer progresses (8). In a study of 28 patients, Nishiyama et al. (8) showed that the level of testosterone remained as castrate for a longer time in patients with a Gleason score <7 who received GnRH agonist therapy (9). In our study, a total of five (10%) patients in the entire study group had testosterone above the castration level. The mean Gleason score of these patients was 9.0±1.0 and that of the 45 patients who remained at the castrated level was 7.68±0.99. Low Gleason score at the time of diagnosis was associated with longer castration period (p=0.078).

Similarly, Fujii et al. (9) compared the effects of GnRH agonists on castration levels in the treatment of metastatic prostate cancer. In their study in which a total of 232 patients participated, 1- and 3-months forms of leuprolide and goserelin were compared. Forty patients received monthly leuprolide acetate, 68 patients received 3-months leuprolide acetate, 50 patients received monthly goserelin acetate, and 74 patients received 3-months goserelin acetate treatment. The mean testosterone levels after 3 months were 0.23 ng/mL, 0.21 ng/mL, 0.18 ng/mL, 0.21 ng/mL. Testosterone levels exceeded castrated levels (0.55-0.65 ng/mL) in 1 patient using the 1-month form of leuprolide acetate and 1 patient using the 3-month form

Table 1. Socio-demographic and clinical data of the patients

	Goserelin acetate 10.8 mg	Leuprolide acetate 22.5 mg	p-value
Age	65.52±7.93	64.48±8.18	0.466
Gleason score	7.84±1.17	7.8±0.95	0.949
Above castration level	3 (12%)	2 (8%)	0.641
Single organ metastasis	9 patients (36%)	12 patients (48%)	
Multiple organ metastasis	16 patients (64%)	13 patients (52%)	0.395
Average testosterone levels after 3 months	0.28 ng/mL	0.26 ng/mL	0.592
Average time above castration level	13 months	16.5 months	0.4
Mean PSA levels at diagnosis	92.35 ng/mL	77 ng/mL	
Average PSA levels after 3 months	5.2 ng/mL	3.87 ng/mL	0.376

PSA: Prostatic specific antigen, Student's t-tests, p<0.05 as statistical significance level

Table 2. Clinical values of the castrate and castration resistant patients

	Patients above castration level	Castrated patients	p-value
Single organ metastasis	1	20	
Multiple organ metastasis	4	25	0.298
Gleason score	9±1	7.68±0.99	0.078
Average PSA value	5.26±4.89	2.36±8.31	0.021

PSA: Prostatic specific antigen, chi-square test, p<0.05 as statistical significance level

of goserelin acetate. There was no statistically significant difference in reaching to the castration levels (10). In our study, median testosterone levels were 0.28 ng/mL at the 3rd month in patients using the 3-month storage form of goserelin acetate and 0.26 ng/mL in patients using the 3-month storage form of leuprolide acetate (p=0.592). All patients remained at castrated levels at the 3rd month of the treatment.

In another study by Dias Silva et al. (10) the u medical castration duration of leuprolide 3.75 mg, 7.5 mg and goserelin 3.6 mg drugs were compared. Three groups, each consisting of 20 patients were formed. After 3 months of treatment, 26.3% of patients using leuprolide 3.75 mg, 25% of patients using leuprolide 7.5 mg, and 35% of patients using goserelin 3.6 mg did not reach castrated levels (cut-off <50 ng/mL). When the cut-off was taken as <20 ng/mL, 68.4%, 30% and 45% of the patients could not reach to castrate levels. No significant differences were found between the groups in terms of reaching to the castration levels (11). In our study, a total of 25 patients using goserelin 10.8 mg and 25 patients using leuprolide 22.5 mg participated in the study. All of the patients reached castrate levels at the 3rd month of the treatment; however, 3 patients and 2 patients in the goserelin 10.8 mg and leuprolide 22.5 mg groups had testosterone levels above castrated levels at an average of 13 months and 16.5 months, respectively (p=0.4).

Fontana et al. (11) evaluated the efficacy and side effects of goserelin 10.8 mg. A total of 115 patients diagnosed with locally advanced prostate cancer or metastatic prostate cancer participated in the study. Testosterone levels decreased to castrated levels by the end of four weeks in all patients. PSA reduction occurred in 86% (99/115) of the patients and none of the patients developed an injection site reaction. Goserelin acetate 10.8 mg was reported to be safe and effective (11). In our study, testosterone levels decreased to castrated levels in all patients in the 3rd months, and a significant decrease was observed in the PSA values (p=0.036). No reaction was observed at the injection site in any of the patients.

Study Limitations

The main limitation of this study was the small number of patients recruited from a single center. Future multi-center studies with more metastatic prostate cancer are required to confirm our study findings.

Conclusion

There were no statistically significant differences in achieving castration levels and the duration to reach castration levels between leuprolide 22.5 mg and goserelin 10.8 mg. Testosterone levels increased earlier among patients with a Gleason score ≥9, multiple organ metastases and higher PSA values. Larger studies are needed to better evaluate the efficacy of these drugs.

Ethics

Ethics Committee Approval: Gaziantep University Clinical Research Ethics Committee (May 20, 2012-subject 124) gave permission to conduct the study.

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

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: G.Ç., F.Y., Design: G.Ç., F.Y., Data Collection or Processing: G.Ç., Analysis or Interpretation: G.Ç., F.Y., Critical Revision of Manuscript: G.Ç., F.Y., Drafting Manuscript: G.Ç., Final Approval and Accountability: G.Ç., F.Y., Writing: G.Ç., F.Y.

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

Bagcilar Med Bull 2023;8(2):155-160
DOI: 10.4274/BMB.galenos.2023.2023-01-05

Early Clinical Outcomes of Congenital Diaphragmatic Hernia and Prognosis: A Retrospective Multicenter Study

Konjenital Diyafram Hernisinde Erken Klinik Sonuçlar ve Prognoz: Retrospektif Çok Merkezli Bir Çalışma

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Abstract

Objective: Investigation of possible prognostic factors affecting survival in the congenital diaphragmatic hernia.

Method: We included all congenital diaphragmatic hernia-diagnosed patients treated in neonatal intensive care units of two centers between 2016 and 2020. We recorded antenatal and birth histories, anthropometric measurements, and clinical features of the hernia. We assessed visceral herniation to the hemithorax, pneumothorax, severely decreased fetal lung volume (<15%), the need for emergency intervention due to pneumothorax in the operating/delivery room, and pulmonary hypertension effects on the survival status. We recorded the data retrospectively.

Results: We enrolled 31 patients in the study. The clinical conditions associated with high mortality were pulmonary hypertension (p=0.006), pneumothorax (p=0.009), severely decreased fetal lung volume (<15%) (p<0.001), hepatic (p=0.024) and gastric (p=0.029) herniations to the thorax. In a binomial regression model, PTX and hypoplastic lung were the most significant confounders (R^2_{McF}: 0.858, p<0.001). 19.4% of patients needed emergency intervention in the operating/delivery room. There was no statistically significant difference between deceased and alive patients in terms of postnatal day of surgery.

Conclusion: Operation time did not statistically affect mortality. Pneumothorax, severely decreased fetal lung volume, hepatic herniation, gastric herniation, and pulmonary hypertension statistically declined survival. PTX and hypoplastic lung were the most significant confounders.

Keywords: Congenital diaphragmatic hernia, pneumothorax, pulmonary hypertension

Öz

Amaç: Konjenital diyafram hernisinde sağkalımı etkileyen olası prognostik faktörlerin belirlenmesidir.

Yöntem: İki yenidoğan yoğun bakım ünitesinde 2016-2020 yılları arasında tedavi edilen tüm konjenital diyafram hernisi tanılı hastalar retrospektif olarak çalışmaya dahil edildi. Antenatal ve doğum öyküleri, antropometrik ölçümler, fıtığın klinik özellikleri, hemitoraksa visseral herniasyon, çok düşük fetal akciğer volümü (<%15) ve ameliyat/doğum odasında pnömotoraks nedeniyle acil müdahale ihtiyacı, pnömotoraks ve pulmoner hipertansiyon gelişimi durumu ve bunların sağkalım durumu üzerindeki etkileri kaydedildi.

Bulgular: Çalışmaya 31 hasta alındı. Pulmoner hipertansiyon (p=0,006), pnömotoraks (p=0,009), çok düşük fetal akciğer volümü (p<0,001), hemitoraksa karaciğer (p=0,024) ve mide (p=0,029) herniasyonunun mortaliteyi istatistiksel olarak artırdığı saptandı. Binomial regresyon modelinde, PTX ve hipoplastik akciğer en önemli karıştırıcı faktörlerdi (R^2_{McF}: 0;858, p<0,001). Hastaların %19,4'ünde ameliyathanede/doğum odasında acil müdahale ihtiyacı oldu. Ölen ve yaşayan hastalar arasında postnatal ameliyat olduğu gün açısından istatistiksel olarak anlamlı bir fark saptanmadı.

Sonuç: Postnatal ameliyat günü mortaliteyi etkilemedi. Pnömotoraks, çok düşük fetal akciğer volümü, pulmoner hipertansiyon, hemitoraksa mide ve karaciğer herniasyonunun sağkalımı azalttığı görüldü. PTX ve hipoplastik akciğer en önemli karıştırıcı faktörlerdi.

Anahtar kelimeler: Konjenital diyafram hernisi, pnömotoraks, pulmoner hipertansiyon

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Cite this article as: Kandemir İ, Alp Ünkar Z, Kersin SG, Köle MT, Yaman A. Early Clinical Outcomes of Congenital Diaphragmatic Hernia and Prognosis: A Retrospective Multicenter Study. Bagcilar Med Bull 2023;8(2):155-160

Introduction

Congenital diaphragmatic hernia is a structural birth anomaly due to defective closure of the pleuroperitoneal folds between 4-10 weeks after fertilization, which causes severe neonatal morbidity and mortality (1), with a rate of 2.5 in ten thousand live births (2). It is left-sided in 80-85% of cases, right-sided in 10-15%, and rarely bilateral (1). Clinicians can detect this deformity by ultrasonography imaging in the antenatal period (3).

The etiology has not yet been fully clarified but is thought to be multifactorial (4). While it occurs as an isolated defect in 50-70% of the patients, 30-50% of cases have gene defects or substantial anomalies in cardiovascular (ventricular septal defect, atrial septal defect, tetralogy of Fallot), central nervous (neural tube defects, hydrocephalus), and musculoskeletal systems (polydactyly, syndactyly, small extremities) (4).

Since herniation occurs during a critical period of lung development, the lungs affect more prominent in the clinical manifestation of congenital diaphragmatic hernia (5); therefore, fetal lung volume is one of the most important survival factors (3). High mortality rates occur if the total lung capacity of the fetus is 25% of normal or less. The prognosis deteriorates if there is a liver herniation association, and patients may develop chronic lung disease (3). Lung compression may cause pulmonary hypoplasia by affecting pulmonary arterial and bronchial development. Decreased arterial branching causes muscular hyperplasia of the pulmonary arterial tree, resulting in pulmonary hypertension (5).

Despite advances in antenatal diagnosis and treatment of congenital diaphragmatic hernia, this birth anomaly challenges pediatricians, neonatologists, and pediatric surgeons. The mortality rate is 30% in centers that can perform extracorporeal membrane oxygenation (ECMO); however, most patients die due to pulmonary hypertension and its complications (6).

This study aimed to present the prognosis and accompanying clinical outcomes of patients with a congenital diaphragmatic hernia in two tertiary neonatal intensive care units.

Material and Methods

We included all patients diagnosed with a congenital diaphragmatic hernia and treated in the neonatal intensive care units of Marmara University and Güngören Hospital between 2016 and 2020, retrospectively. We recorded whether there was a pregnancy-termination recommendation in the prenatal follow-ups of the mothers, birth history, anthropometric measurements (height, weight, head circumference), hemithorax of the diaphragmatic hernia (right/left), liver/stomach/spleen herniation into the hemithorax, lung hypoplasia (in antenatal period) and the need for emergency intervention due to pneumothorax in the operating/delivery room, the development of pneumothorax and pulmonary hypertension in neonatal intensive care unit (NICU) and the survival status. This study aimed to present the prognosis and accompanying clinical outcomes of patients with congenital diaphragmatic hernia.

The ethical committee approval was obtained from Marmara University Ethical Committee (file number: 09.2022.24).

Statistical Analysis

Descriptive data were given as mean ± standard deviation and median (interquartile range) following the distribution pattern. Student's t-test, Welch's t-test, and Mann-Whitney U test were used according to distribution and variance types to compare two groups with continuous variables. The chi-square and Fisher's Exact tests were used to compare groups with categorical variables. In addition, we used a binomial regression test to detect possible confounding factors. The Jamovi 2.3.18 statistical package program was used for statistical calculations. $p<0.05$ was considered of statistical significance.

Results

A total of 31 patients (58.1% male) were eligible for the study. Median birth weight, length, and head circumference of the total patients were 38 (35.7-39.6) weeks, 3020 (2500-3240) grams, and 35 (33.5-36) centimeters, and mean birth length was 49.3±4.45. 83.9% (n=26) patients were born via cesarean section and 16.1% (n=5) with spontaneous vaginal delivery.

The diaphragmatic defect was on the left in 74.2% (n=26) and on the right side in 25.8% (n=5) patients. There was no statistically significant difference in terms of gender (p=0.16, chi-square test), birth weight (p=0.993, Mann-Whitney U test), birth length (p=0.395, Welch's t-test), birth week (p=0.445, Mann-Whitney U test), defect side (p=0.165, chi-square test) and delivery type (p=0.686) between groups who survived and deceased. Ultrasonographic imaging detected liver herniation to the thorax in 38.7%

(n=12) patients, which significantly increased (p=0.024, chi-square test) mortality [mortality rate of 91.7% (n=11) versus 52.6% (n=10) in the liver herniation and non-liver herniation groups, respectively]. There was no statistically significant difference in mortality in spleen herniation (p=0.69, chi-square test). Ultrasonographic imaging detected gastric herniation in 48.4% (n=15) patients, which significantly increased (p=0.029, chi-square test) mortality (mortality rate of 86.7% (n=13) versus 50% (n=8) in gastric herniation and non-gastric herniation groups, respectively).

Clinicians needed emergent tube thoracostomy intervention in 19.4% of the patients (n=6) due to pneumothorax in the first minutes of life in the delivery or operating room. There was no statistically significant difference in survival (p=0.634, Fisher's Exact test) between these patients and those who did not need intervention (mortality rate of 23.8% and 10% for the deceased and survived group, respectively).

During the treatment of the patients, 58.1% (n=18) developed a pneumothorax [48.4% (n=15) on the left side, 58.1% (n=18) on the right side, and 38.7% (n=12) bilateral]. Pneumothorax statistically affected (p=0.006, Fisher's Exact test) mortality (mortality rate of 88.9% (n=16) versus 38.5% (n=5) in pneumothorax and non-pneumothorax groups, respectively).

A total of 87.1% (n=27) patients developed pulmonary hypertension, which significantly increased (p=0.007, Fisher's Exact test) mortality [mortality rate of 77.8% (n=213) versus 0% in pulmonary hypertension and non-pulmonary hypertension groups, respectively].

A total of 45.2% (n=14) of the patients needed more than 30 mm H_2O mean airway pressure in "high frequency ossilation mode" to maintain >85% oxygen saturation while allowing permissive hypercapnia (partial pressure of carbon dioxide 45-65 mmHg with an arterial pH of >7.25). All these patients had below 15% of fetal lung volume. Severely decreased fetal lung volume statistically affected (p<0.001, Fisher's Exact test) mortality [mortality rate of 100% (n=14) and 41.2% (n=7) in severely decreased fetal lung volume and non-severely decreased fetal lung volume, respectively].

In a binomial regression model where collinearity assumption was met, we included PHT, PTX, hypoplastic lung, and liver and stomach herniations as they reached statistical significance and resulted in that PTX (odds ratio: 12.8) and hypoplastic lung (odds ratio: 40) were the most significant confounders in survival (R^2_{McF}: 0.858, X^2: 33.4, p<0.001) (Table 1).

The follow-up gynecologists had recommended pregnancy termination in 45.2% (n=14) of the patients due to associated anomalies incompatible with life; however, the families stated that they had refused medical abortion. None of these patients could survive until the operation as they died within two days. Seventeen patients were born with defects that might be compatible with life, and 58.8% (n=10) of them survived. The anthropometric measurements and gender of the patients with survival status comparison are in Table 2.

Table 1. Likelihood ratio tests of the binomial logistic regression model

Confounder	X^2	p-value
PHT	0	1
PTX	6.65	0.01
Hypoplastic lung	9.44	0.002
Hepatic herniation into hemithorax	2.09	0.148
Gastric herniation into hemithorax	2.09	0.148

PHT: Pulmonary hypertension, PTX: Pneumothorax

Table 2. Anthropometric measurements and gender of the operated patients comparing survival status

	Exitus (n=7)	Survived (n=10)	p-value
Birth week (weeks)	38.8±2.28	38.2±1.94	0.588*
Birth weight (gram)	3100±530	2940±290	0.449*
Birth length (cm)	49.6±4.5	48.5±2.0	0.57**
Head circumference (cm)	34.9±2.0	34.5±1.1	0.634*
Gender	85.7% (n=6) male 14.3% (n=1) female	40% (n=4) male 60% (n=6) female	0.134***

Data presented as mean+/-standard deviation and % (n), *Student's t-test, **Welch's t-test, ***Fisher's Exact test

Pneumothorax history significantly decreased survival in postoperative patients (p<0.05). The clinical problems encountered by the operated patients are shown in Table 3.

A total of 54.8% (n=17) of all patients could be stabilized for the operation. There was no statistically significant difference between the deceased and survived groups (3.4+/-1.4 versus 4.5+/-3, respectively p=0.34, Welch's t-test). In the operated cases, the survival rate was 58.8% (n=10).

Discussion

Congenital diaphragmatic hernia is more common in boys than girls, and the male gender is a defined risk factor (7). There was a male predominance at a 58.1% rate in our study. However, there was no statistically significant difference between the sexes in terms of mortality.

In the literature, it is reported that herniation is in the left hemithorax in most patients (80-85%) (1,4,8). We observed left hemithorax diaphragmatic hernia at a rate of 74.2% of our patients. The right hemithorax diaphragmatic hernia rate is between 10 and 15% in the literature (1,4,8). Thus, this rate was 25.8% in our study.

In infants with a congenital diaphragmatic hernia, visceral organs (including the stomach, liver, and spleen) may enter the thoracic cavity and displace the heart contralaterally, resulting in compression, growth restriction, and dysfunction of both lungs (1). As a result, intrapleural herniation causes pulmonary hypoplasia (3). A study reported that herniation of the stomach and liver results in a poor prognosis in antenatal ultrasonographic imaging, but liver herniation affects more to the severity of clinical outcome (1). Hepatic herniation to the hemithorax results in a very severe clinical course; even 80% of the patients with liver herniation need ECMO (4). Therefore, the position of the liver is used to predict prognosis in the antenatal period and indicates a poor prognosis (4,9). Hepatic herniation to hemithorax was statistically significantly associated with mortality (p=0.024) in our patient group. Spleen herniation did not statistically affect mortality (p=0.69). But gastric herniation statistically increased mortality (p=0.029).

Pneumothorax is one of the factors affecting mortality. The pneumothorax rate is 14% (10) and 10.5% (11) in studies. However, the patients had isolated congenital diaphragmatic hernias. Another study reported that all babies who developed pneumothorax died (12). The pneumothorax rate was 52.9% in our study group and also statistically increased mortality in our study (p=0.009).

