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Mustafa Kemal Üniversitesi Tıp Dergisi	Medical Journal of Mustafa Kemal University	2149-3103	2015-2022

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ABOUT

Interdisciplinary Medical Journal is an open access scientific journal, which publishes original contributions in clinical disciplines pertaining to human medicine. In this context, the Journal publishes original research, case reports and reviews based on clinical studies having interdisciplinary approach on medicine. The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. The manuscript evaluation is based on the principles of blind peer-review process. It is published online three times a year on April, August, and December. The communication, review and publication language of the Journal is English. Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts should be submitted by online system of the Journal. All manuscripts submitted to the Journal are screened in terms of originality.

Focus & Scope

Interdisciplinary medicine can be defined as "an interdisciplinary approach that relies on health professionals from different disciplines, along with the patient, working collaboratively as a team. The most effective teams share responsibilities and promote role interdependence while respecting individual members' experience and autonomy.

By supporting the interdisciplinary research on medicine, The Journal aims to;

Publish original contributions from different scientific disciplines through the advisory board covering a wide range of clinical medical disciplines,

Offer all its content freely available without charge to the user or his/her institution, to make research freely available to the public, and to support a greater global exchange of knowledge,

By permitting authors to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), to lead productive exchanges, as well as earlier and greater citation of published work.

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Family Medicine

Public Health and Preventive Medicine

Internal Diseases

General Surgery

Gynecology and Obstetrics

Ear, Nose and Throat Diseases

Eye Diseases

Orthopedics and Traumatology

Radiology and Radiodiagnostics

Anesthesia and Intensive Care Medicine

Adolescent Diseases

Childhood Diseases

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Cardiovascular System Diseases

Nervous System Diseases

Neurosurgery

Respiratory System Diseases

Infectious Diseases

Occupational Diseases

Nuclear Medicine

Oncological Diseases

Sports Medicine

Genetic Diseases

Medical Pathology

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Abstracting and Indexing

Interdisciplinary Medical Journal is indexed by TÜBITAK TR Index, Turkish Medline, Turkish Citation Index, DOAJ and Index Copernicus World of Journals

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Human and Animal Rights: For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013, www.wma.net) 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, https://nap.nationalacademies.org/catalog/5140/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 The Bulletin of Legal Medicine together with the manuscript.

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If both reviewers agree on acceptance or rejection, the decision stands.

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If a paper is not suitable for publication it will be returned to the author with a statement of reasons for rejection. The author may appeal if he or she believes an erroneous or unfair judgment has been made. A letter to the Editor-in-Chief presenting reasons why the decision should be reconsidered will be subjected to due consideration.

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When authors make revisions to their article in response to the referees' comments, they are asked to submit a list of changes and any replies for transmission to the referees. The author must upload the revised manuscript to the online system within 4 weeks; otherwise, the author will be notified that the paper will be considered withdrawn.

The revised version is usually returned to at least one of the original referees who is then asked whether the revisions are satisfactory. If the referees remain dissatisfied, the paper can be referred to the advisory board of the journal for further consideration.

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Publication Frequency

Interdisciplinary Medical Journal publishes three issues online in April, August and December. The communication, review and publication language of the Journal is English.

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Subject areas include, but are not restricted to the **clinical studies** of the following fields: first aid and emergency medicine, family medicine, public health and preventive medicine, internal diseases, general surgery, gynecology and obstetrics, ear, nose and throat diseases, eye diseases, orthopedics and traumatology, radiology and radiodiagnostics, anesthesia and intensive care medicine, adolescent diseases, childhood diseases, multisystem diseases, physical medicine and rehabilitation, forensic medicine, mental health and diseases, cardiovascular system diseases, nervous system diseases, neurosurgery, respiratory system diseases, infectious diseases, occupational diseases, nuclear medicine, oncological diseases, sports medicine, genetic diseases, medical pathology.