In patients diagnosed with a congenital diaphragmatic hernia, urgent intervention may be required in the delivery/operating room in the first minutes of life due to pneumothorax. The intervention needs for pneumothorax in the delivery/operating room was 19.4% in our patient series. This ratio shows the necessity of preparation for tube thoracostomy in the delivery/operating room, and a portable X-ray device should be ready for imaging.

Decreased pulmonary vascularization, increased pulmonary artery pressure, and pulmonary vascular tonus leads to pulmonary hypertension in congenital diaphragmatic hernia-diagnosed patients. Pulmonary hypertension is one of the leading causes of mortality (1), though ECMO therapy increases the chance of survival (13). A study reported that pulmonary hypertension occurs in 30% to 50% of patients diagnosed with a congenital

Table 3. Clinical problems in operated patients and comparison of survival status

	Operated patients (n=17)	Exitus (n=7)	Survived (n=10)	p-value
Hemithorax % (n)	Left 82.4% (n=14)	35.7% (n=5)	64.3% (n=9)	0.537
	Right 17.6% (n=3)	66.7% (n=2)	33.3% (n=1)	
Splenic herniation % (n)	35.2% (n=6)	33.3% (n=2)	66.7% (n=4)	1
Gastric herniation % (n)	29.4% (n=5)	60% (n=3)	40% (n=2)	0.593
Hepatic herniation % (n)	23.5% (n=4)	75% (n=3)	25% (n=1)	0.25
PTX % (n)	52.9% (n=9)	77.8% (n=7)	22.2% (n=2)	0.002
Left PTX % (n)	35.2% (n=6)	83.3% (n=5)	16.7% (n=1)	0.035
Right PTX % (n)	52.9% (n=9)	77.8% (n=7)	22.2% (n=2)	0.002
Bilateral PTX % (n)	29.4% (n=5)	83.3% (n=5)	16.7% (n=1)	0.035
PTX in the operating/delivery room % (n)	17.6% (n=3)	66.7 (n=2)	33.3 (n=1)	0.537
PHT % (n)	76.5% (n=13)	53.8% (n=7)	46.2% (n=6)	0.103

Fisher's Exact test. PHT: Pulmonary hypertension, PTX: Pneumothorax

diaphragmatic hernia (14). The pulmonary hypertension rate was 87.1% in our study was as statistically significantly affected by mortality (p=0.007) in parallel with the literature.

Pulmonary hypoplasia is also one of the crucial factors affecting mortality (1). Determination of fetal lung volume in prenatal ultrasonographic imaging is critical in predicting prognosis in the antenatal period (9). In our study, all patients with severely decreased fetal lung volume (<15%) died. These patients had not undergone in-utero intervention and had been recommended termination in the antenatal period. Fetal lung volume lower than 15% increases mortality by 88% (3,4,9). For these reasons, interventions that increase the lung capacity in the antenatal period, such as fetal tracheal occlusion, are beneficial (15). In our study, mortality was statistically significantly higher in patients with lower than <15% fetal lung volume (p<0.001), and none of the patients had undergone fetal intervention.

The surgical procedure is one of the essential and indispensable treatment steps. Although there is no published randomized controlled trial, it is crucial to stabilize the patient (16) and particularly wait for the resolution of pulmonary hypertension before surgery (17). Our patients had undergone an operation after stabilization and resolution of pulmonary hypertension. There was no statistically significant difference between the deceased and surviving patients in terms of operation day.

A study in Turkey reported an overall survival rate of 32.5% and 61% in operated newborns (18). Another study reported 50% overall survival rate (19), where the survival rate in our study was 32.3% in all patients and 58.8% in the operated newborns. Prenatal interventions are crucial for increasing successful surgery (18).

Study Limitations

The sample size was small. ECMO was not obtainable during the study dates. We could not reach intra-operational details.

Conclusion

Pregnancy termination-indicated cases affected mortality rates in this case series. Hepatic and gastric herniation to the hemithorax, pulmonary hypertension, pneumothorax, and antenatal severely decreased fetal lung volume (<15%) affected survival. Operation time did not statistically affect mortality.

As patients tend to develop a pneumothorax, clinicians should anticipate an emergency intervention with tube thoracoscopy in the delivery/operating room, where a portable X-ray device is underhand.

Ethics

Ethics Committee Approval: The ethical committee approval was obtained from Marmara University Ethical Committee (file number: 09.2022.24).

Informed Consent: Since the study was retrospective and was written with a file scan, patient consent information was not sent.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Design: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Data Collection or Processing: İ.K., A.Y., S.G.K., Analysis or Interpretation: İ.K., A.Y., M.T.K., Drafting Manuscript: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Critical Revisation of Manuscript: İ.K., A.Y., Z.A.Ü., Final Approval and Accountability: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Technical or Material Support: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Supervision: A.Y., Z.A.Ü., Writing: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K.

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

Bagcilar Med Bull 2023;8(2):161-166
DOI: 10.4274/BMB.galenos.2023.2022-10-084

Retinal Microvascular Changes in Patients with Chronic Heart Failure due to Idiopathic Dilated Cardiomyopathy

İdiyopatik Dilate Kardiyomiyopatiye Bağlı Kronik Kalp Yetmezliğinde Retinal Mikrovasküler Değişiklikler

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Abstract

Objective: Idiopathic dilated cardiomyopathy (IDCM), one of the major causes of chronic heart failure, is a disorder that causes impairment of the systolic function due to left ventricular dilatation without coronary artery disease. In this study, we aimed to investigate retinal vascular density (VD) and the foveal avascular zone (FAZ) area changes in patients with IDCM using optical coherence tomography angiography (OCTA).

Method: Forty-eight patients with IDCM and a left ventricle ejection fraction below 50% (Group 1) and 50 healthy individuals (Group 2) were evaluated using OCTA. FAZ area, superficial and the deep parafoveal VDs and peripapillary area VDs were measured and compared between the groups.

Results: The FAZ values were significantly higher in Group 1 (0.29±0.09, 0.20±0.05; p<0.001, respectively). Moreover, the mean VD values were significantly lower in the deep capillary plexus of the parafoveal area in Group 1 (49.05±3.81, 54.81±2.88; p<0.001, respectively). The mean VD values were also significantly lower in the peripapillary area in Group 1 (50.54±3.38, 54.66±1.42; p<0.001, respectively).

Conclusion: OCTA may possess the potential to be used in the follow-up of this patient group.

Keywords: Dilated cardiomyopathy, heart failure, microvascular density, optical coherence tomography angiography

Öz

Amaç: Kronik kalp yetmezliğinin en önemli nedenlerinden biri olan idiyopatik dilate kardiyomiyopati (KMP), koroner arter hastalığı olmaksızın sol ventrikül genişlemesine bağlı olarak, sistolik fonksiyonun bozulmasına neden olan bir hastalıktır. Bu çalışmada, optik koherens tomografi anjiyografi (OKTA) kullanarak KMP'si olan hastalarda foveal avasküler zon (FAZ) alanı ve retinal vasküler dansite (VD) değişikliklerini araştırmayı amaçladık.

Yöntem: Sol ventrikül ejeksiyon fraksiyonu %50'nin altında olan KMP'li 48 hasta (Grup 1) ve 50 kişiden oluşan sağlıklı kontrol grubu (Grup 2) OKTA ile değerlendirildi. FAZ alanı, yüzeyel ve derin parafoveal VD değerleri ve peripapiller alan VD değerleri ölçülerek, gruplar arasında karşılaştırma yapıldı.

Bulgular: FAZ değerleri Grup 1'de anlamlı olarak daha yüksekti (sırasıyla 0,29±0,09, 0,20±0,05; p<0,001). Ayrıca Grup 1'de parafoveal alanın derin kapiller pleksus ortalama VD değeri anlamlı olarak daha düşüktü (sırasıyla 49,05±3,81, 54,81±2,88; p<0,001). Peripapiller alanın ortalama VD değeri de Grup 1'de anlamlı olarak daha düşük bulundu (sırasıyla 50,54±3,38, 54,66±1,42; p<0,001).

Sonuç: Çalışmamızın sonuçları bu hasta grubunun takibinde OKTA'nın kullanılabileceğini düşündürmektedir.

Anahtar kelimeler: Dilate kardiyomiyopati, kalp yetmezliği, mikrovasküler dansite, optik koherens tomografi anjiyografi

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Cite this article as: Alkan AA, Düzgün E, Karapapak M, Karataş ME, Özcan D, Sığırcı S. Retinal Microvascular Changes in Patients with Chronic Heart Failure due to Idiopathic Dilated Cardiomyopathy. Bagcilar Med Bull 2023;8(2):161-166

Introduction

Chronic heart failure (CHF) is a severe disease in which the feeding of tissue is impaired as a result of the loss of the heart's pumping function due to various reasons (1). Although the pathogenesis of CHF remains uncertain, it is thought to be associated with microvascular dysfunction (2-6). Idiopathic dilated cardiomyopathy (IDCM), one of the major causes of CHF, is a disorder that causes impairment of the systolic function due to left ventricular dilatation without coronary artery disease (CAD) (7,8). As a spontaneous consequence of the impaired pumping function of the heart, the circulation in the tissues is also impaired (1).

The retina is unique in that it allows for the monitoring of the effects of systemic diseases *in vivo*. Retinal vascular alterations can be evaluated using different imaging methods. For this reason, many previous studies have been conducted to reveal the effects of cardiac diseases, such as CHF and hypertension (HT), on retinal and choroidal tissues (9-13).

Optical coherence tomography angiography (OCTA) is a new imaging method to assess retinal vascularization. In recent years, many OCTA studies have reported that retinal microvascularization is affected by systemic diseases. OCTA studies have also revealed retinal vascular impairment in patients with CAD, congenital heart disease, (CHD), and CHF (14-16).

In the current study, we tried to reveal the changes in the retinal vascular network quantitatively in patients with IDCM for the first time.

Materials and Methods

This study received approval from the Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital and was conducted under the Declaration of Helsinki (05/02/2019; 2245). Based on a study conducted with a similar subject and methodology, at least 37 participants in each group should be included in the study, according to the power analysis result when α: 0.05, and power (1-β): 0.80 were taken with the G*Power 3.1 program. All participants stated that they agreed to participate in the study with written consent. Patients who are followed in cardiology clinic between February 2019 and June 2019 have been evaluated. Patients with no CAD were determined by coronary angiography and a dilated left ventricle cavity with left ventricle ejection fraction (LVEF) below 50% were documented by echocardiography (echo) included in the study. All patients were stratificated according to New York Heart Association (NYHA) functional classification (17,18). Exclusion criteria were: 1) history of congenital diseases, 2) systemic diseases and conditions that might affect the retina [HT, diabetes mellitus (DM), systemic inflammatory diseases, systemic corticosteroids], 4) history of ocular trauma or surgeries, uveitis, optic nerve pathologies, macular degeneration or another ocular pathology, respectively.

Patients were referred from the cardiology clinic to the ophthalmology clinic for the study. An ophthalmological examination was performed for each patient. Patients who are involved in this study had 1) a refractive error < ±2D, 2) a best corrected visual acuity of 20/20, 3) an intraocular pressure lower than 21, 4) a cup-to-disc ratio ≤0.3.

The control group formed by volunteers without additional pathology. Two groups were thus formed: 1) a IDCM group, 2) a control group.

Imaging Protocol

OCTA images were obtained using the AngioVue Imaging System version 2017.1 (Optovue, Inc., Fremont, CA, USA). Foveal avascular zone (FAZ) area, foveal and parafoveal vascular density (VD) determined by the device. Superficial capillary plexus (SCP) and the deep capillary plexus (DCP) were segmented automatically. VDs measured in the optic disc region contained the radial peripapillary capillary (RPC) density. Scans with a signal strength index <70 were excluded. Previous articles have describe the algorithm (19,20).

Statistical Analysis

SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for analyses. Mean, standard deviation and percentage were used for descriptive statistics. Chi-square test and independent t-test were used to comparison of the datas.

Results

Right eyes of 98 participants were included in the study. The IDCM group included 48 patients and the control group were formed with 50 patients. Table 1 represents the demographic and clinical features of the participants.

Table 2 shows the imaging results. FAZ values in the IDCM group were significantly higher ($p<0.001$). There was no significant difference between the SCP density values of the two groups ($p>0.05$ for all). However, the DCP and RPC density values of the IDCM group were significantly lower in all quadrants of peripapillary area (Figure 1).

Discussion

Decreases in ocular blood flow and choroidal thickness in patients with CHF as well as retinal arteriolar narrowing due to HT, myocardial infarction, and CHF have been reported in previous studies (9,10,21-23). It has also been shown that retinal arteriolar narrowing and retinopathy findings can be used to predict CHF risk in patients with HT and CHD (22-24).

The low cardiac output due to impaired ventricular function causes compensatory vasoconstriction in the peripheral tissues to ensure feeding in more critical tissues, such as the brain and heart (25,26). Low perfusion also causes vasospasms and vasoconstriction in the ocular vessels. In addition, Almeida-Freitas et al. (21) showed ophthalmic artery blood flow impairment in patients with CHF in their Doppler study. Alnawaiseh et al. (16) found that retinal perfusion was correlated with LVEF in their OCTA study on CHF.

Based on these findings, we evaluated the data of IDCM patients considering that OCTA may reveal peripheral microvascular changes in patients with CHF. Our study revealed FAZ enlargement and an impairment in the DCP and RPC densities in patients with IDCM.

In their research on patients with CAD, Wang et al. (14) found a decrease in parafoveal VD and proposed that this was associated the location of the occluded coronary artery. However, coronary microvascular dysfunction has been shown in patients with signs of myocardial ischemia without CAD via angiography and even in asymptomatic patients with cardiovascular risk factors in previous studies (4,27). An animal study supports these results (28). In addition, left ventricular dysfunction and heart failure are thought to occur as a result of microvascular processes (5,6). Wang et al. (14) stated that OCTA can be used to detect early-stage CHF. As in our study, the results of the OCTA study of Li et al. (29) on patients with CHD revealed decreased VD in the DCP and RPC, especially among cyanotic patients, although there were no decreases in the SCP density.

The difference between the SCP and the DCP ischemic findings could be due to their specific structures and locations. In their OCTA study on rhegmatogenous retinal detachment, Woo et al. (30) proposed that perfusion pressure may be higher in the SCP, as its branches leave the retinal artery earlier than those of the DCP, and the DCP may be particularly vulnerable to tissue hypoxia and pressure changes (31,32). OCTA studies on DM and HT have shown that VD decreases specifically in the DCP as well as FAZ enlargement, similar to our results (33,34). In contrast, Rakusiewicz et al. (35) found a decrease in the SCP (not the DCP) density in their OCTA study in children with IDCM, stating that this was an unexpected result. We believe that the difference between the results is due to the difference between the patient groups. Although there is no consensus yet, VD decreases due to LVEF decreases can

Table 1. Demographic features

		IDCM group (n=48) Mean ± SD/n-%		Control group (n=50) Mean ± SD/n-%		p
Age		43.43±10.24		45.32±10.58		0.373*
Gender	Male	33	68.75%	33	66.00%	0.774**
	Female	15	31.25%	17	34.00%	
Systolic BP (mmHg)		116.97±9.38		115.1±9.23		0.320*
Diastolic BP (mmHg)		75.20±9.72		73.50±7.96		0.343*
BMI		21.97±0.97		22.22±1.34		0.311*
AL (mm)		22.56±0.85		22.85±0.76		0.073*
IOP (mmHg)		14.47±1.54		14.00±1.91		0.177*
Hb (g/dL)		14.33±0.87				
Htc (%)		41.97±2.62				
LVEF (%)		30.00±7.57				
Disease duration (year)		3.58±1.79				
NYHA	**Class 1**	30	62.50%			
	Class 2	11	22.92%			
	Class 3	7	14.58%			

*Independent t-test, **chi-square test, IDCM: Idiopathic dilated cardiomyopathy, SD: Standard deviation, BP: Blood pressure, BMI: Body mass index, AL: Axial lenght, IOP: Intraocular pressure, Hb: Haemoglobin, Htc: Haematocrit, LVEF: Left ventricle ejection fraction, NYHA: New York Heart Association

be demonstrated quantitatively with OCTA; therefore, we presume that OCTA may be useful in the follow-up of this patient group in addition to echo.

Although there are several possible explanations, underlying etiological mechanisms in the relationship between optic neuropathies and ocular ischemia remain unknown. In terms of vascular factors, it has been suggested that there may be insufficient blood supply to nourish the optic nerve (36,37). OCTA is insufficient to demonstrate the aetiology of decreased VD in the RPC. Nevertheless, in regard to our study, two possible explanations for this decrease are the loss of vascular structure and vasoconstriction as a result of chronic hypoxia and endothelial dysfunction. Excessive overlapping of radial capillaries near the optic disc may have caused errors in our results. In addition, the fact that retinal nerve fibre layer thickness was not evaluated in our study may have negatively affected our results.

Study Limitations

There was another limitation in our study. The number of participants decreased due to the exclusion of patients with additional systemic disease and poor-quality images. Prospective studies are needed to better understand microvascular changes in this patient group. With continued advances in technology, peripheral retinal VD changes may perhaps be observed via OCTA in the future.

Table 2. OCTA imaging results

	IDCM group (n=48)	Control group (n=50)	p*
	Mean ± SD/n-%	Mean ± SD/n-%	
FAZ (mm^2)	0.29±0.09	0.20±0.05	**<0.001**
SCP density (%)			
Parafovea	48.92±2.11	50.51±2.73	0.624
Superior-hemi	49.79±2.95	50.24±2.81	0.448
Inferior-hemi	50.21±2.73	50.61±2.87	0.474
Parafoveal temporal	48.16±2.93	48.78±2.98	0.3
Parafoveal superior	51.33±3.36	51.85±3.03	0.421
Parafoveal nasal	48.59±2.34	47.29±5.59	0.138
Parafoveal inferior	51.46±2.77	51.98±3.04	0.382
DCP density (%)			
Parafovea	49.05±3.81	54.81±2.88	**<0.001**
Superior-hemi	49.17±3.91	54.62±2.80	**<0.001**
Inferior-hemi	49.71±3.67	54.78±3.10	**<0.001**
Parafoveal temporal	49.02±4.04	54.69±2.97	**<0.001**
Parafoveal superior	49.37±4.05	54.44±3.33	**<0.001**
Parafoveal nasal	50.09±3.59	54.77±3.56	**<0.001**
Parafoveal inferior	49.01±3.67	54.38±3.48	**<0.001**
RPC density (%)			
Peripapillary	50.54±3.38	54.66±1.42	**<0.001**
Superior-hemi	51.52±3.54	54.78±1.78	**<0.001**
Inferior-hemi	49.85±4.32	53.52±1.78	**<0.001**
Superotemporal	55.22±4.56	56.02±3.83	**0.355**
Superonasal	48.68±5.11	52.34±4.21	**<0.001**
Nasal superior	47.83±3.87	52.34±4.28	**<0.001**
Nasal inferior	47.68±4.15	50.42±2.79	**<0.001**
Inferonasal	49.77±4.29	52.88±4.84	**0.001**
Inferotemporal	53.22±6.24	56.98±3.46	**<0.001**
Temporal inferior	50.27±4.24	53.82±2.85	**<0.001**
Temporal superior	54.60±3.76	56.67±3.89	**0.009**

*Independent t-test, OCTA: Optical coherence tomography angiography, IDCM: Idiopathic dilated cardiomyopathy, SD: Standard deviation, FAZ: Foveal avascular zone, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, RPC: Radial peripapilllary capillary

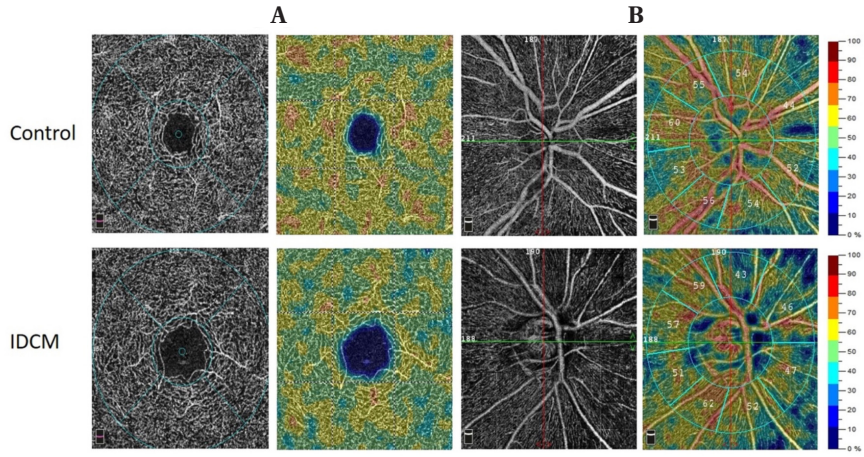

Figure 1. Images taken using the AngioVue Imaging System version 2017.1 (Optovue, Inc., Fremont, CA, USA)

A) DCP angiogram of 3×3 mm^2 and deep macular capillary network of healthy control and patient with IDCM, B) RPC angiogram of 4.5×4.5 mm^2 and peripapillary capillary network of healthy control and patient with IDCM

DCP: Deep capillary plexus, IDCM: Idiopathic dilated cardiomyopathy, RPC: Radial peripapillary capillary, ST: Superotemporal, SN: Superonasal, NS: Nasal superior, NI: Nasal inferior, IN: Inferonasal, IT: Inferotemporal, TI: Temporal inferior, TS: Temporal superior

Conclusion

The results of our study revealed a VD decrease in the DCP and RPC in addition to FAZ enlargement in patients with IDCM. Our results suggest that OCTA may possess the potential to be used in the follow-up of this patient group.

Ethics

Ethics Committee Approval: This study received approval from the Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (05/02/2019;2245).

Informed Consent: All participants stated that they agreed to participate in the study with written consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S., Concept: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S., Design: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S., Data Collection or Processing: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S., Analysis or Interpretation: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S., Literature Search: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S., Writing: A.A.A., E.D., M.K., M.E.K., D.Ö., S.S.

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

Bagcilar Med Bull 2023;8(2):167-171
DOI: 10.4274/BMB.galenos.2023.2022-10-082

Effect of the Most and the Least Favorite Music Genre of Youngs on Their ECGs

Gençlerin En Sevdiği ve En Az Sevdiği Müzik Türünün EKG'lerine Etkisi

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Abstract

Objective: Does music really touch our heart? To answer this question, this study aimed to investigate the effect of the most and least favorite type of music on echocardiography (ECG) of boys or girls.

Method: While we were recording the lead II ECG, the most and the least favorite songs of the participants were listened by a total of 54 participants (33 girls and 21 boys). The heart rates (HR), the amplitudes, and durations of the waves in the ECGs, and the durations of the intervals [P-R (s) and Q-T (s)] of the resting period 1, favorite song period, resting period 2 and least favorite song period were analyzed.

Results: Girls' HRs increased significantly ($p<0.05$) while they were listening to their most favorite music however listening to their least favorite song did not change their HRs. Unlike that, boys' HRs did not change significantly while listening to their most or least favorite music. In addition, the amplitudes and durations of the waves in the ECGs, and the durations of the intervals did not change significantly by listening to either music genre in boys or girls.

Conclusion: Girls reacted more to the type of music they liked than men. This may be due to girls having more emotional nature and thus limbic system activation.

Keywords: ECG, heart rate, most and the least favorite music, music, pulse

Öz

Amaç: Müzik gerçekten kalbimize dokunuyor mu? Bu soruyu cevaplamak amacıyla bu çalışma, genç kız ve erkeklerde en çok ve en az sevdikleri müzik türünün ekokardiyografilerine (EKG) etkisini araştırmak için tasarlandı.

Yöntem: Toplam 54 katılımcıdan (33 kız ve 21 erkek) en sevdikleri ve en sevmedikleri müzikleri dinlemeleri istendi ve II. derivasyona göre EKG kaydı yapıldı. Gönüllülerin kalp atım hızları, EKG dalgalarının genlikleri, süreleri ve intervallerin [P-R(s) ve Q-T(s)] süreleri dinlenme periyodu 1, favori şarkı periyodu, dinlenme periyodu 2 ve en az sevilen şarkı periyodu esnasında hesaplandı.

Bulgular: Kızların kalp atım hızları en sevdikleri müzik türünü dinlerken anlamlı olarak arttı ($p<0,05$), ancak en az sevmedikleri şarkıyı dinlemek kalp atım hızlarını değiştirmedi. Aksine, erkeklerin kalp atım hızları en sevdikleri veya en az sevmedikleri müzik türlerini dinlerken anlamlı bir değişiklik göstermedi. Ayrıca hem kızlarda hem de erkeklerde EKG dalgalarının ve intervallerinin genlikleri ve süreleri her iki müzik türüne göre anlamlı bir değişiklik göstermedi.

Sonuç: Sonuç olarak kızlar en sevdikleri müzik türüne erkeklerden daha çok tepki verdiler. Bunun nedeni, kızların daha duygusal bir yapıya sahip olmaları olabilir.

Anahtar kelimeler: EKG, en çok ve en az sevilen müzik, müzik, nabız

Introduction

Nowadays, music plays a meaningful role in our lives. Our body's response to music can be conscious or unconscious, involving hormonal and neurological reactions and changes in emotions and mood. But does music really touch our heart?

The question of whether and how music affects the human heart has been a popular topic of interest for scientists. The use of music in medicine dates to the 6th century. At the beginning of the 20th century, views advocating the validation and application of music for therapeutic purposes increased in modern medicine (1). It is thought that music may provide cardiovascular benefits through

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Cite this article as: Pamuk NN, Kılıç A, Meral İ. Effect of the Most and the Least Favorite Music Genre of Youngs on Their ECGs. Bagcilar Med Bull 2023;8(2):167-171

complex interactions between respiratory activity and autonomic cardiovascular control. Experimental results show that music therapy can effectively reduce the activity of sympathetic nerves and increase the activity of parasympathetic nerves (2). Several studies suggest that listening to music may have longer-term effects on the balance of sympathetic vs. parasympathetic activity (3).

Even though there have, been some studies about the effect of music on the human body, the physiological effects of listening to the most favorite and the least favorite musical genre on the heart are still not clear enough. Based on this information, this study investigates the effect of the most and the least favorite music genres of boys or girls on their ECGs.

Materials and Methods

Students between the ages of 18-30 and studying at the Faculty of Medicine of Bezmialem Vakıf University were included in the study (33 females and 21 males). The ethic regulations have been followed in accordance with the National and Institutional guidelines. All ethical procedures were approved by the Non-Interventional Research Ethics Committee, Bezmialem University (04.06.2021-18725). An informed consent form was read and signed to obtain the participants' consent that they voluntarily participate. The compliance of the patients who will participate in the study with the inclusion and exclusion criteria has been checked. Selection criteria included similar age (18-30 years old), body mass index (20-25), being student in faculty of medicine, not using any treatment or medication during the study period. Exclusion criteria included that the participants had any acute or chronic illness.

ECG Recording

A total of 54 participants (33 females and 21 males) were asked to listen to their favorite and least favorite music while we recorded a lead II ECG. The ECG signals were recorded through the PowerLab data system (PowerLab System, ADInstruments), which contained an input amplifier (BioAmp). A five-lead patient cable was connected to the input of the BioAmp. The inner aspect of the right forearm just above the wrist was rubbed briskly with alcohol. A disposable electrode was then placed onto the cleansed area. The electrodes were placed in the same way for both legs, attaching the electrodes a few inches above the subject's ankle. For the record from Lead II, cables were snapped on the electrodes as follows: Negative to the right arm, positive to the left leg, and earth to the right leg. The paper speed was adjusted to 25 mm/sec, and 1 cm =1 mV.

The subjects lied in a supine position on a wheeled bed and calmed down for 4 min to get rid of stress and slow down their heart rate (HR) (resting 1 period, R1). They were told to close their eyes and try not to think about anything so that their emotional state would not affect their hearts' responses. Afterwards, they listened to their self-chosen favorite song for 4 min (favorite song period, FavS) before resting for another 4 minutes (resting 2 period, R2). During this period, they were allowed to think about anything they wanted, and to feel freely what their favorite song made them to feel. Finally, their least favorite song was played for 4 min (least favorite song period, LFavS), and the process was done. The ECGs were recorded at the beginning of the study and at the end of each period. The HRs, the amplitudes and durations of the waves [P (s), P (mV), QRS (s), QRS (mV), T (s) and T (mV)] in the ECG, and the durations of the intervals [P-R (s) and Q-T (s)] were calculated.

Statistical Analysis

Statistical analysis was performed with Instat Statistical Package Program (GraphPad Prism Version 8.0.1 Software Program San Diego, CA) at a significancy level of $p<0.05$. The normality of the data was tested with Shapiro-Wilk test. The data with a normal distribution analyzed by One-Way ANOVA and the data without normal distribution analyzed by Kruskal-Wallis test. The post-hoc Bonferroni and Dunn tests were used to indicate differences between the groups. All results were expressed as ± standard deviation of means (standard deviation).

Results

It was found that the female's HRs decreased ($p<0.05$) during the R1 period with an average of 82,33/min at the beginning and 73,76/min at the end of the R1 period (Figure 1). Listening to their favorite song increased ($p<0.05$) the HR significantly, shown as an average of 79,10/min at the end of the FavS period. However, listening to their least favorite song did not change significantly ($p>0.05$) the HR (only slight increase was observed) with an average of 75,93/min at the end of their LFavS period (Figure 2). On the other hand, male's HRs did not change significantly while listening to their favorite nor their least favorite music (Figure 2). In addition, the amplitudes, and durations of the waves in the ECGs, and the durations of the intervals did not change ($p>0.05$) by the listening of either music genre in males or females (Table 1).

Discussion

Since ancient times music has been considered a form of expression that affects both the body and the soul of people. The rhythm of a piece of music is perceived acoustically and translated into motor movement patterns that motivate physical movement or clapping. Music is one of the factors of the environment, which is one of the influences on health. Nowadays, the use of music is part of the medical standard of treatment in various medical fields, such as in pain and palliative medicine, in neurology and psychiatry or in pediatrics as well as in the field of rehabilitation medicine or in curative and special education (4-7).

The effect that music has on physical processes is explained by the effects of the nervous system and emotional states on the human body and organs (8). With its harmonic, melodic and rhythmic elements, music can influence the human body, its heart rhythm, and other physiological processes in such a way because the central nervous system, especially through the structures of the limbic system, has a direct influence on various organs (9). The limbic system regulates emotional processes and is involved in learning and memory formation: The enjoyment and artistic understanding of music are not possible without the cooperation of the limbic system (10). Hypothalamus, one of the major centers of the limbic system, controls the autonomic nervous system, itself another negative feedback loop with excitatory (sympathetic) and inhibitory (parasympathetic) components.

Music can cause cardio-respiratory modifications. Music is associated with changes in activity in brain structures known to modulate cardiac activity (11). While predominantly

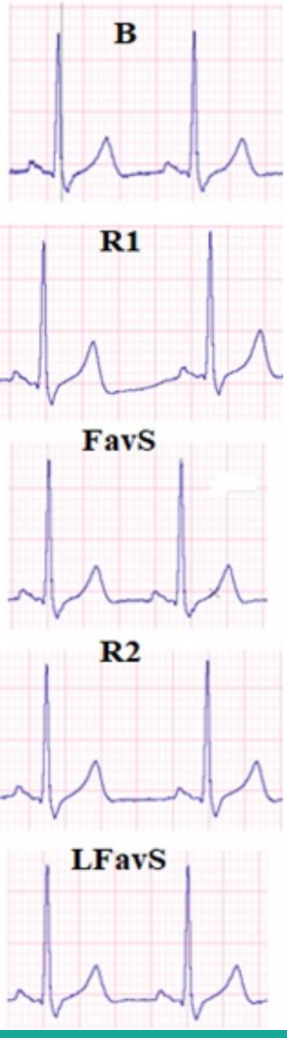

Figure 1. Representative ECGs of girls (n=33)

B: Beginning, R1: Resting 1, FavS: Favorite song, R2: Resting 2, LFavS: Least favorite song. Paper speed =25 mm/sec, 1 cm =1 mV

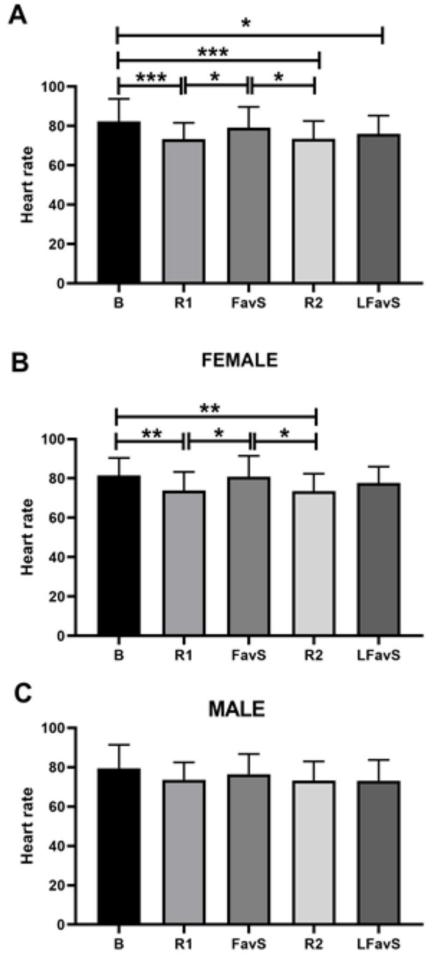

Figure 2. The heart rate values of all participants (A, n=54), females (B, n=33) and males (C, n=21)

*B: Beginning, R1: Resting 1, FavS: Favorite song, R2: Resting 2, LFavS: Least favorite song. Data are presented as mean ± standard deviation. *p<0.05, **p<0.01, ***p<0.001 statistical significancy*

Table 1. The amplitudes and durations of the waves, and the durations of the intervals in ECGs of girls (n=33)

Female					
Parameter	**B**	**R1**	**FavS**	**R2**	**LFavS**
P (s)	0.1089±0.016	0.117±0.015	0.1082±0.017	0.1112±0.019	0.1071±0.017
P (mV)	0.1039±0.021	0.1038±0.025	0.0976±0.025	0.0995±0.027	0.0964±0.027
QRS (s)	0.085±0.016	0.0904±0.021	0.0819±0.015	0.0888±0.019	0.12±0.2
QRS (mV)	0.8073±0.317	0.8308±0.33	0.8009±0.31	0.8157±0.332	0.8032±0.336
T (s)	0.2112±0.107	0.2052±0.046	0.1974±0.043	0.2095±0.047	0.202±0.046
T (mV)	0.1901±0.068	0.2108±0.07	0.1992±0.062	0.2116±0.073	0.2009±0.064
P-R (s)	0.1552±0.026	0.1624±0.027	0.1596±0.023	0.1622±0.022	0.1604±0.019
Q-T (s)	0.3660±0.038	0.3928±0.039	0.3786±0.039	0.3842±0.038	0.3766±0.032

B: Beginning, R1: Resting 1, FavS: Favorite song, R2: Resting 2, LFavS: Least favorite song, Data were presented as mean ± standard deviation, $p<0.05$, statistical significance compared to B group

quiet music has a relaxing effect on the psyche and body and therefore produces a general calming effect with lowering the HR and blood pressure, loud and rhythmic music has a stimulating effect and causes an acceleration of the pulse and an increase in blood pressure (12). Magnetic resonance tomography studies on healthy subjects showed increased cerebral activity in the prefrontal, auditory, and parietal areas, as well as in the cingulate and lower gyrus, which are closely related to the limbic system, and are thought to affect cardiopulmonary mechanisms in this way (13,14). In a study, it was determined that classical music had a significantly lower effects on cardiovascular parameters such as blood pressure and HR in both human and animal subjects (15). Trappe (16) found that heavy metal music increased HR and can lead to stress and arrhythmias. Escher and Evéquoz (17) investigated the effect of relaxing music on HR and HR variability in 23 healthy young individuals by means of 24-hour holter-ECG. They suggested that relaxing music (Bach, Vivaldi, Mozart) significantly decreased the HR and HR variability. Suguna and Deepika (12) have suggested that listening to slow beat music activates parasympathetic nervous system thus causing a decrease in HR, while listening to fast beat music activates sympathetic nervous system thus causing an increase in HR. Similarly, Koelsch and Jäncke (18) reported that HR and respiratory rate were increased in response to exciting music compared with calming music. Trappe and Voit (19) also found that the music by Mozart and Strauss lowered the subjects' blood pressure and HR.

There are only a few studies showing the direct effect of one's personal choices of music genres on the heart by using an ECG. Sills and Todd (20) investigated the change in HR by letting twenty-four high-school students listen to a selection of six pieces of music, each of a different type (classical, electronic, jazz, world, RnB, and rock). A hand-held HR monitor was used to measure and record the HR of each student. The results suggested that students' average HRs throughout their favorite music selection (rock) were not significantly different from their resting HRs, but students' HRs increased significantly after listening to their favorite music selection.

According to our results, a decrease in resting HR was an expected finding since it is known that the parasympathetic nervous system is stimulated at rest, thus increasing the mean resting heart rate to 60-100 bpm (21). Listening to one's favorite song is mostly associated with having good mood and feeling excitement due to activation of sympathetic system. These two things lead to increase the HR. It is still unclear why the favorite song has a significant effect on the increase whereas least favorite songs only slightly increase the HR. This is may be related to the control of the limbic system over the cardiac centers. Thus, when listening to the least favorite type of music, limbic system is not activated and may not exert a stimulating effect on the cardio regulatory centers.

Study Limitations

One of the limitations of our study was the lack of the population and the equipment required for continuous blood pressure measurement. However, we considered that blood pressure results are also in line with the results of the heart rate with the activation of cardiac regulatory centers.

Conclusion

The results suggested that listening to favorite music has an increasing effect on heart rate. This increment may have occurred by increasing sympathetic tone and activating the cardio-regulatory center through the activated limbic

system. Additionally, listening to favorite song was more effective on heart rates in females than in males. That may be the emotional nature of girls and with more limbic discharge.

Ethics

Ethics Committee Approval: All ethical procedures were approved by the Non-Interventional Research Ethics Committee, Bezmialem University (04.06.2021-18725).

Informed Consent: An informed consent form was read and signed to obtain the participants' consent that they voluntarily participate.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: İ.M., Design: İ.M., Data Collection or Processing: N.N.P., A.K., İ.M., Analysis or Interpretation: N.N.P., A.K., İ.M., Drafting Manuscript: N.N.P., A.K., Writing: İ.M., Final Approval and Accountability: İ.M.