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Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Manuscript Preparation

All manuscripts which will be published in the journal must be in accordance with research and publication ethics. All authors should have contributed to the article directly either academically or scientifically. Presentations at congresses or in symposia are accepted only if they were not published in whole in congress or symposium booklets and should be mentioned as a footnote.

Manuscripts are received with the explicit understanding that they have not been published in whole or in part elsewhere, that they are not under simultaneous consideration by any other publication. Direct quotations, tables, or illustrations that have appeared in copyrighted material must be accompanied by written permission for their use from the copyright owner and authors. All articles are subject to review by the editors and referees.

Process of Peer Review

The journal utilizes a standard online site (https://dergipark.org.tr/en/pub/interdiscip), supported by Tubitak Ulakbim, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to the journal, the journal manager and editorial staff review the submission to assure all required components as outlined in this Guide for Authors are included. The manuscript is then assigned to one of the co-editors (either the editor in chief or an associate editor) who directs and oversees the peer-review process. The co-editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made. Acceptance is based on significance, and originality of the material submitted. If the article is accepted for publication, it may be subject to editorial revisions to aid clarity and understanding without changing the data presented.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

About the scientific language to be used in writing your manuscript

In line with the recommendation of the international directories we applied to increase the scientific effectiveness of our journal and enrich its content, our Editorial Board has decided that the studies to be published in English. So, the manuscripts sent to our journal are subject to English language control and revision.

Our experience from previous articles has shown that most of the articles prepared in English need to be improved in terms of fluent readability and intelligibility, as well as scientific and technical examination. Most of the manuscripts should undergo a comprehensive review and revision process in terms of language, before they were included in the review stage.

Therefore, we recommend that you receive professional English editing and proofreading services before submitting your manuscript to our journal, although it is not mandatory.

Our journal does not have any commercial partnership with any translation or proofreading service company, and our authors are absolutely free to make their choices as they wish.

By uploading the revised English full text of your manuscript to our Journal system by ensuring that English Editing and Proofreading is carried out by a local or foreign professional, you may minimize the possibility of rejection due to translation errors.

Use of first person

In addition, it is necessary to make the necessary checks and revisions in terms of language of your work and to ensure integrity in terms of language and time use throughout the entire article.

Expressions such as ... "Our study, in our study, we, we did, we found, we aimed, I did, I found, I think ... etc." should be revised as follows;

- In this study, ... it was found/determined/... or
- In this study ... it was aimed to ...

Names made up of single word should not be abbreviated.

Instead of,

- Hypertension (HT) is one of the most ...

Throughout the manuscript, you should use;

- Hypertension is one of the most ...

Instead of,

- Rituximab (RTX) is an IgG1 kappa chimeric monoclonal

Throughout the manuscript, you should use;

• Rituximab is an ...

Numbers should always be used to indicate statistics, age and measurements (including time as in the 3 weeks example). In specifying the others, only the numbers one to nine should be written in letters. (Numbers between 1-10 should be written with letters, except for the date and number of cases)

For example;

• In 2 studies, ...

Should be replaced with;

• In two studies ...

For example;

• ... perivascular lymphotic infiltration in only 10 percent and fibrosis in 7 percent of the patients,

Should be replaced with;

• ... perivascular lymphotic infiltration in only 10% of patients ... in 7% of patients ...

Prejudiced expressions should be avoided in expressions other than classical textbook knowledge, which has been verified by dozens of studies and has become the industry standard in the literature.

• determined to be high

Should be replaced with;

• ... was found to be high.

Or throughout the entire manuscript;

• found to be significantly higher ...

If diametrically opposite findings are mentioned among the studies mentioned in the Discussion section, it should be stated as "... a significant relationship was found / observed / reported", rather than "a significant relationship was determined" etc.

• While no significant relationship was determined between blood pressure and disease severity (26,27), a strong relationship was determined in some studies (28,29).

Should be replaced with;

While no significant relationship was observed between blood pressure and disease severity (26,27), it was reported that a strong relationship was found in some studies (28,29).

General Principles

The text of articles reporting original research should be divided into Introduction, Method, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

Sections of the manuscript

Article title

The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Information about the study design could be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Please avoid capitalizing all letters of the title and capitalize only the capital letter of first word of the title, proper nouns, proper adjectives. Other words and conjunctions (e.g., and, but, both, or, either, neither, nor, besides, however, nevertheless, otherwise, so, therefore, still, yet, though etc.) should be in small letters. No abbreviations or acronyms should be used within the titles.

Short title

You should add a running title not exceeding 40 characters to be placed at the header of the inner pages.

Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical method), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Please, do not cite figures, tables or references in the abstract.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. All the articles submitted to the journal require to include abstract in English. Abstracts of original articles should not exceed 250 words.

Keywords

Three to six words or determinative groups of words should be written below the abstract. Abbreviations should not be used as keywords. Keywords in English should be chosen from MESH (Medical Subject Headings http://www.nlm.nih.gov/mesh) index. Abbreviations cannot be used as keywords, but instead they should be written explicitly. Letters that do not exist in Latin alphabet (e.g., alpha, beta, delta etc.) should be used with their pronunciation.

Examples: carbon monoxide, firearms, sexual abuse, oral mucosa

Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Method

The guiding principle of the Method section should be clarity about how and why a study was done in a particular way. The Method section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results.

The authors should clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), autopsied persons, including eligibility and exclusion criteria and a description of the source population.

In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the method section.

The Method section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential.

Informed consent should be obtained in human studies, and it should be stated in the manuscript.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Statistical Analysis

The authors should describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. They should define statistical terms, abbreviations, symbols and should specify the statistical software package(s) and versions used.

Results

You should present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Please, do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Method Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

You should give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. You should restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Please, use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Discussion

It is useful to begin the discussion by briefly summarizing the main findings and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular,

distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted but label them clearly.

In-text Citations and References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. 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. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Laws (e.g., penal code), statutes and regulations are not scientific writings. In addition to being published on the official gazette, since it is published on various internet sites, a reference number should not be given to laws, statutes and regulations. If it is to be cited within the text, the law could be cited by specifying the number of the law, the date and number of publications in the official gazette (e.g., A Review of Article 5 of the Turkish Criminal Penal Code No. 5237). They should not be numbered within the text, or in the reference list.

To minimize citation errors, references can be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Reference list should be numbered consecutively in the order in which they are first mentioned in the text. Roman numerals should be avoided. Identify references in text, tables, and legends by Arabic numerals (1, 2, 3 ... 9, 0) in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).

If you refer to a work more than once, use the first number also for the second and following references. References to more than one source in the same phrase may be entered like this: (2-4), i.e., references 2 through 4 in the reference list, and (2-4, 8), i.e. the references 2 through 4, plus reference no 8 in the list of references.

Sample for in-text citation:

In a clinical research in healthy individuals, Ellis (25) has studied the sciatic nerve excursion using ultrasound technique.

Wright and Ellis (10) has investigated the excursion of nerves around the elbow joint.

In another and similar cadaveric study by Wright et al (13), the radial nerve median excursion values were 4.1, 8.8, and 0.2, 0.1 mm with motions of shoulder, elbow, wrist and fingers respectively.

Suicide is a major public health problem and globally the second leading cause of death among young adults (1). Studies focusing on how mental health risk factors impact on youth suicidal behaviors suggest that psychopathological symptoms are associated with suicidal behavior (3,4). Adverse effects of H2S on human health vary from local irritation to immediate death depending on the form, concentration, duration and route of exposure (9, 13-15).