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

Bagcilar Med Bull 2023;8(2):172-178
DOI: 10.4274/BMB.galenos.2023.2022-10-083

Serum Endocan Levels as a Valuable Biomarker for Discrimination of Critical and Stable COVID-19 Patients

Kritik ve Stabil COVID-19 Hastalarının Ayırımı için Değerli Bir Biyobelirteç Olarak Serum Endokan Düzeyleri

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Abstract

Objective: The primary aim of the study was to investigate the relationship between serum endocan levels and clinical condition of Coronavirus disease-2019 (COVID-19) patients. The secondary aim was to investigate the associations between the serum endocan levels and other inflammatory parameters with regard to clinical outcomes.

Method: A total of 80 COVID-19 patients, 44 in stable and 36 in critical condition, with positive polymerase chain reaction test result, older than 18 years of age and whose first admission complaint was not either heart attack or ischemic stroke were included in this study. Patients' characteristics and clinical outcome, hematological and biochemical parameters, thorax computed tomography, treatment approach, vital signs, and COVID-19 symptoms were analyzed.

Results: The mean age of the critical patients was significantly higher than that of the stable patients (71.00±13.27 and 53.36±17.80; p<0.001). Blood and serum parameters (C-reactive protein, ferritin, procalcitonin, lactate, neutrophil-to-lymphocyte ratio, D-dimer, troponin T, urea, creatinine, white blood cell, and international normalized ratio) were significantly higher in critical patients (p<0.05). Serum endocan levels were significantly higher in critical patients (518.9±513.31 ng/mL; p<0.001). Endocan, age, lactate, and troponin T were found to be significantly effective to distinguish critical patients from the stable patients in the multivariate model. Receiver operating characteristic curve analysis revealed that 244.9 ng/mL endocan level had 88.9% sensitivity and 63.6% specificity for critical patients.

Öz

Amaç: Çalışmada primer amaç, Koronavirüs hastalığı-2019 (COVID-19) hastalarında serum endokan düzeyleri ile klinik durumları arasındaki ilişkiyi değerlendirmekti. Sekonder olarak ise klinik sonuçlar açısından serum endokan seviyeleri ile diğer enflamatuvar parametreler arasındaki ilişkileri ortaya koymayı hedefledik.

Yöntem: Çalışmaya, polimeraz zincir reaksiyon testi pozitif olan, 18 yaşından büyük, 44'ü stabil, 36'sı kritik durumda, ilk başvuru şikayeti kalp krizi veya iskemik inme olmayan toplam 80 COVID-19 hastası dahil edildi. Hastaların özellikleri ve klinik sonuçları, hematolojik ve biyokimyasal parametreleri, endokan düzeyleri, toraks bilgisayarlı tomografileri, tedavi yaklaşımları, vital bulguları ve COVID-19 semptomları değerlendirildi.

Bulgular: Kritik hastaların ortalama yaşı stabil hastalardan anlamlı derecede yüksekti (71,00±13,27 ve 53,36±17,80; p<0,001). Kritik hastalarda kan ve serum parametreleri (C-reaktif protein, ferritin, prokalsitonin, laktat, nötrofil-lenfosit oranı, D-dimer, troponin T, üre, kreatinin, beyaz kan hücresi ve uluslararası normalleştirilmiş oran) anlamlı olarak daha yüksekti (p<0,05). Kritik hastalarda serum endokan düzeyleri anlamlı olarak yüksekti (518,9±513.31 ng/mL; p<0,001). Endokan, yaş, laktat ve troponin T'nin kritik hastaları stabil hastalardan ayırt etmede önemli ölçüde etkili olduğu bulundu. Kritik hastalar için 244,9 ng/mL endocan seviyesinin %88,9 duyarlılığa ve %63,6 özgüllüğe sahip olduğu görüldü.

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Cite this article as: Öztürk D, Altınbilek E, Melekoğlu A, Çalık M, Demirci B, Coşkun A. Serum Endocan Levels as a Valuable Biomarker for Discrimination of Critical and Stable COVID-19 Patients. Bagcilar Med Bull 2023;8(2):172-178

Abstract

Conclusion: Serum endocan levels are a useful biomarker to predict the clinical condition on the admission and may predict the prognosis and outcomes of COVID-19 patients.

Keywords: COVID-19, endocan, prognosis

Öz

Sonuç: Serum endokan seviyeleri, başvurudaki klinik durumu tahmin etmek için yararlı bir biyobelirteçtir ve COVID-19 hastalarının prognozunu ve sonuçlarını öngörebilir.

Anahtar kelimeler: COVID-19, endokan, prognoz

Introduction

Coronavirus disease-2019 (COVID-19) that emerged from China is a multisystem disease (1). Various symptoms fewer, dyspnea, fatigue, headache, loss of smell and taste were reported for COVID-19 (2-5), however, the complete list of manifestations of COVID-19 is yet to be clarified. In addition, other COVID-19 symptoms such as cardiovascular events ranging from arrythmias to sudden death in patients with or without an accompanying cardiovascular disease (6,7). Moreover, coagulopathy has been reported in approximately 50% of severe COVID-19 patients (8).

A serious effort has been made in the diagnosis and classification disease severity in COVID-19. For this purpose, various studies have investigated the possible biomarkers and associations between them, COVID-19 severity, and outcome (9-11). Serum endothelial-specific molecule-1 (endocan) is a proteoglycan that has been implicated as a marker of endothelial cell damage (12,13) and was found that its secretion is induced by pro-inflammatory cytokines, lipopolysaccharides (14) and pro-angiogenic factors (15). Several studies reported that serum endocan levels were elevated in various endothelium-related pathologies including diabetes (16), coronary artery disease (17), hypertension (18) and pulmonary thromboembolism (19,20).

Serum endocan levels were associated with the mortality in patients with coagulopathy and mortality in patients with disseminated intravascular coagulation (21). In addition, endocan levels were indicated to be a potential inflammatory and cardiovascular disease marker (12). On the other hand, in COVID-19 patients, endocan was reported to be useful prognostic biomarker (7,22). Therefore, in this study, the primary aim was to investigate the serum endocan levels in COVID-19 patients according to their clinical condition with regards to mortality and morbidity. The secondary aim of the study was to investigate the associations between the serum endocan levels and other inflammatory parameters with regards to clinical outcome.

Materials and Methods

Study Design and Population

This prospective single-centered study was conducted between 01/01/2021 and 31/12/2021 after the approval by Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (date: 22.12.2020, number: 1753). All procedures performed were in line with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments.

A total of 80 COVID-19 patients, 44 of them were stable and 36 of them were critical, were included in the study. The patients admitted to our hospital serving as a pandemic hospital and whose COVID-19 polymerase chain reaction (PCR) test result were detected positive in the emergency department (ED), patients older than 18 years of age and patients whose first admission complaint was not either heart attack or ischemic stroke were included in this study. The exclusion criteria were being younger than 18 years of age, having negative PCR test result, having missing data in the patient files, and having the first admission complaint as either heart attack or ischemic stroke. Written informed consents of the patients were obtained on arrival to the hospital for their anonymized information to be published.

Patients' clinical outcomes were recorded as discharge, hospitalization in ward, referral to intensive care unit (ICU), and death. Hematological and biochemical parameters, thorax computed tomography (CT), treatment that they received, vital signs, COVID-19 symptoms and chronic disease were investigated and compared between the patient groups who were in stable condition and who were in critical condition.

Intensive Care Admission Criteria

- Patients whose vitals are unstable:

- Dyspneic and tachypneic patients (respiratory rate ≥30/min)
- SpO_2 <90% or PaO_2 <70 mmHg despite 5 L/min oxygen therapy

- Tachycardia >100/min
- Hypotension (systolic blood pressure <90 mmHg and more than 40 mmHg decrease from normal systolic blood pressure (SBP) and mean arterial pressure <65 mmHg

- Clinical and laboratory abnormality:

- Increased oxygen requirement in follow-ups
- Patients with acute kidney injury, acute liver function tests, confusion, acute organ dysfunction such as acute bleeding diathesis and immunosuppression
- Troponin elevation and arrhythmia
- In arterial blood gas: Lactate >2 mmol and PaO_2/FiO_2 <200
- Presence of skin disorders such as skin findings of capillary return disorder

Measurement of Serum Endocan Levels

Serum endocan levels were measured by using Human Endothelial cell-specific molecule 1 (Endocan) Enzyme-Linked ImmunoSorbent Assay (ELISA) Kit (E3160Hu; Bioassay Technology Laboratory) according to manufacturer's instruction. Basically, whole blood samples collected were incubated at room temperature for 20 minutes and centrifuged at 3000 rpm for 20 minutes. The serum samples collected were aliquoted and stored at -80 °C until the analyses. Serum endocan levels were determined by measuring absorbance of the samples on a microplate reader at 450 nm by using a microplate reader (ELx800 Absorbance Microplate Reader (BioTek Instruments).

Statistical Analysis

Statistical analyses were conducted by using SPSS version 22.0 (IBM, USA). In descriptive statistics, mean, standard deviation, median, frequency, and ratio were used. Kolmogorov-Smirnov test was used to evaluate the distribution of the data. Quantitative independent data were analysed by using either unpaired t-test or Mann-Whitney U test depending on the distribution of the data. Qualitative independent data were analysed by using the chi-square test in case of the test conditions were met, or else Fischer's Exact test was used. Univariate or multivariate logistic regression analyses were performed to investigate the level of effect. Receiver operating curve ROC analysis was performed to investigate the effect of endocan in predicting the clinical status of the patient. A p-value lower than 0.05 was considered as statistically significant.

Results

The mean age of the patients were 61.30±18.11 years, while the mean age of the critical patients was significantly higher than the stable patients (71.00±13.27 vs. 53.36±17.80; p<0.001). On the other hand, there were no significant associations between the gender and the clinical status of the patients (p>0.05). With regards to the symptoms, coughing was more common in stable patients (p=0.020), while general status instability was more common in critical patients (p=0.001). However, there were no associations between the patients' clinical status and the presence of chronic diseases. SBP and diastolic blood pressure was significantly lower, while heart rate (HR) was significantly higher in critical patients (p<0.05). Moreover, body temperature and respiratory rate were significantly higher in critical patients, while oxygen saturation was significantly lower in stable patients (p<0.001; Table 1).

Serum endocan levels were significantly higher in the critical patients than stable patients (p<0.001). On the other hand, while alanine transaminase (ALT) levels did not significantly differ between the groups, all other hematological parameters were significantly higher in critical patients (p<0.05). However, PaO_2/FiO_2 was significantly lower in critical patients (p<0.001; Table 2).

Among the thorax CT infiltrative involvements of the patient groups at the time of admission to the ED, moderate and severe involvements were seen critical group, and advanced involvement was significantly higher in this group than in the stable group (p< 0.001). It was determined that 18 patients in the critically ill group received endotracheal mechanical ventilation therapy. None of the patients in the stable group received mechanical ventilation. Antiviral treatment was given to all patients, while the number of patients receiving anticoagulant, antibiotics, steroid, high-flow O_2 therapy and positive inotropic agents was significantly higher in the critical group than in the stable group (p<0.05). Mortality was observed in 14 patients, and all of these patients were in the critical group (Table 3).

In the univariate model, endocan, age, C-reactive protein, procalcitonin, ferritin, lactate, neutrophil-to-lymphocyte ratio, D-dimer, high-sensitivity troponin T and international normalized ratio levels showed significant effectiveness in distinguishing the critical group from the stable group (p<0.05). On the other hand, it was determined

Table 1. Symptoms, chronic diseases present and vital signs of the patients according to clinical status of the patients

	Critical [n (%)]	Stable [n (%)]	Total [n (%)]	p-value
Gender				
Male	22 (61.1%)	25 (56.8%)	47 (58.8%)	0.873 χ^2
Female	14 (38.9%)	19 (43.2%)	33 (41.2%)	
Age (mean ± SD)	71.0±13.27	53.3±17.79	61.3±18.1	**0.001 t**
Symptoms-chronic diseases				
Fewer	11 (30.6%)	10 (22.7%)	21 (26.3%)	0.592 χ^2
Dyspnea	33 (91.7%)	33 (75.0%)	66 (82.5%)	0.075 χ^2
Cough	13 (36.1%)	22 (50.0%)	35 (43.8%)	0.308 χ^2
Diarrhea	2 (5.5%)	4 (9.1%)	6 (7.5%)	0.685 χ^2
Myalgia	5 (13.9%)	7 (15.9)	12 (15.0%)	0.801 χ^2
Loss of taste/smell	3 (8.3%)	9 (20.5%)	12 (15%)	0.208 χ^2
Sore throat/ headache	1 (2.7%)	9 (20.5%)	10 (12.5%)	**0.020 χ^2**
General status instability	11 (30.6%)	1 (2.2%)	12 (15.0%)	**0.001 χ^2**
CAD	9 (25.0%)	13 (29.5%)	22 (27.5%)	0.840 χ^2
HT	13 (36.1%)	17 (38.6%)	30 (37.5%)	0.816 χ^2
DM	11 (30.6%)	15 (34.1%)	26 (32.5%)	0.924 χ^2
KOAH	5 (13.9%)	4 (9.1%)	9 (11.3%)	0.724 χ^2
Malignancy	4 (11.0%)	3 (6.8%)	7 (8.75%)	0.695 χ^2
CKD	2 (5.5%)	1 (2.2%)	3 (3.75%)	0.585 χ^2
CVE	3 (8.3)	2 (4.5%)	5 (6.3%)	0.653 χ^2
Vital signs (median/min-max)				
SBP (mmHg)	105.0 (7-160)	120.0 (90-160)		**0.001ᴍ**
DBP (mmHg)	70.0 (40-100)	76.0 (60-100)		**0.005ᴍ**
HR (beat per min)	110.0 (90-130)	88.0 (70-115)		**<0.001ᴍ**
Body temperature (°C)	37.6 (36.7-39.0)	36.0 (36.5-38.0)		**<0.001ᴍ**
SO_2 (%)	84.5 (50-94)	95.0 (80-97)		**<0.001ᴍ**
Respiratory rate (min)	29.5 (20-40)	16.0 (14-30)		**<0.001ᴍ**

CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVE: Cerebrovascular event, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HR: Heart rate, HT: Hypertension, SBP: Systolic blood pressure (Statistical analysis: t: t-test; χ^2: chi-square (Fisher's Exact test) ᴍ: Mann-Whitney U), t: t-test, SD: Standard deviation

Table 2. Hematological parameters of the patients according to their clinical status

Parameters	Critical Median (min-max)	Stable Median (min-max)	p
Endocan (ng/mL)	343.4 (187-2651)	223.3 (100-1923)	**<0.001**
CRP (mg/L)	84.0 (6-300)	27.0 (2.5-196)	**0.001**
Ferritin (µg/L)	470.0 (45-6396)	143.5 (17-2478)	**0.001**
PCT (µg/L)	0.11 (0.01-10)	0.01 (0.01-7.5)	**0.001**
Lactate (µg/L)	2.6 (1.2-21)	1.4 (0.8-3.4)	**0.001**
PaO_2/FiO_2	189.0 (98-306)	326.0 (131-457)	**0.001**
NLR	7.04 (1.8-53.3)	3.4 (1-12)	**0.001**
D-dimer (µg/L)	930.0 (200-11650)	391.0 (120-6918)	**0.001**
High-sensitivity troponin T (ng/L)	0.04 (0.04-0.35)	0.009 (0.01-0.064)	**0.001**
Urea (mg/dL)	52.5 (10-120)	32.5 (13-108)	**0.001**
Creatinine (mg/dL)	1.15 (0.65-1.8)	0.92 (0.5-2.0)	**0.005**
WBC (x10^9/L)	11.8 (4.3-22)	6.9 (3.4-18)	**0.001**
INR	1.11 (0.9-2.1)	0.99 (0.87-1.39)	**0.001**
AST (U/L)	38.0 (15-131)	26.5 (14-177)	**0.001**
ALT (U/L)	23.5 (8-133)	18.5 (7-120)	0.057

ALT: Alanine transaminase, AST: Aspartate aminotransferase, CRP: C-reactive protein, INR: International normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin, WBC: White blood cell. Statistical analysis: Mann-Whitney U test

Table 3. Thorax CT findings and treatment approach in patient groups

	Critical [n (%)]	Stable [n (%)]	Total [n (%)]	p
Thorax CT findings				
Mild	-	16 (36.4%)	16 (20.0%)	**0.001**
Moderate	13 (36.1%)	17 (38.6%)	30 (37.5%)	
Severe	23 (63.9%)	11 (25.0%)	34 (42.5%)	
Treatment approach				
Mechanical ventilation	18 (50.0%)	-	18 (22.5%)	**0.001**
Antiviral	36 (100%)	44 (100%)	80 (100%)	-
Antibiotics	27 (75.0%)	8 (18.2%)	35 (43.8%)	**0.001**
Steroid	34 (94.4%)	8 (18.2%)	42 (52.5%)	**0.001**
Anticoagulant	33 (91.7%)	13 (29.5%)	46 (57.5%)	**0.001**
High-flow oxygen therapy	30 (83.3%)	9 (20.5%)	39 (48.8%)	**0.001**
Positive inotropic agents	17 (47.2%)	1 (2.3%)	18 (22.5%)	**0.001**
Mortality	14 (38.9%)	-	14 (17.5%)	**0.001**

CT: Computed tomography; χ^2: chi-square (Fisher's Exact) test

that endocan, age, lactate and high-sensitivity troponin T showed significant effectiveness in distinguishing the groups in the multivariate model (p<0.05; Table 4).

It was determined that serum endocan levels higher than 244.9 ng/mL was significant in distinguishing the critically ill group from the stable patient group (p<0.05) (area under the curve: 0.75, confidence interval: 0.639-0.855) with sensitivity and specificity as 88.9% and 63.6%, respectively (Figure 1).

We analyzed whether there was a correlation between age and endocan level, but found no statistical correlation (p=0.313 correlation coefficient: -0.114) (not shown in the tables).

Table 4. Multivariate logistic regression analysis results of the parameters

Variables	Odds ratio	95% confidence interval Lower-upper	p
Endocan	**1.003**	**0.994-0.999**	**0.015**
Age	1.099	0.828-0.989	**0.028**
CRP	1.017	0.965-1.002	0.74
PCT	0.537	0.108-3.106	0.533
Ferritin	0.046	0.998-1.002	0.994
Lactate	1.861	0.040-0.610	**0.038**
NLR	0.184	0.646-1.070	0.152
D-dimer	0.999	0.999-1.003	0.160
High-sensitivity troponin T	70.12	0.100-0.440	**0.022**
INR	1.971	0.001-16.006	0.416

CRP: C-reactive protein, INR: International normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin. Nagelkerke R square =0.81

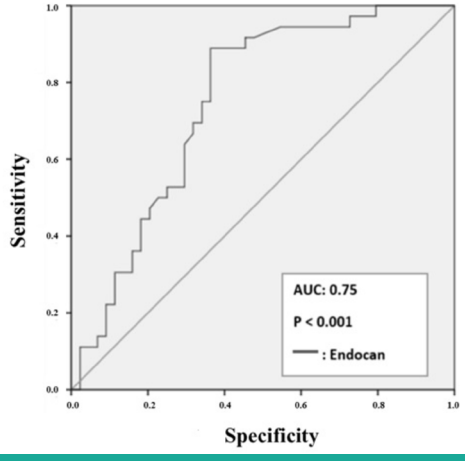

Figure 1. ROC curve analysis of endocan
ROC: Receiver operating characteristic

Discussion

In the present study, we aimed to investigate whether serum endocan levels may have a prognostic value in COVID-19 patients according to their clinical condition with regards to mortality and morbidity and endocan levels can be used to discriminate the clinical condition of the patients. Endocan levels of patients in critical condition were significantly higher than the patients with stable condition (p=0.000). Moreover, serum endocan levels higher than 244.9 ng/mL significantly distinguish the critically ill patient from the stable patient (p<0.001).

Various conditions related with endothelial dysfunction have been associated with elevated serum endocan levels (23-27). On the other hand, highly elevated endocan levels have been shown in other various conditions such as cancer (28,29), diabetes (30) and multiple sclerosis (31). Elevated levels of endocan in these conditions can be explained by both either the vascular inflammation due to the condition or the elevated expression levels of endocan by in the tissue itself (28-31).

COVID-19 has been associated with both macro/micro inflammation in both pulmonary and extrapulmonary vasculature (32) leading to thromboembolic complications that may be useful for prediction of prognosis of the patients (33). An earlier study reported a significant association between endocan levels and poor prognosis (7). Previously, it was shown that serum endocan levels are elevated in COVID-19 patients (34). Moreover, the first study reported that serum endocan levels of 276.4 ng/mL predicts poor prognosis with 97% sensitivity and 85% specificity (7) and the latter indicated serum endocan levels of 202 ng/mL at the admission predicts COVID-19 with 86.7% sensitivity and 50% specificity (34). In our study, we have found that serum endocan levels were significantly higher in the patients in critical condition and serum endocan levels of 244.9 ng/mL predicts the clinical status of the patients with 88.9% sensitivity and 63.6% specificity.

Several factors were investigated to predict the severity and outcomes of COVID-19 (35-39). In our study, multivariate logistic regression analysis revealed that endocan, age, lactate and high-sensitivity troponin T are associated with the clinical status of COVID-19 patients and that is in line with the previous studies (35-39).

In Liang et al.'s (40) study, which was defined as a composite measure of critical illness, ICU admission, invasive ventilation, or death among hospital-admitted COVID-19 patients, they found that increasing age and high

lactate level were associated with poor prognosis. Due to the decreasing vital capacity with advanced age, the clinical course is more severe in COVID-19 patients. In our study, we found that being old is associated with a poor prognosis. In addition, increased lactate levels associated with tissue perfusion impairment indicate a poor prognosis. These parameters were higher in the critically ill group compared to the stable group.

Study Limitations

Our study had several limitations. First of all, serum endocan levels were measured only on admission. Although the study primarily aimed to predictive capacity of the condition of a COVID-19 patient on admission, it could be relevant to take several measurements to make a comment on the correlation between the alterations in the endocan levels throughout the disease progression. Secondly, number of patients included in this study were low, therefore, statistical power for the analysis to check the relationship between factors, such as comorbid factors, and clinical status of the patients was low.

Conclusion

Our results suggests that serum endocan levels are useful to predict the patients' clinical condition on the admission and may predict the prognosis and outcomes of COVID-19 patients.

Ethics

Ethics Committee Approval: This prospective single-centered study was conducted between 01/01/2021 and 31/12/2021 after the approval by Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (date: 22.12.2020, number: 1753).

Informed Consent: Required consent has been obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ö., Concept: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Design: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Data Collection or Processing: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Analysis or Interpretation: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Literature Search: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Writing: D.Ö., E.A., A.M., M.Ç., B.D., A.C.

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

Bagcilar Med Bull 2023;8(2):179-187
DOI: 10.4274/BMB.galenos.2023.2023-03-025

Evaluation of Health Literacy and Obesity-related Well-being in Obese Adults

Obez Yetişkinlerde Sağlık Okuryazarlığının ve Obeziteyle İlişkili İyi Olma Halinin Değerlendirilmesi

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Abstract

Objective: Obesity can cause many diseases and reduces the quality of life. Health literacy (HL) can play a decisive role in terms of the health status of the obese person. In this study; it was aimed to evaluate the relationship between HL and obesity-related well-being in obese adults and examine the affecting factors.

Method: This cross-sectional study consisted of individuals aged 18-65 years who were admitted to the family medicine outpatient clinic of a tertiary hospital, between April and July, 2022, with a body mass index (BMI) of 30 kg/m^2 and above for the last year, and who met the inclusion criteria. The patient information form, the obesity-related well-being questionnaire (ORWELL 97-TR), and the health literacy scale-short form (HLS-SF) was used to obtain data.

Results: Among 201 participants in the study, 70.6% (n=142) were mildly obese. The mean value of the HLS-SF index score was 32.71±9.93, and the ORWELL 97-TR total score was 41.22±14.86. A significant correlation was determined between HLS-SF and ORWELL 97-TR relevance-"social relations" sub-dimension score (r=0.292; p<0.001). There was a significant difference between the HLS-SF score and obesity duration (p=0.030), weight change in the last year (p=0.048), diet (p=0.048), and exercising (p<0.001). A significant difference was observed between ORWELL 97-TR total score and age (p=0.007), educational status (p=0.001), BMI (p=0.016), weight change in the last year (p=0.001), diet (p<0.001) and exercising (p=0.009).

Conclusion: According to the scores obtained from the scales in this study, the quality of life of the participants was moderate, while HL was found to be moderate-good. However, as HL increased, the quality of life

Öz

Amaç: Obezite; pek çok hastalığa yol açabilmekte olup yaşam kalitesini de düşürmektedir. Sağlık okuryazarlığı (SOY) ise obez kişinin sağlık durumu açısından belirleyici rol oynayabilmektedir. Bu çalışmada; obez yetişkinlerde SOY ile obeziteyle ilişkili iyi olma hali arasındaki ilişkinin değerlendirilmesi ve etkileyen faktörlerin incelenmesi amaçlanmıştır.

Yöntem: Kesitsel bu çalışma; üçüncü basamak bir hastanenin aile hekimliği polikliniğine Nisan-Temmuz 2022 tarihleri arasında başvuran 18-65 yaş arası kişilerden, son 1 yıldır beden kitle indeksi (BKİ) 30 kg/m^2 ve üzeri olan ve çalışmaya dahil etme kriterlerini karşılayanlar ile gerçekleştirildi. Verileri elde etmede; hasta bilgi formu, obezite ile ilişkili iyi olma anketi (ORWELL 97-TR) ve sağlık okuryazarlığı ölçeği-kısa form (SOY-KF) kullanıldı.

Bulgular: Çalışmaya dahil edilen 201 katılımcının %70,6'sı (n=142) hafif obez idi. SOY-KF indeks puanı 32,71±9,93, ORWELL 97-TR toplam puanı 41,22±14,86 idi. SOY-KF ile ORWELL 97-TR Alaka- "sosyal ilişkiler" alt boyut puanı arasında anlamlı ilişki saptandı (r=0,292; p<0,001). SOY-KF puanı ile obezite süresi (p=0,030), son 1 yılda kilo değişimi (p=0,048), diyet (p=0,048) ve egzersiz yapma (p<0,001) arasında istatistiksel olarak anlamlı farklılık saptandı. ORWELL 97-TR toplam puanı ile ise yaş (p=0,007), eğitim durumu (p=0,001), BKİ (p=0,016), son 1 yılda kilo değişimi (p=0,001), diyet (p<0,001) ve egzersiz yapma (p=0,009) arasında anlamlı bir farklılık bulundu.

Sonuç: Bu çalışmada; ölçeklerden alınan puanlara göre katılımcıların yaşam kalitesi orta düzeyde iken, SOY orta-iyi düzeyde bulundu. Ancak SOY arttıkça obez kişilerin yaşam kalitesi sosyal ilişkiler açısından olumsuz etkilenmekte idi. Daha önce diyet ve egzersiz yapanlarda SOY

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Cite this article as: Acar Ceyhan Ş, Tunç Karaman S, Basat O. Evaluation of Health Literacy and Obesity-related Well-being in Obese Adults. Bagcilar Med Bull 2023;8(2):179-187

Abstract

of obese individuals was negatively affected in terms of social relations. While HL level was higher in those who previously dieted and exercised, weight gain and longer duration of obesity were associated with lower HL. High education level, young age and weight gain negatively affected the quality of life. Our data are important in terms of emphasizing the importance of increasing HL in order for the society and health professionals to effectively manage obesity in the long-term.

Keywords: Health literacy, obesity, ORWELL 97-TR, quality of life, well-being

Öz

düzeyi daha yüksek iken kilo alımı ve uzun obezite süresi daha düşük SOY ile ilişkili idi. Yüksek eğitim düzeyi, genç yaş ve kilo alımı yaşam kalitesini olumsuz yönde etkilemekte idi. Verilerimiz toplumun ve sağlık profesyonellerinin obeziteyi uzun vadede etkili bir şekilde yönetebilmesi hususunda SOY'yi artırmanın önemini vurgulaması açısından önem arz etmektedir.

Anahtar kelimeler: İyi oluş, obezite, ORWELL 97-TR, sağlık okuryazarlığı, yaşam kalitesi

Introduction

Obesity is defined by the World Health Organization as the accumulation of an excess or abnormal amount of fat in the body. More than 1 billion adults are predicted to be obese by 2025 (1,2). In addition to being an important cause of mortality and morbidity, obesity can negatively affect people psychologically, socially and economically, reducing well-being. Awareness of obesity needs to be increased in order to prevent obesity, to treat it when it occurs, and to reduce all the negative consequences it causes (3).

In this context, the concept of health literacy (HL), defined as the ability of individuals to receive basic health information and services, and to understand and process the information they reach, plays a vital role so that they can make appropriate health decisions (4). People with a good HL level are known to adopt behavior that positively affect health, such as healthy eating habits and regular exercise (5). On the contrary, there is new evidence that poor HL is significantly associated with overweight and obesity, might be involved in the etiology of obesity, and could be a critical reason for facing difficulties in overcoming obesity (6).

This study aimed to evaluate the relationship between HL and obesity-related well-being in obese patients admitted to a tertiary hospital and to examine the factors affecting it.

Materials and Methods

This study was planned as a single-center and cross-sectional research. It was performed with 201 participants who were admitted to the family medicine outpatient clinic of a tertiary hospital between April 15 and July 10, 2022. Participants between the ages of 18-65, with a body mass index (BMI) of 30 kg/m^2 and above for the last year, who agreed to participate in the study, could understand and answer the questions asked, and were literate were included in the study. Those under the age of 18 and over the age of 65, those with a BMI of <30 kg/m^2, those with obesity for less than 1 year, those who were pregnant or breastfeeding, those with hearing and speech disorders, those with impaired cognitive functions, those who could not cooperate and those who were illiterate were excluded.

Participants were informed in detail, their verbal and written consents were obtained. All procedures were carried out per the Declaration of Helsinki. The study was performed with the approval of the Local Ethics Committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (date: March 2, 2022, no: 40). Patient information form, obesity-related well-being questionnaire (ORWELL 97-TR), and health literacy scale-short form (HL-SF) were used to obtain data.

Data Collection Tools

Patient information form

Socio-demographic characteristics (age, gender, marital status, educational status, income status), medical history (presence of chronic disease, drug use), obesity-related features (weight change in the last year, obesity duration, treatment, family history, diet and exercise status, and education on nutrition) were questioned with the patient information form created by the authors.

Obesity definition and grading were evaluated with the formula "BMI=weight (kg)/height (m^2)" based on BMI. According to BMI, 30.00-34.99 kg/m^2 were mildly obese, 35.00-39.99 kg/m^2 were moderately obese, 40.00-49.99 kg/m^2 were morbidly obese, and >50.00 kg/m^2 were super-obese (7).

ORWELL 97-TR

ORWELL 97-TR, developed by Mannucci et al. (8), evaluates the quality of life in obese individuals. It was adapted into Turkish by Usta et al. (9) (Cronbach's alfa=0.906). ORWELL 97-TR consists of 18 items and three sub-dimensions: Psychological aspect, the social relations and sexuality. Each item is scored on a 4-point Likert-type scale,

ranging from 0 to 3 points for the occurrence/severity of symptoms from patients and the subjective relevance of the symptom-related disorder in one's own life. The sum of the "Occurrence" and "Relevance" points gives the total score. A total of 0-90 points can be obtained from ORWELL 97-TR, and an increase in the score indicates a decrease in the quality of life (9).

HL-SF

HL-SF was developed by Duong et al. (10). It was adapted into Turkish by Karahan Yılmaz and Eskici (11). HLS-SF includes 4-point Likert-type response options ranging from 1 (very difficult) to 4 (very easy) and consists of 12 items. The formula [index= (Average-1) x 50/3] is used in its evaluation. The average is calculated by dividing the scale's total score by the number of items on the scale. The index value calculated by the formula ranges from 0-50, and a higher score indicates better HL. The Cronbach's alpha value of the scale is 0.856 (11).

Statistical Analysis

The SPSS 25.0 package program was used for data analysis in the study. Descriptive data on the socio-demographic information of the participants were presented in the form of frequency tables. Pearson correlation analysis, one of the parametric tests, was performed to determine the relationship between the scale and subscale scores. Furthermore, the Independent Samples t-test and ANOVA test, which are parametric tests, were applied to determine whether there was a significant difference between the scale and subscales and the socio-demographic data of the participants. In case of a significant difference between the groups, the LCD test, which is one of the post-hoc tests, was used to determine from which groups the significance originated. A p-value of <0.05 was considered statistically significant.

Results

Ages of 201 participants included in the study ranged from 18 to 65 (mean: 38.78±11.25), and the mean duration of obesity was 8.80±7.13 (min: 2.00-max: 40.00) years. The distribution of socio-demographic, general medical, and obesity-related features is presented in Table 1. The distribution of the scores obtained from the scales and subscales is summarized in Table 2.

Table 3 reveals the correlations between the scores obtained from the scale applied to the participants and the sub-dimensions. A positive and statistically significant correlation was determined between the HLS-SF index score and the "Social Relationships" score, one of the ORWELL TR-97 "Relevance" sub-dimensions (r=0.292 p<0.001) (Table 3).

The comparison of the total and sub-dimension mean scores obtained from the scales according to the socio-demographic characteristics of the participants is presented in Table 4. Accordingly, HLS-SF scores were

Table 1. Socio-demographic and medical characteristics of the participants

Variables		n	%
Age	≤45	138	68.7
	>45	63	31.3
Gender	Female	147	73.1
	Male	54	26.9
Education level	Literate	11	5.5
	Primary school	53	26.4
	Middle school	19	9.5
	High school	49	24.4
	University	69	34.3
Marrital status	Married	135	67.2
	Single	66	32.8
Income status	Low	87	43.3
	Middle	80	39.8
	High	34	16.9
Chronic disease	No	84	41.8
	Yes	117	58.2
Family history of obesity	No	138	68.7
	Yes	63	31.3
Obesity degrees	Mild obese	142	70.6
	Moderate obese	45	22.4
	Morbid obese	12	6.0
	Super obese	2	1.0
Obesity duration	1-5 years	81	40.3
	6-10 years	72	35.8
	≥11 years	48	23.9
Weight change in the last 1 year	Increased	88	43.8
	Decreased	35	17.4
	No change	78	38.8
Diet history	No	79	39.3
	Yes	122	60.7
Obesity treatment	No	176	87.6
	Yes	25	12.4
Exercise history	No	80	39.8
	Yes	121	60.2
Getting education about nutrition	No	159	79.1
	Yes	42	20.9

Data presented as number (%) of participants

higher in patients without chronic disease (p=0.024). A significant difference was observed between the ORWELL 97-TR-total score and age and educational status, and it was determined to be higher in those aged 45 years and younger and with undergraduate degrees (p=0.007 and p=0.001). A significant difference was also found between the ORWELL 97-TR total score and BMI. It was observed to be higher in the "super obese" group compared to other BMI groups (p=0.016) (Table 4).

The comparison of the average scores of the participants from the scales and sub-dimensions according to their obesity characteristics is summarized in Table 5. A statistically significant difference was determined between the HL-SF score and the duration of obesity of the participants. HL-SF scores were higher in those between "1-5 years" compared to other obesity durations (p=0.030). HL-SF scores were higher in those who lost weight in the last year and those who had dieted and exercised before

Table 2. Distribution of scores from scales and subscales

	Min-max	Mean ± SD
HLS-SF score	6-50	32.71±9.93
ORWELL 97-TR-T	11-76	41.22±14.86
ORWELL 97-TR-O	1-37	18.76±8.63
Psychological aspects	1-28	12.76±6.34
Social relations	0-9	3.39±2.12
Sexuality	0-6	2.61±1.56
ORWELL 97-TR-A	7-41	22.46±7.03
Psychological aspects	1-28	13.14±5.90
Social relations	1-9	6.36±1.74
Sexuality	0-6	2.96±1.74

Data presented as mean ± SD and min-max. SD: Standard deviation, HLS-SF: Health literacy scale-short form, ORWELL 97-TR-A: Obesity-related well-being questionnaire relevance, ORWELL 97-TR-O: Obesity-related well-being questionnaire occurrence, ORWELL 97-TR-T: Obesity-related well-being questionnaire total

Table 3. Correlation results of scale and sub-dimensional relations

		1	2	3	4	5	6	7	8	9	10
1-HLS-SF score	r	1									
	p										
2- ORWELL 97-TR-T score	r	-0.033	1								
	p	0.639									
3- ORWELL 97-TR-O score	r	-0.048	0.958**	1							
	p	0.503	**<0.001**								
4- O-Psychological aspects	r	-0.021	0.910**	0.960**	1						
	p	0.772	**<0.001**	**<0.001**							
5- O-Social relations	r	-0.114	0.713**	0.759**	0.597**	1					
	p	0.106	**<0.001**	**<0.001**	**<0.001**						
6- O-Sexuality	r	-0.024	0.635**	0.602**	0.434**	0.418**	1				
	p	0.735	**<0.001**	**<0.001**	**<0.001**	**<0.001**					
7- ORWELL 97-TR-A score	r	-0.012	0.936**	0.797**	0.745**	0.574**	0.602**	1			
	p	0.866	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**				
8- A-Psychological aspects	r	-0.097	0.919**	0.824**	0.808**	0.594**	0.470**	0.929**	1		
	p	0.172	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**			
9- A-Social relations	r	0.292**	0.188**	0.019	-0.031	0.047	0.170*	0.374**	0.097	1	
	p	**<0.001**	**0.007**	0.786	0.662	0.511	**0,016**	**<0.001**	0.169		
10- A-Sexuality	r	-0.012	0.480**	0.405**	0.301**	0.259**	0.667**	0.517**	0.267**	0.182**	1
	p	0.870	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	

Pearson correlation analysis *p<0.05. HLS: Health literacy scale-short form, ORWELL 97-TR-A: Obesity-related well-being questionnaire relevance, ORWELL 97-TR-O: Obesity-related well-being questionnaire occurrence, ORWELL 97-TR-T: Obesity-related well-being questionnaire total

(p=0.048; p=0.048; p<0.001, respectively). ORWELL TR-97 total score was statistically significantly higher in those with weight gain in the last year and those who dieted and exercised before (p=0.001; p<0.001; p=0.009, respectively) (Table 5).

Discussion

In this study, which aimed to evaluate the relationship between HL and obesity-related well-being in obese adults and to examine the affecting factors, based on the scale scores, the quality of life of the participants was moderate, while the HL levels were moderate-good. However, it was observed that the social relations of obese people were negatively affected as the HL level increased. HL was higher, but the quality of life was lower in those who dieted and exercised before. While HL was higher in patients without chronic disease, who lost weight in the last year and had a short period of obesity, high education level, young age, and weight gain negatively affected their quality of life.