Reference Style

The Vancouver system, also known as Vancouver reference style or the author–number system, is a citation style that uses numbers within the text that refer to numbered entries in the reference list. Vancouver style is used by MEDLINE and PubMed. The names "Vancouver system" or "Vancouver style" have existed since 1978. The latest version of the latter is Citing Medicine, per the References > Style and Format section of the ICMJE Recommendations. In 1978, a committee of editors from various medical journals, the International Committee of Medical Journal Editors (ICMJE), met in Vancouver, BC, Canada to agree to a unified set of requirements for the articles of such journals. This meeting led to the establishment of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). Part of the URMs is the reference style, for which the ICMJE selected the long-established author–number principle.

Since the early to mid-2000s, the United States National Library of Medicine (which runs MEDLINE and PubMed) has hosted the ICMJE's "Sample References" pages. Around 2007, the NLM created Citing Medicine, its style guide for citation style, as a new home for the style's details. The ICMJE Recommendations now point to Citing Medicine as the home for the formatting details of Vancouver style.

Interdisciplinary Medical Journal, since the first day of its publication uses the PubMed/NLM reference style. Thus, references list should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles web page and detailed in the NLM's Citing Medicine, 2nd edition.

According to the Vancouver rules, you can only refer to the literature you have read yourself. If you find anything interesting in a text where it is referred to another text, you must read and refer to the original.

References List

The references list should be ordered numerically in the order in which the references appear in the text.

The journal's name may be abbreviated, according to the abbreviation rules for journal titles. Records retrieved from a search for the full journal title in the National Library of Medicine's search page include the abbreviated title.

Authors' names should be given as surname followed by initials. There should be a space between surname and initials. A maximum of two initials are allowed for each author, they should be entered without spaces or punctuation. Different authors should be separated by a space and a comma. A period (.) should follow the last author's name. If six or more authors, list the first six authors followed by et al.

Only capital letter of the first word of the title, proper nouns, proper adjectives, acronyms, and initialisms should be capitalized.

The most reliable method for calculating the impact factor of our journal and number of citations of articles published in our journal or calculating the number of times your own article is cited in a healthy way, is to add DOIs to the references section. In order to give the DOIs to the articles published in Interdisciplinary Medical Journal, the CrossRef membership application has been completed and all the research articles, case reports, and reviews are being assigned DOIs. For this reason, DOIs need to be added to the References section if available for those references. We hope that the Simple Text Query Form will be helpful in referencing articles published in our journal.

With the help of the Simple Text Query Form web page, which has a link in the full-text template, DOI records need to be added to the sources.

https://apps.crossref.org/SimpleTextQuery

Note: Please, **do not insert Pubmed ID (PMID) or Pubmed Central ID (PMCID) records** to the reference list since they are useless in determining the citation counts.

We place great importance to the addition of DOIs to the references list.

Sample for Journal Article without DOI

Dokgöz H, Kar H, Bilgin NG, Toros F. Forensic Approach to Teenage Mothers Concept: 3 Case Reports. Turkiye Klinikleri J Foren Med 2008;5(2):80-4

Kaufman DM, Mann KV, Miujtjens AM, Van der Vleuten CP. A comparison of standard setting procedures for an OSCE in undergraduate medical education. Academic Medicine 2000;75:267–71.

Sample for Journal Article with DOI

Koçak U, Alpaslan AH, Yağan M, Özer E. Suicide by Homemade Hydrogen Sulfide in Turkey a Case Report. Bull Leg Med. 2016;21(3):189-192. https://doi.org/10.17986/blm.2016323754

Article not in English

Kar H, Dokgöz H, Gamsız Bilgin N, Albayrak B, Kaya Tİ. Lazer Epilasyona Bağlı Cilt Lezyonlarının Malpraktis Açısından Değerlendirilmesi. Bull Leg Med. 2016;21(3):153-158. https://doi.org/10.17986/blm.2016323748

Books and Other Monographs

Personal author(s)

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Editor(s), compiler(s) as author

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113

Emmerson BT. Gout and renal disease. In: Massry SG, Glassock RJ (Editors). Textbook of Nephrology 1. Baskı, Baltimore: Williams and Wilkins; 1989. p. 756–760.