Table 4. Evaluation of scales' total and sub-dimension scores according to socio-demographic and clinical features of the participants

	HLS-SF	ORWELL 97-TR-T	ORWELL 97-TR-O	O-Psychological aspects	O-Social relations	O-Sexuality	ORWELL 97-TR-A	A-Psychological aspects	A-Social relations	A-Sexuality
Age	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
≤45	31.95±9.69	43.12±14.94	19.91±8.56	13.80±6.25	3.43±2.08	2.69±1.47	23.20±7.22	14.04±5.84	6.18±1.67	2.98±1.64
>45	34.37±10.32	37.06±13.89	16.22±8.31	10.48±5.98	3.32±2.22	2.43±1.72	20.84±6.35	11.17±5.57	6.76±1.82	2.90±1.97
p=	0.110	**0.007**	**0.005**	**<0.001**	0.734	0.273	**0.027**	**0.001**	**0.027**	0.796
Gender	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Female	32.73±9.90	41.56±14.73	18.82±8.49	12.96±6.24	3.22±2.08	2.65±1.59	22.74±7.16	13.70±5.80	6.29±1.73	2.76±1.71
Male	32.66±10.11	40.28±15.29	18.57±9.10	12.20±6.65	3.87±2.19	2.50±1.46	21.70±6.68	11.63±5.96	6.57±1.75	3.50±1.72
p=	0.968	0.587	0.857	0.456	**0.053**	0.556	0.355	**0.027**	0.298	**0.007**
Education status	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
1) Literate	27.90±18.29	28.36±10.03	11.45±5.99	8.64±4.99	1.55±1.75	1.27±1.35	16.91±4.50	9.27±4.36	5.55±1.29	2.09±1.70
2) Primary sch.	33.36±9.88	37.32±14.26	15.47±7.95	10.21±6.42	3.00±1.93	2.26±1.61	21.85±7.34	12.19±6.29	6.89±1.92	2.77±1.84
3) Middle sch.	29.97±7.6	40.95±14.57	19.89±8.96	13.53±6.27	3.95±2.04	2.42±1.50	21.05±6.02	13.00±5.74	5.42±1.68	2.63±1.46
4) Hisg sch.	31.32±9.10	42.00±14.93	19.45±8.01	13.22±5.41	3.24±2.19	2.98±155	22.55±7.31	13.14±5.73	6.49±1.70	2.92±1.86
5) University	34.72±8.99	45.78±14.33	21.64±8.53	14.83±6.30	3.94±2.09	2.87±1.42	24.14±6.72	14.54±5.68	6.26±1.56	3.35±1.61
p=	0.089	**0.001**	**<0.001**	**<0.001**	**0.002**	**0.003**	**0.016**	**0.039**	**0.009**	0.112
Post-hoc tests=	-	1-3,4,5 2-5	1-3,4,5 2-3,4,5	1-3,4,5 2-3,4,5	1-2,3,4,5 2-5	1-2,3,4,5 2-4,5	1-2,4,5	1-4,5 2-5	1-2 2-3,5 3-4	-
Marrital status	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Maried	32.83±10.28	41.02±15.43	18.10±8.96	12.26±6.51	3.26±2.12	2.59±1.68	22.92±7.17	13.25±5.91	6.65±1.59	3.01±1.77
Single	32.47±9.25	41.62±13.71	20.09±7.82	13.77±5.90	3.67±2.11	2.65±1.27	21.53±6.70	12.92±5.93	5.77±1.87	2.83±1.68
p=	0.811	0.789	0.126	0.112	0.202	0.756	0.189	0.713	**0.001**	0.489
Income status	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
1) Low	31.98±11.16	38.62±13.21	17.39±7.58	11.84±5.63	3.11±1.85	2.44±1.60	21.23±6.57	12.54±5.37	6.10±1.85	2.59±1.71
2) Middle	32.85±7.94	42,20±16.06	19.24±9.41	13.23±7.17	3.39±2.15	2.63±1.57	22.96±7.27	13.49±6.20	6.46±1.62	3.01±1.70
3) High	34.27±10.86	45.56±15.01	21.12±8.88	14.00±5.82	4.12±2.56	3.00±1.37	24.44±7.22	13.88±6.48	6.79±1.63	3.76±1.69
p=	0.516	0.051	0.083	0.169	0.064	0.200	0.055	0.426	0.116	**0.003**
Chronic disease	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
No	34.47±7.77	40.23±15.31	18.52±8.91	12.37±6.56	3.43±2.04	2.73±1.52	21.70±7.33	12.42±6.20	6.33±1.79	2.95±1.68
Yes	31.45±11.09	41.93±14.55	18.92±8.46	13.03±6.19	3.37±2.18	2.52±1.58	23.01±6.79	13.67±5.65	6.38±1.70	2.96±1.79
p=	**0.024**	0.424	0.747	0.465	0.841	0.358	0.195	0.139	0.837	0.984

Independent t-test, ANOVA test, post-hoc; LSD test. HLS-SF: health literacy scale-short form, ORWELL 97-TR-A: Obesity-related well-being questionnaire relevance, ORWELL 97-TR-O: Obesity-related well-being questionnaire occurrence, ORWELL 97-TR-T: Obesity-related well-being questionnaire total, SD: Standard deviation

Main findings on obesity-related well-being and HL

Many studies observed that obesity reduces the quality of life by negatively affecting many areas of people's lives (3). In a study by Marchitelli et al. (12) with 45 patients who had planned to have bariatric surgery, the total score of ORWELL-97 was 42.02±20.24, and the quality of life of people with a higher BMI was lower. Wooldridge et al. (13) examined the relationship between eating disorders and quality of life in people with a BMI >25, ORWELL-97 total score was found 49.58±29.20, and BMI was reported to be associated with a higher ORWELL score. In another study the ORWELL-97 total score was 46.38±27.07 and, although there was no relationship between the decrease in BMI and the occurrence score, a relationship was determined with the relevance score (14). In our study, the quality of life of the individuals was evaluated as moderate, and as the degree of obesity increased, the effect of obesity increased. The number of studies conducted with the Turkish form of ORWELL in the literature is limited, and the results we obtained were found to be similar to other forms of the scale.

Table 5. Evaluation of scales' total and sub-dimension scores according to obesity characteristics of the participants

Variables	HLS-SF	ORWELL 97-TR-T	ORWELL 97-TR-O	O-Psychological aspects	O-Social relations	O-Sexuality	ORWELL 97-TR -A	A-Psychological aspects	A-Social relations	A-Sexuality
Obesity degrees	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
1) Mild	33.39±10.12	40.19±14.65	17.96±8.64	12.32±6.41	3.11±2.16	2.53±1.51	22.23±6.70	12.73±5.59	6.59±1.64	2.91±1.80
2) Moderate	31.82±9.82	46.31±14.96	22.18±8.31	14.89±5.80	4.29±1.85	3.00±1.75	24.13±7.56	15.16±6.11	5.93±1.98	3.04±1.68
3) Morbid	28.70±8.08	33.00±12.78	15.67±7.39	10.25±6.45	3.42±2.02	2.00±1.13	17.33±6.12	9.33±6.30	5.17±1.27	2.83±1.19
4) Super	28.47±0.98	49.00±0.00	17.00±0.00	11.00±0.00	3.00±0.00	3.00±0.00	32.00±0.00	20.00±0.00	7.00±0.00	5.00±0.00
p=	0.343	**0.016**	**0.018**	**0.049**	**0.013**	0.158	**0.005**	**0.003**	**0.010**	0.388
Post-hoc test=	-	1-2, 2-3	1-2, 2-3	1-2, 2-3	1-2	-	1-3,4 2-3, 3-4	1-2,3 2-3, 3-4	1-2,3	-
Obesity duration	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
1) 1-5 years	34.88±9.02	43.09±15.48	19.88±9.00	13.72±6.53	3.25±2.21	2.91±1.46	23.21±7.01	13.51±5.71	6.62±1.45	3.09±1.71
2) 6-10 years	30.73±10.42	41.93±14.89	18.88±8.56	12.89±6.46	3.53±2.16	2.46±1.64	23.06±7.16	13.71±6.27	6.35±1.65	3.00±1.85
3) ≥11 years	32.03±10.12	37.00±13.09	16.69±7.87	10.94±5.53	3.44±1.93	2.31±1.53	20.31±6.56	11.69±5.51	5.96±2.19	2.67±1.62
p=	**0.030**	0.069	0.126	0.053	0.708	0.062	0.051	0.143	0.113	0.404
Post-hoc tests=	1-2	-	-	-	-	-	-	-	-	-
Weight change	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
1) Increased	32.75±9.08	45.59±13.82	21.42±7.90	14.66±5.67	3.69±2.04	3.07±1.34	24.17±6.84	14.72±5.27	6.28±1.69	3.17±1.70
2) Decreased	36.11±9.61	39.23±14.37	17.14±8.50	11.43±7.52	3.46±1.87	2.26±1.44	22.09±7.37	12.31±6.66	7.03±1.92	2.74±1.90
3) No change	31.14±10.69	37.18±15.04	16.47±8.75	11.21±5.98	3.03±2.28	2.24±1.71	20.71±6.71	11.74±5.86	6.15±1.64	2.81±1.71
p=	**0.048**	**0.001**	**<0.001**	**0.001**	0.126	**0.001**	**0.006**	**0.003**	**0.039**	0.299
Post-hoc tests=	2-3	1-2,3	1-2,3	1-2,3	-	1-2,3	1-3	1-2,3	1-2, 2-3	-
Diet history	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
No	31.00±9.86	35.67±13.48	15.67±7.83	10.94±6.18	2.71±1.95	2.03±1.48	20.00±6.52	11.37±5.88	6.20±1.64	2.43±1.68
Yes	33.82±9.85	44.81±14.65	20.75±8.57	13.93±6.19	3.84±2.12	2.98±1.49	24.06±6.91	14.30±5.65	6.47±1.80	3.30±1.70
p=	**0.048**	**<0.001**	**<0.001**	**0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**	0.292	**0.001**
Obesity treatment	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
No	32.57±9.73	40.75±15.15	18.45±8.81	12.60±6.50	3.35±2.14	2.50±1.56	22.30±7.18	13.02±6.05	6.38±1.71	2.90±1.72
Yes	33.72±11.42	44.52±12.32	20.92±7.04	13.88±5.04	3.68±2.04	3.36±1.35	23.60±5.91	14.00±4.71	6.24±1.96	3.36±1.87
p=	0.588	0.236	0.181	0.345	0.471	**0.009**	0.389	0.440	0.706	0.215
Exercise history	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
No	29.44±9.96	37.86±14.53	17.43±8.31	12.08±6.34	3.04±2.11	2.31±1.63	20.44±6.90	12.03±5.81	5.83±1.82	2.59±1.60
Yes	34.87±9.34	43.44±14.71	19.64±8.76	13.21±6.33	3.63±2.11	2.80±1.48	23.80±6.82	13.88±5.87	6.72±1.59	3.20±1.79
p=	**<0.001**	**0.009**	0.075	0.217	0.053	**0.029**	**0.001**	**0.028**	**<0.001**	**0.015**
Post-hoc tests=	**1-2,3** **2-3**	**2-3**	**1-2** **2-3**	**1-2** **2-3**	-	-	**2-3**	-	**1-2,3**	-

Independent t-test, ANOVA test, post-hoc; LSD Test HLS-SF: Health literacy scale-short form, ORWELL 97-TR-A: Obesity-related well-being questionnaire relevance, ORWELL 97-TR-O: Obesity-related well-being questionnaire occurrence, ORWELL 97-TR-T: Obesity-related well-being questionnaire total, SD: Standard deviation

In general, it is seen that people with high BMI have low HL (5,6,15,16). In fact, as the degree of obesity increases, it has been observed that HL decreases even more (17). However, some studies detected no relationship between HL and body weight (18). In our study, the HL level was evaluated as moderate-good. Although the HL level was higher in our study compared to the literature, there was no significant difference in the degree of obesity. This situation may be due to the differences in socio-cultural distributions, as well as supporting that different results can be obtained with different measurement tools.

The quality of life is known to be better in people with high HL levels (19-21). Although no significant relationship was determined between the level of HL and quality of life in obese individuals in our study, social relations, a crucial sub-factor of quality of life, were negatively affected as the level of HL increased.

Factors affecting obesity-related well-being

Studies have shown that increasing age negatively affects the quality of life. In the study of Yıldız and Çetinkaya (22), a lower quality of life was found between the ages of 50-65. On the contrary, Itani et al. (23) was not found any relation of age and well-being. In our study, the quality of life of those aged 45 years and younger was lower. It is thought that this may be since obese individuals at younger ages are more affected by the negative effects of obesity, especially on psychological symptoms and severity.

As in the general population, studies have reported that the quality of life is low in women with obesity (24,25). The increase in BMI in obese patients was associated with an increase in ORWELL-97 scores and, therefore, a decrease in quality of life in obese patients by Itani et al. (23). However, this relationship was observed only in women and not significant in men. In the study by Tambelli et al. (26), no difference was determined between men and women regarding the quality of life. In our study, although there was no significant difference between the genders in terms of quality of life, partially similar to the study of Itani et al. (23), the quality of life in women was more affected due to the higher incidence of psychological symptoms.

The quality of life was generally lower in people with low education (24). In our study, well-being was negatively affected in obese patients with a higher education level, similar to the literature.

It is known that, an increase in physical activity increases the quality of life (27). However, in our study, obesity-related quality of life was lower in those who exercised. It is considered that individuals who exercise and follow the exercise plan have higher awareness; thus, they may perceive the adverse effects of obesity on their quality of life more.

Factors affecting HL

In a study in 2022, HL level was high in young people, especially in the 16-34 age group (28). While Cheong et al. (29) was found HL higher in middle-aged adults, Toçi et al. (17) found it lower. In our study, unlike the literature, there was no statistically significant difference between HL level and age. Age may not be an effective factor in HL alone, the people may need to be evaluated together with other characteristics.

Studies evaluating the HL determined that the HL level increases as the education level increases (28,30,31). Although no statistically significant difference was found in our study, similar to the literature, those with higher education levels had higher HL scores. As the level of education increases, people can better access and understand the information they are curious about their health.

Individuals with sufficient HL levels were observed to adopt behaviors that positively affect health, such as healthy eating habits and regular exercise (5). In our study, similarly, the HL level was higher in those who lost weight and those who dieted and exercised before. By informing obese people with high HL levels about nutrition or directing them to a nutritionist, it can contribute to a more efficient weight loss process.

Study Limitations

The limitation of our study is that it did not examine the changes in the quality of life of individuals according to the course of obesity. Contribution to the literature can be achieved with different studies in which obese people are followed for a long time, and their changes in their quality of life are monitored.

Conclusion

According to our study the quality of life of obese adults was moderate, and HL levels were moderate-good. Moreover, it was observed that the social relations of obese individuals were negatively affected as the HL

level increased. While HL was higher in patients without chronic disease, who lost weight in the last year and had a short period of obesity, high education level, young age, and weight gain negatively affected their quality of life. Increasing the HL is essential in enabling society and health professionals to manage obesity effectively in the long-term.

Ethics

Ethics Committee Approval: The study was performed with the approval of the Local Ethics Committee of University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (date: March 2, 2022, no: 40).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Internally peer-reviwed.

Authorship Contributions

Concept: Ş.A.C., S.T.K., O.B., Design: Ş.A.C., S.T.K., O.B., Data Collection or Processing: Ş.A.C., S.T.K., O.B., Analysis or Interpretation: Ş.A.C., S.T.K., O.B., Drafting Manuscript: Ş.A.C., S.T.K., O.B., Critical Revision of Manuscript: Ş.A.C., S.T.K., O.B., Final Approval and Accountability: Ş.A.C., S.T.K., O.B., Writing: Ş.A.C., S.T.K., O.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

Bagcilar Med Bull 2023;8(2):188-193
DOI: 10.4274/BMB.galenos.2023.2022-11-097

Can the Use of Omega-3 During Pregnancy Prevent Striae Gravidarum?

Gebelikte Omega-3 Kullanılması Stria Gravidarum Oluşumunu Önleyebilir mi?

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Abstract

Objective: The main aim of the study was to investigate the effect of Omega-3 use on the formation of striae gravidarum in pregnant women.

Method: In 2020 and 2021, 201 primigravida pregnant women who had at least four antenatal check-ups in a first-trimester pregnancy outpatient clinic and gave birth in the same center were included in the study. These patients were grouped according to the drugs they used (Omega-3 group, multivitamin and irregular medication group). Age, education level, weight gained during pregnancy, history of the additional disease, medication use and birth weight of the baby was recorded. During pregnancy follow-up and at the 24th hour of birth, striae in four parts of the body (abdomen, hips, buttocks, and breasts) were scored according to their color and number with the scoring system developed by Atwal et al.

Results: A severe striae score was detected in one puerperium in the patients included in the study. Striae started between 21 and 24 weeks in about one-third of the patients (26.9%). There was a significant difference between the SG scores of pregnant women on regular medication and those on the irregular medication (p<0.001). Pregnant women on irregular medication had a higher postpartum striae score. There was also a positive correlation between SG score and young pregnancy, high weight gain during pregnancy, and early onset of striae. No significant correlation was found between infant weight and SG score (p>0.05).

Conclusion: According to the results of our study, a regular multivitamin along with Omega-3 reduces the occurrence of striae gravidarum.

Keywords: Omega-3, pregnancy, stretch marks, striae gravidarum

Öz

Amaç: Bu çalışmanın ana amacı gebelerde Omega-3 kullanımının stria gravidarum oluşumuna etkisini araştırmaktır.

Yöntem: Bu prospektif olgu kontrol çalışmasına 2020-2021 yılları arasında ilki 1. trimesterde olmak üzere en az 4 antenatal takibi yapılmış 201 primigravid gebe dahil edildi. Çalışmaya alınan gebeler kullandıkları ilaçlara göre (multivitamin, Omega-3 ile beraber multivitamin kullananlar ve düzensiz ilaç kullananlar) gruplandırıldı. Kadının yaşı, eğitim seviyesi, gebelikte aldığı kilo, ek hastalıkları, kullandığı ilaçlar, bebeğin doğum kilosu kaydedildi. Gebelik takibi yapılmış ve doğumu aynı merkezde olmuş hastalara doğum sonrası 24. saatte vücudun 4 bölgesindeki (karın, kalça, basen ve memeler) stria gravidarumları Atwal ve ark. tarafından belirlenmiş kriterlere göre puan verildi.

Bulgular: Çalışmaya alınan 201 kadından 1 tanesinde şiddetli stria skoru saptandı. Stria gravidarum hastaların yaklaşık 1/3'ünde (%26,9) 21-24. gebelik haftaları arasında başlamıştı. Düzenli vitamin kullanan gebelerin SG skorları arasında anlamlı fark saptandı (p<0,001). Vitamin ilaçlarını düzensiz kullanan kadınlarda SG skoru düzenli ilaç kullanan lohusalardan daha yüksek bulundu. SG skoru genç yaş, gebelikte fazla kilo almak ve erken başlayan stria oluşumu ile artmıştı. Doğan bebeğin kilosu ile SG skoru arasında anlamlı bir ilişki bulunmadı (p>0,05).

Sonuç: Çalışmamızın sonuçlarına göre, Omega-3 ile birlikte düzenli bir multivitamin, stria gravidarum oluşumunu azaltır.