Conference proceedings

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Article published on the Internet ahead of the print version:

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Part of a homepage/Web site [Edited 28 Dec 2016]

American Medical Association [Internet]. Chicago: The Association; c1995-2016 [cited 2016 Dec 27]. Office of International Medicine; [about 2 screens]. Available from: https://www.ama-assn.org/about/office-international-medicine

Thesis

Skrtic L. Hydrogen sulfide, oil and gas, and people's health [Master's of Science Thesis]. Berkeley, CA: University of California; 2006.

Weisbaum LD. Human sexuality of children and adolescents: a comprehensive training guide for social work professionals [master's thesis]. Long Beach (CA): California State University; 2005. 200 p.

For the reference types not listed here, please visit Samples of Formatted References for Authors of Journal Articles available at Medline Web site (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

It would be appropriate to place the tables at the end of the main text. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text. Give each column a short or an abbreviated heading. In the tables, case counts (n) and percentages (%) should be specified in separate columns, not in the same cell.

Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes and use symbols to explain information if needed. Symbols may be as alphabet letters or such symbols as *, p t> T §). Please, identify statistical measures of variations, such as standard deviation and standard error of the mean.

Illustrations (Figures)

The lexical meaning of figure constitutes a number symbol (numeral, digit), a written or printed character, a diagram or pictorial illustration of textual matter, arithmetical calculation or digits representing an amount when plural. While definition of picture includes a design or representation made by various means (as painting, drawing, or photography), illustration means a picture or diagram that helps make something clear or attractive. Although these terms bear distinctive meanings, they are too often used interchangeably. Thus, we meant them in the same way without distinction.

Digital images

The 300 DPI Story

In the ancient times when digital cameras have not been invented, the photos taken by analogue cameras were used to be printed on photo papers. In order to transfer these photos to the digital environment, they had to be scanned by optical devices called scanners. On the same dates, desktop publishing and printing technology was far beyond the digital photography, and many years had passed since the invention of laser printing technology. Here, several technical terms should be explained to make the concept clearer. DPI is used to describe the resolution number of dots per inch in a digital print and the printing resolution of a hard copy print dot gain, which is the increase in the size of the halftone dots during printing. A dot matrix printer, for example, applies ink via tiny rods striking an ink ribbon, and has a relatively low resolution, typically in the range of 60 to 90 DPI (420 to 280 µm). An inkjet printer sprays ink through tiny nozzles and is typically capable of 300–720 DPI. A laser printer applies toner through a controlled electrostatic charge and may be in the range of 600 to 2,400 DPI. Along with the cheaper memory chips, 1200 dpi printers have been widely available in the consumer market since 2008. Monitors do not have dots but do have pixels. The closely related concept for monitors and images is pixels per inch or PPI. Old CRT type video displays were almost universally rated in dot pitch, which refers to the spacing between the sub-pixel red, green and blue dots which made up the pixels themselves. The DP measurement of a printer often needs to be considerably higher than the pixels per inch (PPI) measurement of a video display in order to produce similar-quality output. This dithered printing process could require a region of four to six dots (measured across each side) in order to faithfully reproduce the color in a single pixel. An image that is 100 pixels wide may need to be 400 to 600 dots in width in the printed output; if a 100×100-pixel image is to be printed in a one-inch square; the printer must be capable of 400 to 600 dots per inch to reproduce the image. The dpi of early model laser printers was 300 to 360, thus scanning images at 300 DPI was a common practice at that time.