Anahtar kelimeler: Çatlaklar, gebelik, Omega-3, stria gravidarum

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Cite this article as: Okuyan E, Karabay Akgül Ö. Can the Use of Omega-3 During Pregnancy Prevent Striae Gravidarum?. Bagcilar Med Bull 2023;8(2):188-193

Introduction

Striae gravidarum (SG) is a cosmetic problem specific to pregnancy. SG affects 50-90% of pregnant women and occurs mostly in primigravidae. It usually starts in the second or third trimester and most commonly occurs in the abdomen and breasts (1). Other symptoms may include an increased volume of subcutaneous fat and muscle tissue during pregnancy accompanied by a gradual expansion of the skin that is itchy, erythematous in the acute phase, and white silver colored linear lesions when chronic. Risk factors for SG include genetic predisposition, hormonal status, teenage pregnancy, being overweight before pregnancy, gaining excess weight during pregnancy, and having an overweight baby (2). The pathogenesis of striae has not been clearly explained, but it is thought to be caused by the separation and disorganization of collagen bundles due to physical stresses in the extracellular matrix (3,4). Omega-3 fatty acids have shown anti-allergic and anti-inflammatory effects on the skin and have been an important metabolite for the remodeling of skin cells (5,6).

Although there are a large number of studies on the pathogenesis and treatment of SG in the literature, publications on its prevention are limited. In this study, we wanted to conduct a study investigating the effects of the systemic administration of vitamins and Omega-3 to prevent the development of striae in pregnancy.

Materials and Methods

This prospective observational study was performed in a tertiary hospital under the principles of the Helsinki Declaration. After Ethics Committee approval of Batman Training and Research Hospital (no: 2020-02) the study commenced. The study included 201 primiparous pregnant women who were followed up in the antenatal outpatient clinic of the tertiary center between 2020 and 2021 and who voluntarily agreed to participate in the study and gave written informed consent. The patients who gave birth by cesarean section were excluded from the study due to the possibility of the drugs used during surgery affecting the striae. Twenty-four patients who did not meet the inclusion criteria for the physical study performed 24 hours after delivery by normal vaginal delivery were also excluded from the study (Flow Chart). Every pregnant woman included in the study was initially given a multivitamin (Fe+2 80 mg, folic acid 0.35 mg) during their first examination in the first trimester. Starting from the 12th week of pregnancy, Omega-3 [380 mg eicosapentaenoic acid (EPA), 200 mg docosahexaenoic acid (DHA)] was offered as an option and the drugs were started according to the wishes of the pregnant women. At each follow-up visit, the pattern of drug use of pregnant women was recorded. Patients who were followed up throughout their pregnancies were given a daily follow-up chart, and at each visit, the patients were divided into three groups by looking at the regularity of the drugs used in the follow-up chart (without directing the patients and without considering the company's interest relationship):

- Pregnant women who did not use drugs every day (irregular drug users);

- Pregnant women who did not use Omega-3 and used only multivitamins (containing Fe+2 and folic acid); and

- Pregnant women who used Omega-3 and multivitamins (containing Fe+2 and folic acid).

Pregnant women who did not attend regular follow-up visits at the center where the study was conducted and/or delivered in another hospital were excluded from the study. Pregnant women with surrenal disease, diabetes mellitus, dermatologic disease, thyroid disease, autoimmune disease, physical mobility restriction, chronic constipation, as well as those who had undergone surgery before or during pregnancy and pregnant women with alcohol, smoking, and substance abuse were excluded from the study. Pregnant women who used local skin products such as massage oils, moisturizing creams or natural skin solutions (e.g., olive oil applications) before pregnancy and until delivery, pregnant women with malnutrition, pregnant women younger than 18 years of age, and betamethasone use for preterm delivery were excluded. Multiple pregnancies, scarred uterus pregnancies, and deliveries with breech presentation were also not included. In the study, primigravida pregnant women, whose first examination was performed between the sixth and twelfth week of gestation, who had at least four antenatal visits at the hospital where the study was conducted, who gave birth between 37 and 40 weeks, who gave birth to a baby between 2,500 g and 4,000 g, and who gave written and verbal consent were evaluated. According to the inclusion criteria, pregnant women who were included in the study were informed that they should not use any skin solutions, moisturizers, or creams, and if they did, they would be excluded from the study follow-up and they should inform their physicians during their examinations. The age, parity, educational status, gestational week, and weight gained during the entire pregnancy and weight of the newborn were recorded. In antenatal controls, in the first visit

of pregnancy and Atwal et al.'s (1) SG score at 24 hours postpartum was noted after delivery. For scoring, four regions of the pregnant woman (abdomen, hips, buttocks, and breasts) were examined. The striae in each region were graded from 0 to 6 according to color and number of striae (0-3 points for the number of striae, 0-3 points for the striae color). The total striae score (TSS) ranged from 0 to 24. Those with a TSS score of ≤12 were classified as mild striae; those with a TSS score of 13 to 18 as moderate striae and those with a TSS score >18 as severe striae (1). White-cream colored striae were not evaluated as they were old striae.

Statistical Analysis

Mean, standard deviation, median, and minimum maximum values were given in descriptive statistics for continuous data, and number and percentage values were given in discrete data. The Shapiro-Wilk test was used to examine the conformity of the continuous data to the normal distribution. The Kruskal-Wallis Analysis of Variance for comparisons of total scores between groups was used. The Kruskal-Wallis multiple comparison tests were used to determine which groups were different. The relationships between continuous data were analyzed with Spearman's correlation coefficient.The IBM SPSS version 20 (Chicago, IL, USA) program was used in the evaluations with $p<0.05$ being accepted as the limit of statistical significance.

Results

The study commenced with 229 pregnant women and 28 non-compliant pregnant women were excluded from the study. The mean age of the patients was 21.97±2.23 years with a minimum patient age of 18 and a maximum patient age of 29 (Table 1). Approximately 60% of the pregnant women were high school graduates (Table 1). The SG score was higher in younger pregnant women ($r=-0.169$ $p<0.05$) (Table 2).

When the Kruskal-Wallis multiple comparison tests was performed, the SG score was found to be lower in the pregnant women who used regular medication compared to the pregnant women who did notuse regular medication ($p<0.001$, $p<0.001$, respectively) (Table 3). SG was observed in every pregnant woman included in the study with one patient having a total score of over 18 points (severe striae). In 155 patients (76%), we obtained a score of less than 12 points (mild striae). The mean SG score was 9 points (minimum 3, maximum 18) (Table 4). Striae started on average during the 27th week of gestation (min. 16 weeks, max. 38 weeks). Lesions started between 21 and 24 weeks in approximately one-third of the patients (26.9%). There was a negative correlation between the SG onset week and SG score ($r=-0.719$, $p<0.001$) (Tables 1 and 4). The average weight gain of the pregnant women until birth was 10 kg. The SG score was also found to be higher in pregnant women who gained more weight ($r=-0.195$, $p<0.01$) (Table 4). The pregnant women in the study gave birth on average at 39 weeks of gestation. The total SG score of the pregnant women whose SG development started early gestational weeks was found to be higher ($r=-0.719$, $p<0.001$). Approximately 90% of the pregnant women delivered

Table 1. Characteristics of the patients

Age mean ± SD, (min-max)	**21.97±2.23 (1729)**
Education n (%)	
Elementary school	79 (39.3)
High school	120 (59.7)
University	2 (1.0)
SG onset week mean ± SD, median (min-max)	27.15±5.11 27 (1638)
SG onset weeks n (%)	
≤20 weeks	25 (12.4)
21-24 weeks	54 (26.9)
25-28 weeks	28 (13.9)
29-32 weeks	54 (26.9)
≥33 weeks	40 (19.9)
Weight gained mean ± SD, median (min-max)	10.40±1.35 10 (714)
Birth week mean ± SD, median (min-max)	38.94±0.70 39 (3740)
Baby weight n (%)	
2500-3000 g	6 (3)
3100-3500 g	178 (88.6)
3600-4000 g	17 (8.4)
Medication use during pregnancy	
Multivitamin	55 (27.4)
Multivitamin + Omega-3	100 (49.8)
Irregular medication use	46 (22.8)

SD: Standard deviation, SG: Striae gravidarum

Table 2. Correlations between age, weight gain, week of SG onset and time to delivery and total scores

	Total score	
	r*	**p**
Age (year)	**-0.169**	**0.016**
Weight gain (kg)	**0.195**	**0.005**
SG onset week (week)	**-0.719**	**<0.001**
Baby's weight	-0.102	0.152

*Spearman's correlations coefficient, SG: Striae gravidarum

Table 3. Comparison of total scores of multivitamin, multivitamin + Omega-3 and irregular medication users

	Total score		
	Mean ± SD	Median (min-max)	p-value
Medication use during pregnancy			
Multivitamin	11.53±2.31	11 (818)	<0.001*
Multivitamin + Omega-3	6.41±1.43	6 (311)	
Irregular medication use	13.85±1.78	14 (1017)	

*Kruskal-Wallis Analysis of Variance, SD: Standard deviation

Table 4. Patients' striae gravidarum scores

	Median (min-max)
Abdomen score	3 (06)
Breast score	2 (05)
Hip score	2 (15)
Buttocks score	2 (13)
Total score	9 (318)

3100-3500 g babies. No significant correlation was found between infant weight and SG score (p>0.05). The reason why we did not do power analysis before the study; since patients in 2021 were selected, we included all patients who met the inclusion criteria. Thus, we wanted to see the rates of vitamin use. In the study where 55 patients using MV, 100 patients using MV + Omega-3, 46 patients not using drugs, and the total score of pregnancy stretch marks as a primary outcome, the power of the test was f=0.25 with effect size (effect size), type I error =0.05, power =0.89 (89%) found as the calculation was made using the "G*Power 3.1.9.4" package program.

A difference was found between the total scores of those who used MV + Omega-3 and those who did not use drugs (p<0.00). The total scores of MV+ Omega-3 users were found to be lower than those who did not use drugs. Post-hoc test results:

1. MV - MV+ Omega-3 p=0.000 p<0.001 difference

2. MV - no drug p=0.023 p<0.05 difference

3. MV+ Omega-3 - no drug p=0.000 p<0.001 difference

Discussion

According to the results of our study, multivitamin use significantly decreases the SD score. In particular, SG is significantly milder in pregnant women who use multivitamins with Omega-3. Ninety percent of the SG is seen in primigravids (1). New lesions would usually begin after the 24th week of pregnancy and are most commonly seen in the abdomen, breasts, and hips (7). In pregnant women with striae, it was also observed that there was a decreased serum relaxin level in their serum (8). Other publications in the literature show increases in estrogen and epinephrine facilitating the formation of SG (9). Since it occurs in more women during pregnancy, new mechanical, hormonal, cellular, and immunologic causes of pregnancy will also be important in the development of striae (2,8,10-12). SG is an indicator of skin quality and has been reported in the literature. The perineal tear rate increases in pregnant women with SG if they give birth vaginally (13-15).

In the literature, several studies have determined the independent risk factors for the occurrence of SG. Despite many studies, the results are conflicting, and confounding factors (such as diet, nutritional content, fluid intake, mobility, alcohol consumption, and stress) cannot be eliminated. It is difficult to determine which of the many coexisting factors is the main influencing factor (16). Among the risk factors for SG, maternal weight and age are the most debated factors. Findik et al. (17) found pre-pregnancy weight or maternal age as a risk factor. Atwal et al. (1) considered maternal age, maternal BMI, total weight gained by the mother during pregnancy, and birth weight of the baby as independent risk factors for SG. Picard et al. (9) observed pre-pregnancy weight as an important risk factor. Osman et al. (10) found maternal age, weight gain, infant weight, family history of SG, and birth week to be effective. Current evidence has revealed that in addition to the positive effects of Omega-3 on skin health, it reverses the negative effects of chemotherapy on the skin in the adjuvant treatment of psoriasis and eczema (14). High estrogen level may be induced by pregnancy, slowing the anti-inflammatory process and skin regeneration, and there are positive effects with the use of systemic Omega-3 preparations. In addition, the fact that striae were observed with lower scores in pregnant women who used multivitamins even if they did not use Omega-3 may have provided vitamin and mineral supplementation effectively on collagen synthesis and skin structure.

Elastin provides mechanical elasticity in the skin, as well as cell growth and wound healing, and it has other effects such as regeneration and dermis remodeling (15). Inflammation disrupts the structure of elastin; however, Omega-3 fatty acids have anti-inflammatory effects (15). In our results, the striae score of women with Omega-3 supplementation was even lower than the patients using only vitamins. This may be related to the curative effect of EPA and DHA on possible inflammation and edema. It is possible to attribute the fact

that our group, which does not contain Omega-3, has less SG than those who did not take vitamins regularly, due to the high levels of vitamins and minerals in the circulating blood and since they are more attentive to themselves and their babies psychologically and mentally. Those pregnant women who participated in the study but did not use the vitamin supplements regularly or never used them had TSSs that were 13 and above. In other words, the number and severity of striae increased in pregnant women who used an inadequate amount of supplements or no supplements at all. This suggests that patients with better socio-economic circumstances had fewer striae. The fact that our group without Omega-3 also had less SG compared to those who did not take regular vitamins can be attributed to the high levels of vitamins and minerals in the circulating blood and to the fact that they were pregnant women who were psychologically and mentally more attentive to themselves and their babies.

In a large-scale SG study conducted on 420 women in 2022, who being younger than 25 years of age, having an abdominal circumference greater than 100 cm, gaining more than 15 kg in weight in total during pregnancy, having SG in the family, having gestational DM, having altered bowel movements during pregnancy and having striae in the breasts, hips, and upper leg were considered independent risk factors (16). In this research, we found that factors such as gaining a large amount of weight during pregnancy and young maternal age would increase the frequency of SG; however, the weight of the baby did not affect the SG score.

Although there are several studies in the literature evaluating SG by looking at vitamin levels in the blood, blood levels, and tissue utilization may not be the same. It is also possible that pregnant women who received vitamin and Omega-3 supplements spent the pregnancy process more wisely and diligently and were more successful in terms of exercise, quality food consumption, and stress-coping strategies. The most important strength of our study is that we prospectively followed the development of SGs in young, healthy first pregnancies in which the inclusion criteria were clearly defined, the exclusion criteria were strictly adhered to, and the scoring system was performed regularly. The fact that we evaluated SGs that occurred before 24 weeks of gestation also shows that hormonal and chemical changes in the skin, which are specific to pregnancy, begin during the earlier weeks of pregnancy. Although the history of striae in the mother and sister was taken in our study, the reliability of this anamnesis data is limited due to the low socio-cultural levels of the participants, and since striae are seen in all pregnant women, we could not obtain sufficient data to discuss whether it is possible to prevent striae with this study. In addition to these factors, the most important limitations are that vitamin and Omega-3 levels were not examined in tissue and serum simultaneously. It is not cost-effective to look at serum vitamin levels in pregnant women in clinical observational or prospective studies.

There are promising signs that the impact of clinical nutrition on skin health will be more comprehensively interconnected scientifically soon. Therefore, it is obvious that more precise data can be obtained with well-designed studies including serum vitamin levels, especially in experimental animal studies.

Conclusion

Pregnant women should be given multivitamins and/or Omega-3 supplements to prevent SG. The presence of Omega-3 in multivitamins to be used as pregnancy supplements in the next generation of pharmaceuticals may play a role as a preventive measure against the development of SD.

Ethics

Ethics Committee Approval: This study was approved Batman Training and Research Hospital Local Ethics Committee of the Medical Center; Ethics Committee approval (no: 2020-02).

Informed Consent: Informed consent was obtained.

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., Drafting Manuscript: E.O., Ö.K.A., Critical Revision of Manuscript: E.O., Ö.K.A., Final Approval and Accountability: E.O., Ö.K.A., Writing: E.O., Ö.K.A.

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

Bagcilar Med Bull 2023;8(2):194-197
DOI: 10.4274/BMB.galenos.2023.2023-03-023

A Newborn with Patent Omphalomesenteric Duct with Fecaloid Umbilical Drainage

Fekaloid Umblikal Drenajı Olan Patent Omfalomezenterik Kanal Tanılı Bir Yenidoğan

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Abstract

Umbilical anomalies are seen quite frequently in the neonatal period. Knowing the embryological development steps and anatomy is essential for accurate diagnosis and treatment in cases with umbilical pathology. A rare type of these anomalies is the patent omphalomesenteric duct, which can be diagnosed on the first day of life. It was observed that a term male newborn was hospitalized in our unit due to transient tachypnea of the newborn having umbilical yellow-green colored, foamy fecaloid drainage. The umbilical cord had a tissue compatible with cherry-colored mucosa. Following the examinations, the diagnosis of the patent omphalomesenteric duct was operated on and discharged with complete recovery. We wanted to report a rare neonatal omphalomesenteric duct anomaly among umbilical anomalies.

Keywords: Congenital anomaly, neonate, omphalomesenteric duct

Öz

Yenidoğan döneminde umblikal anomaliler oldukça sık görülmektedir. Göbek patolojili olgularda embriolojik gelişim basamaklarını ve anatomiyi bilmek doğru tanı ve tedavi için esastır. Bu anomalilerin nadir bir tipi patent omfalomezenterik kanal olup hayatın ilk gününde tanı koyulabilir. Yenidoğanın geçici taşipnesi nedeniyle ünitemize yatırılan miadında bir erkek bebeğin umbilikustan sarı-yeşil renkli, köpüklü fekaloid drenajı olduğu görüldü. Göbek kordonunda vişne renkli mukoza ile uyumlu doku görüntüsü mevcuttu. Tetkikleri sonucu patent omfalomezenterik kanal tanısı koyularak opere edildi. Umblikus anomalileri arasında nadir olarak görülen patent omfalomezenterik kanal anomalisi olgusunu bildirmek istedik.

Anahtar kelimeler: Konjenital anomali, omfalomezenterik kanal, yenidoğan

Introduction

The omphalomesenteric duct (OMD), also entitled the vitelline duct, is an embryonic form that connects the primitive yolk sac to the primitive midgut through the umbilical coelom and includes the omphalomesenteric vessels, which supply alimentation to the early growing embryo in advance of the placenta is initiated (1). It comes by obliteration at 5-9 weeks of gestation. The defect of this duct closing, seen in almost 2% of the population, can bring about varied OMD residues (2).

Complete or partial defect of the involution of the embryonic OMD can remain an abnormal connection between the umbilical cord and the gastrointestinal tract. It can lie behind several degrees of abnormalities that can result in drainages from the umbilicus, such as Meckel diverticulum (partly patent at the intestinal side), umbilical sinus (patent at the umbilical side), omphalic cyst (patent centric part), omphalomesenteric fistula (entirely patent duct) or an umbilical polyp (mucosal residue at umbilicus) (3).

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Cite this article as: Aycan N, Yürektürk E, Ateş A, Ayengin K, Toplar EN, Karaman S, Tuncer O. A Newborn with Patent Omphalomesenteric Duct with Fecaloid Umbilical Drainage. Bagcilar Med Bull 2023;8(2):194-197

We wanted to report a rare neonatal OMD anomaly among umbilical anomalies diagnosed on the first day of life.

Case Report

As the fifth surviving neonate of a 33-year-old mother with non-consanguineous marriage, 2830 gr (10% p) 50 cm (50% p) height and 35 cm (50% p) head circumference born at term by cesarean section, was hospitalized in our unit considering transient tachypnea of the newborn. The newborn was delivered after an uncomplicated pregnancy, and the APGAR score was 7 at 1st minute, 8 at 5th minute and 9 at 10th minute. In the baby's physical examination, vital signs were stable, and bowel sounds were normoactive. The umbilical had a cherry-colored appearance compatible with the intestinal mucosa. The abdomen was non-tender, non distended, and without organomegaly.