In printing, DPI (dots per inch) refers to the output resolution of a printer or imagesetter, and PPI (pixels per inch) refers to the input resolution of a photograph or image. DPI refers to the physical dot density of an image when it is reproduced as a real physical entity, for example printed onto paper. A digitally stored image has no inherent physical dimensions, measured in inches or centimeters. Some digital file formats record a DPI value, or more commonly a PPI (pixels per inch) value, which is to be used when printing the image. This number lets the printer or software know the intended size of the image, or in the case of scanned images, the size of the original scanned object. For example, a bitmap image may measure 1,000 × 1,000 pixels, a resolution of 1 megapixel. If it is labeled as 250 PPI, that is an instruction to the printer to print it at a size of 4 × 4 inches. Changing the PPI to 100 in an image editing program would tell the printer to print it at a size of 10×10 inches. However, changing the PPI value would not change the size of the image in pixels which would still be 1,000 × 1,000. An image may also be resampled to change the number of pixels and therefore the size or resolution of the image, but this is quite different from simply setting a new PPI for the file.

Therefore, an image that is 2048 pixels in width and 1536 pixels in height has a total of 2048×1536 = 3,145,728 pixels or 3.1 megapixels. One could refer to it as 2048 by 1536 or a 3.1-megapixel image. Or you can think of it as a very low-quality image (72 ppi) if printed at about 28.5 inches wide, or a very good quality (300 ppi) image if printed at about 7 inches wide.

Since the 1980s, the Microsoft Windows operating system has set the default display "DPI" to 96 PPI, while Apple/Macintosh computers have used a default of 72 PPI. The choice of 72 PPI by Macintosh for their displays arose from the convenient fact that the official 72 points per inch mirrored the 72 pixels per inch that appeared on their display screens. (Points are a physical

unit of measure in typography, dating from the days of printing presses, where 1 point by the modern definition is 1/72 of the international inch (25.4 mm), which therefore makes 1 point approximately 0.0139 in or 352.8 µm). Thus, the 72 pixels per inch seen on the display had exactly the same physical dimensions as the 72 points per inch later seen on a printout, with 1 pt in printed text equal to 1 px on the display screen. As it is, the Macintosh 128K featured a screen measuring 512 pixels in width by 342 pixels in height, and this corresponded to the width of standard office paper (512 px ÷ 72 px/in ≈ 7.1 in, with a 0.7 in margin down each side when assuming 8.5 in × 11 in North American paper size (in Europe, it's 21 cm x 30 cm - called "A4")).

In computing, an image scanner—often abbreviated to just scanner, is a device that optically scans images, printed text, handwriting or an object and converts it to a digital image. Although the history of digital cameras dates back to the 1970s, they have become widely used in the 2000s. While the resolution of the first digital camera invented by Kodak was as low as 100 by 100 pixels (0.01 megapixels), the first commercially available digital camera, Fujix DS-1P had a resolution of 0.4 megapixels. On the other hand, modern scanners are considered the successors of early telephotography and fax input devices. The pantelegraph was an early form of facsimile machine transmitting over normal telegraph lines developed by Giovanni Caselli, used commercially in the 1860s, that was the first such device to enter practical service. The history of the first image scanner developed for use with a computer goes back to 1957. Color scanners typically read RGB (red-green-blue color) data from the array. This data is then processed with some proprietary algorithm to correct for different exposure conditions and sent to the computer via the device's input/output interface. Color depth varies depending on the scanning array characteristics but is usually at least 24 bits. High quality models have 36-48 bits of color depth. Another qualifying parameter for a scanner is its optical resolution, measured in pixels per inch (ppi), sometimes more accurately referred to as samples per inch (spi).

Images in web pages, video, and slide shows can be as low as 72 PPI for a static image or 150 PPI if we are going to focus in on the image. For printing, the DPI needs to be larger, with images scanned in at least 300 DPI. The DPI standard for and images to be printed within journals and books is 300 DPI and for museum exhibits, it's 600 DPI.

The most important factors determining image quality of digital images can be considered as pixel dimensions and color depth. Increasing the dpi value of an image by resampling in Photo Editors (e.g., Adobe Photoshop) has no improving effect on its quality, but it lets us to determine target printing size.