The pediatric surgeon was consulted when a bubble, yellow-green-colored fecal drainage came from this orifice (Figure 1). With the preliminary diagnosis of omphalomesenteric fistula, radiopaque material using a 6 fr catheter was given through the fistula opening on the cord. The plain abdominal radiographs showed that the contrast material continued to pass through the intestine (Figure 2a, 2b). Blood count, acute phase reactants, infection markers, coagulation, and biochemical parameters were normal. Abdominal and cranial ultrasonographic imaging of additional anomalies revealed no pathological conditions. There was a distal meconium outlet. He was operated on with a patent OMD diagnosis, and interrelated intestinal parts were resected (Figure 3). No complications were observed in the postoperative follow-up, and the patient was discharged with complete recovery on the seventh postoperative day. The histopathology showed that the OMD was compatible with intestinal tissue.

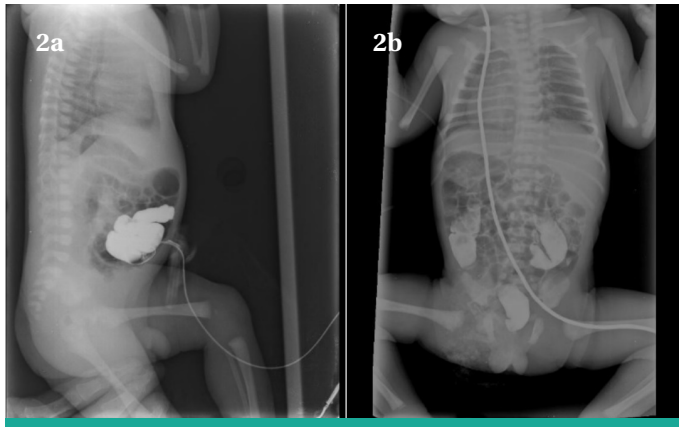

Figure 2a, 2b. The contrast material continued to pass through the intestine plain in plain abdominal radiographs

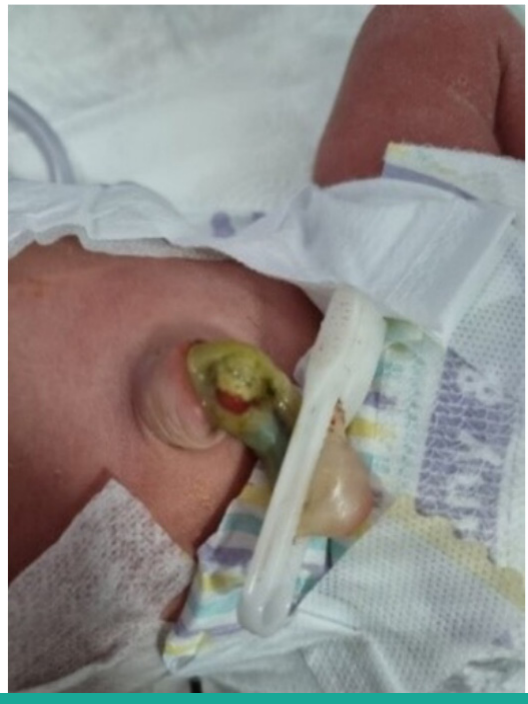

Figure 1. Fecaloid content from the umbilicus and cherry-colored duct orifice

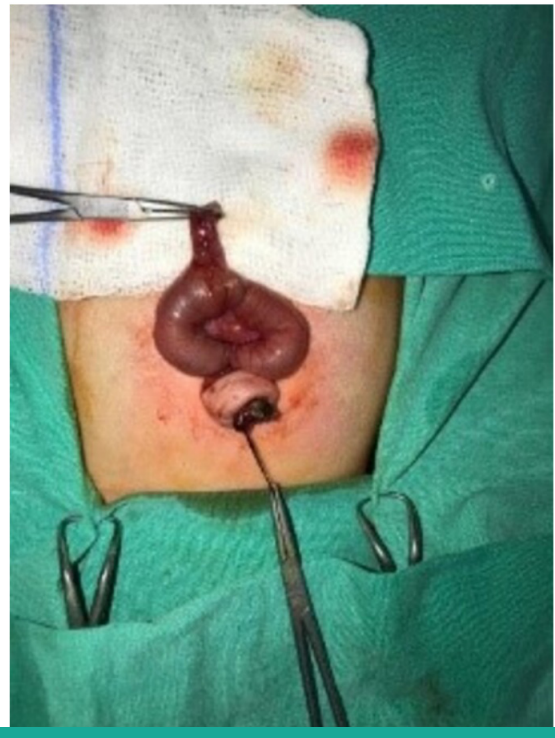

Figure 3. Peroperative patent omphalomesenteric duct

Discussion

Many variants of the OMD remnants have been declared in the literature. While Meckel diverticulum is the most widespread abnormality caused by the failure of OMD's resorption, patent OMD is unusual (4). A persistent OMD residue is pathological and rarely appears in adult age, but it is typically an anomaly type present in the pediatric population (2).

A 10-day-old girl newborn with patent OMD presented fecal umbilical discharge and was operated on with a semicircular periumbilical incision up to the abdominal cavity. The OMD, which was pursued to the intersection with the small intestine, was resected (5). At a 32-week preterm, the umbilical cord was sectioned for vein catheterization, resulting in watery content from a lumen. Following the aspiration of intestinal contents from the catheter inserted through this orifice, patent OMD was diagnosed and operated on (6). In 2021 Zvizdic et al. (7) declared a case of a newborn with a functional intestinal obstruction due to peritonitis produced by necrosis of iatrogenically clamped patent OMD in the congenital hernia into the umbilical cord. While very unusual, analogous complications have been noticed in the literature. Preventing unintentional gut injury in the course of cord cliping at delivery is possible with raised perception and experience concerning congenital hernia into the cord (7). After the detailed examinations of two newborns, one of which was examined with umbilical bleeding and one with omphalitis, it was reported that patent OMDs were revealed to be diagnosed (8). When a case of a patent OMD in an umbilical cord hernia is determined without delay, potential complications could be prevented with surgery (9).

The diagnosis of the patent OMD was made in a 6-week-old male newborn baby with a small volume of fluid and bile-stained small intestine with the appearance of umbilical drainage and a raspberry-sized mass under the umbilicus by detecting that the contrast agent administered with a catheter inserted into the stoma had entered the lumen of the small intestine (10). The simultaneous attendance of more than one abnormality of OMD in the same patient has also been declared (2). An adolescent with vomiting and intermittant periumbilical abdominal pain defined with coincident omphalomesenteric cyst and ileal diverticulum, inducing internal hernia and gut obstruction that was treated with surgery, has been presented recently (11). In the literature, although sporadic, adult cases that may be present with urachal anomalies (12) and the OMD remnants that may transform into cancerous tissue have also been reported (13).

As in our case, it is probable to diagnose the entity of the OMD in early life by attentive physical examination of all neonates at birth. In this newborn, we identify a four mm orifice on the umbilical cord enabling an early surgical approach of the newborn and interception of complications. A segmental intestine resection containing the fistula or a simple diverticulum excision is admissible. Assessment of the umbilical cord is a routine part of every newborn examination in the delivery room. Umbilical discharge should enhance the question of a patent OMD. Either any suspicious unnatural sight of the umbilical cord or any other malformations detected should be upwards assessed by a pediatric surgeon or neonatologist.

Ethics

Informed Consent: The consent form from the family of the case is obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: N.A., A.A., E.N.T., Design: N.A., A.A., E.N.T., Data Collection or Processing: N.A., A.A., S.K., E.Y., Analysis or Interpretation: N.A., A.A., S.K., O.T., Drafting Manuscript: E.Y., E.N.T., S.K., Critical Revision of Manuscript: N.A., A.A., K.A., O.T., Final Approval and Accountability: S.K., O.T., K.A., N.A., E.Y., A.A., E.N.T., Technical or Material Support: N.A., O.T., A.A., E.N.T., K.A., Writing: S.K., O.T., K.A., N.A., E.Y., A.A., E.N.T.

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

Bagcilar Med Bull 2023;8(2):198-201
DOI: 10.4274/BMB.galenos.2023.2023-03-031

The Effect of Regional Anesthesia in the Management of High-risk Abdominal Emergencies During Pandemics

Salgın Dönemlerinde Yüksek Riskli Abdominal Acillerin Yönetiminde Rejyonel Anestezinin Etkisi

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Abstract

The Coronavirus disease-2019 pandemic has shown us that the number of intensive care beds can be severely limited for postoperative care of high-risk patients. This situation has led to the need to develop a perioperative plan without intensive care support in the management of high-risk abdominal emergencies that cannot be postponed. In this case series, we shared our experiences of awake laparotomy under combined spinal epidural anesthesia in four cases in the related patient group. The patients' age and ARISCAT score median (min-max) values were respectively 73 years (56-85) and 68 (52-74), ASA scores were III, and all were at high risk for pulmonary complications. The probabilities of mortality, serious complications and expected hospital stay were 23% (11-36%), 40% (34-48%), and 15.5 (13.5-19) days. It was planned to operate the patients under combined spinal-epidural anesthesia. Epidural catheters were placed to cover the dermatome range of the planned surgical incision. Spinal anesthesia dose and initial level target was individualized according to the age and hemodynamic status of the patients, and 0.5% heavy-bupivacaine was administered. All patients underwent gastrointestinal resection at different levels, accompanied by anastomosis or stoma opening. The median (min-max) of the surgical times was 155 (120-210) minutes. No new clinical condition requiring intensive care or not in the preoperative period was observed in the service care of any patient. The hospital stay was observed as 7.5 (5-13) days.

Keywords: COVID-19, epidural anesthesia, laparotomy, major abdominal surgery, pandemic, regional anaesthesia

Öz

Koronavirüs hastalığı-2019 pandemisi bize yoğun bakım yatak sayısının yüksek riskli hastaların postoperatif takibi için ciddi şekilde kısıtlanabileceğini göstermiştir. Bu durum, ertelenemeyecek yüksek riskli abdominal acillerin yönetiminde yoğun bakım desteği olmaksızın bir perioperatif plan geliştirme ihtiyacı doğurmuştur. Bu olgu serisinde, ilgili hasta grubunda olan dört olguda kombine spinal epidural anestezi altında uyanık laparotomi deneyimlerimizi paylaştık. Hastaların yaş ve ARISCAT skor medyan (min-maks) değerleri sırasıyla 73 yıl (56-85) ve 68 (52-74), ASA skorları III ve hepsi pulmoner komplikasyonlar yönünden yüksek risklilerdi. Mortalite ve ciddi komplikasyon olasılıkları ile beklenen hastane yatış süreleri sırasıyla %23 (%11-36), %40 (%34-48), 15,5 (13,5-19) gün şeklindeydi. Hastaların kombine spinal-epidural anestezi altında opere edilmesi planlandı. Epidural kateterler planlanan cerrahi kesinin dermatom aralığını kapsayacak şekilde yerleştirildi. Spinal anestezi doz ve ilk seviye hedefi hastaların yaş ve hemodinamik durumuna göre bireyselleştirilerek %0,5 heavy-bupivakain ile yapıldı. Tüm hastalara farklı seviyelerden gastrointestinal rezeksiyon ve beraberinde anastomoz veya stoma açılması uygulaması yapıldı. Cerrahi süreler medyanı (min-maks) 155 (120-210) dakikaydı. Hiçbir hastanın servis takibinde yoğun bakım ihtiyacı gerektirecek veya preoperatif dönemde olmayan yeni bir klinik durum izlenmedi. Hastane yatış süreleri 7,5 (5-13) gün olarak izlendi.

Anahtar kelimeler: COVID-19, epidural anestezi, laparotomi, majör abdominal cerrahi, pandemi, rejyonel anestezi

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Cite this article as: Gökduman HC, Abdullah T, Gümüş Özcan F. The Effect of Regional Anesthesia in the Management of High-risk Abdominal Emergencies During Pandemics. Bagcilar Med Bull 2023;8(2):198-201

Introduction

The Coronavirus disease-2019 (COVID-19) pandemic has increased the demand for intensive care beds worldwide, resulting in serious disruptions in the follow-up and treatment of patients who need intensive care for non-pandemic reasons. This situation has also affected high-risk abdominal emergency cases that require surgical treatment and require intensive care follow-up in the postoperative period. The insufficient number of beds necessitated the creation of different perioperative plans that could reduce the need for intensive care for these patients. While the usual practice for emergency abdominal surgeons is general anesthesia, regional anesthesia techniques have become more preferred in order to avoid the need for postoperative intensive care hospitalizitions during the pandemic period and to avoid aerosol exposure that occurs during general anesthesia in this patient group, whose COVID-polymerase chain reaction (PCR) result cannot be expected. In this series of 4 cases, it was aimed to share the experiences of the related patient group.

Case Report

Between November 2020 and July 2021, 4 patients who needed urgent abdominal surgery and whose age and ARISCAT score median (min-max) values were 73 years (56-85) and 68 (52-74) were consulted. The ASA scores of the patients were III, and all were considered to be at high risk for pulmonary complications. The probabilities of mortality and major complications and expected hospital stay were 23% (11-36%), 40% (34-48%) and 15.5 (13.5-19) days. The preoperative characteristics of the patients are given in Table 1.

Each patient underwent PCR testing with nasopharyngeal swabs for the diagnosis of COVID-19 preoperatively. However, since the operations in question could not be postponed, they were carried out without waiting for the test results. Therefore, patients were considered positive until proven otherwise and were provided with a face mask during all procedures in the operating room.

There was no coagulation disorder, use of anticoagulant drugs, infection in the area where the procedure would be performed, or any other medical condition that would make neuraxial anesthesia an absolute contraindication. Therefore, they were planned to be operated under combined spinal-epidural anesthesia. Invasive arterial cannulation was performed with local anesthesia along with intraoperative routine anesthetic monitoring. The patients were placed in a sitting position, their feet were suspended from the operating table, and a step was placed under their feet. Epidural catheters (with 18 gauge Tuohy needle) were placed at different levels to cover the dermatome of the planned surgical incision. Spinal anesthesia (with a 27 gauge Quincke needle) dose and first level target was individualized according to the age and hemodynamic status of the patients, and 0.5% heavy-bupivacaine was administered at the L3-4 or L4-5 level. Anesthesia levels were checked with cold sensory loss test before the surgical incision. The data related to the regional techniques are given in Table 2.

Table 1. Preoperative data and risk scores

Patient no	Age	Preop SpO_2	ARISCAT score	Lee index	ACS-NSQIP mortality	ACS-NSQIP major complications	Estimated hospital stay
1	85	94	74	2	34%	48%	19 days
2	64	90	73	1	36%	39%	15 days
3	56	93	52	2	11%	41%	16 days
4	82	93	63	1	12%	34%	13.5 days

ACS-NSQIP: It is a scoring system developed by the American College of Surgeons for predicting patient's mortality and morbidity probabilities and length of hospital stay.
Preop: Preoperative, SpO_2: Arterial oxygen saturation calculated by a pulse oximeter

Table 2. Data on regional interventions

Patient no	Surgical incision	Level of epidural catheter	Spinal block: Dose*/ targeted dermatome level	First epidural injection	Total volume injected
1	T6-L1	T9-10	13 mg/T8	0 min	10 cc
2	T6-L1	T9-10	19 mg/T4	110 min	19 cc
3	T10-L1	T11-12	13 mg/T8	30 min	12 cc
4	T6-L1	T9-10	18 mg/T4	90 min	20 cc

*Isobaric Heavy-bupivacaine was administered

Mask oxygen therapy was avoided as long as SpO_2 was >90%. Only one patient received 2 liter/min oxygen therapy with a nasal cannula under a surgical mask.

All of the cases were completed under neuraxial anesthesia without the need to switch to general anaesthesia. No complications related to local anesthetic or neuraxial block were encountered in any of the patients. An intraoperative routine sedation protocol was not applied. Only one patient needed sedation and after a 1 mcg/kg loading dose of dexmetedomide was given to the patient within 15 minutes, 0.5 mcg/kg/hour infusion was started.

All patients underwent gastrointestinal resection at different levels, accompanied by anastomosis or stoma opening. The median (min-max) of surgical times was 155 (120-210) minutes. The characteristics of the surgeries performed are given in Table 3.

After the patients were observed in the recovery room and their Bromage scores were ≤1, they were taken to their services. No new clinical condition requiring intensive care or not in the preoperative period developed in any patient's service follow-up. All preoperative nasopharyngeal swabs for the diagnosis of COVID-19 were negative. The hospital stay was observed as 7.5 (5-13) days. Data regarding the intraoperative fluid-catecholamine requirement and the postoperative period are presented in Table 4.

Discussion

Despite the high complication rates predicted in our case series, which is particularly high-risk in pulmonary terms, no perioperative complications were observed, and all patients were discharged from the hospital within a shorter period of hospitalization. This situation can be explained on several points. Neuraxial anesthesia has the advantages of not requiring airway manipulation, not affecting respiratory control, and not requiring neuromuscular blockade. Therefore, it is associated with a decrease in the need for postoperative respiratory support (1). In a review of 141 prospective, randomized studies comparing neuraxial blocks and general anesthesia, postoperative pulmonary (pneumonia, pulmonary embolism, respiratory depression, etc.) and cardiac complications, renal complications, in patients operated under neuraxial block. It has been shown that the incidence of insufficiency and deep vein thrombosis is reduced (2). Neuraxial anesthesia can improve postoperative complication and morbidity scores, and shorten hospital stays, especially in elderly and frail patient groups with a high risk of cardiovascular and respiratory complications (3-6).

Since general anesthesia requires the use of an endotracheal tube or laryngeal mask for airway control, it definitely requires close contact with the patient and causes aerosol formation (7,8). For this reason, it may be preferable to perform operations with central and peripheral blocks in cases where possible, to avoid airway interventions in patients who will be operated without a PCR result under emergency conditions.

Considering these situations, anesthesia management with combined-spinal epidural anesthesia in selected patients who require long-term emergency major abdominal surgery can be considered an effective, safe and advantageous alternative method both for the rational use of hospital/intensive care beds and for better patient outcomes (9).

Table 3. Surgical indications and surgeries performed

Patient number	Diagnosis	Surgery	Surgical time
1	Colon Ca-GIS bleeding	Total colectomy + end ileostomy	130 min
2	Brid ileus	Bridectomy	210 min
3	Strangulated hernia	Small intestine resection-anastomosis + hernia repair	120 min
4	Colon Ca-ileus	Right hemicolectomy + anastomosis	180 min

Ca: Carcinoma, GIS: Gastrointestinal system

Table 4. Intraoperative and postoperative period

Patient number	Total fluid	Vasopressor need	Sedation need	Length of hospital stay (days)	Postoperative complication
1	1500 cc	20 mg ephedrine	-	7	-
2	4500 cc	25 mg ephedrine	-	13	-
3	2500 cc	-	α-2 agonist	8	-
4	4000 cc	25 mg ephedrine	-	5	-

This case series includes experiences in a single center and a small group of patients. Patients were reviewed retrospectively. Although there are case reports and case series (10-12) on the subject, data on larger patient groups will be needed to reveal the advantages and disadvantages of the methods to be applied.

Ethics

Informed Consent: Informed consent was obtained from all 4 patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.C.G., Concept: H.C.G., F.G.Ö., Design: H.C.G., F.G.Ö., Data Collection or Processing: H.C.G., T.A., Analysis or Interpretation: T.A., Literature Search: T.A., F.G.Ö., Writing: H.C.G.

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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