For vector images, there is no equivalent of resampling an image when it is resized, and there is no PPI in the file because it is resolution independent (prints equally well at all sizes). However, there is still a target printing size. Some image formats, such as Photoshop format, can contain both bitmap and vector data in the same file. Adjusting the PPI in a Photoshop file will change the intended printing size of the bitmap portion of the data and also change the intended printing size of the vector data to match. This way the vector and bitmap data maintain a consistent size relationship when the target printing size is changed. Text stored as outline fonts in bitmap image formats is handled in the same way. Other formats, such as PDF, are primarily vector formats which can contain images, potentially at a mixture of resolutions. In these formats the target PPI of the bitmaps is adjusted to match when the target print size of the file is changed. This is the converse of how it works in a primarily bitmap format like Photoshop but has exactly the same result of maintaining the relationship between the vector and bitmap portions of the data.

Long story short, it is not technically possible to talk about DPI value for images that were taken by digital cameras or any type of digital images that were transferred to the computer's storage media. The DPI value stored within exif information of images is just a virtual value just to guide the photo editing software and the graphic artist to determine the target printing size of that image.

Requirements for Digital Media

Figures and Figure Legends

Dear author, since the Journal has decision of publishing online, there is no need to upload the photos, pictures, drawings or shapes in the article as a separate file. However, to avoid blurring of images in the pdf of the article, you should add the photos or other images (X-ray, BT, MR etc.) in your Microsoft Word program as follows.

Insert menu - Pictures - Related image file in your computer

You must add the related image file on your computer and add the picture width to 16 cm. Since the need to upload each image (photo, X-ray, BT, MR or other images) is eliminated, please do not upload it to the system during submission. Place only at the end of full text and blind text.

Due to the reasons explained above, images should be taken by a digital camera of 5 megapixels or more in JPEG, RAW, or TIFF format, and should be inserted in their original form as JPEG, PNG or TIFF files.

Paper-printed images or documents should be scanned at 300 DPI resolution and should be inserted as TIFF, PNG or JPEG files.

Each vector graphic software has its own built-in settings and may have been preset at 72 dpi. So, the document should be created enough big to obtain the image in the desired dimensions. The vector graphics should be exported to a rasterized image format and inserted such as JPEG, PNG or TIFF files.

For X-ray films, CT scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, you should insert high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, we may require deposition of the original photographs of blots on the journal website.

Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication.

Figures should be made as self-explanatory as possible. Titles and detailed explanations belong in the legends— not on the illustrations themselves.

Figures should be numbered consecutively according to the order in which they have been cited in the text.

In the manuscript, legends for illustrations should be in Arabic numerals corresponding to the illustrations. Roman numerals should be avoided. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, you should identify and explain each one clearly in the legend.

Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Authors must consult the International System of Units (SI).

Authors should add alternative or non-SI units, when SI units are not available for that particular measurement. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

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

Types of paper

Interdisciplinary Medical Journal publishes the following types of articles.

1. Original Articles: Original prospective or retrospective studies **clinical research** in areas relevant to medicine.

The manuscript should contain English abstract, a maximum of 250 words, and the structured abstract should contain the following sections: objective, method, results, and conclusion. Three to six words or determinative groups of words should be written as keywords below the abstract.

The text of articles reporting original research might contain up to 5000 words (excluding abstract, references list and tables) and should be divided into Introduction, Method, Results, and Discussion sections. References list should also be included so that their number does not exceed 50. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles need subheadings within these sections to further organize their content.

2. Review Articles: The authors may be invited to write or should be expert in that subject of review article.

The manuscript should contain English abstract, a maximum of 250 words, but a structured abstract is not required. The main text should include subtitles or related topics to further organize the content. The text of review articles might contain up to 5000 words (excluding Abstract, references list and Tables). Number of references list should not exceed 90.

3. Case Reports: Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens.

The manuscript should contain English abstract, a maximum of 250 words, but a structured abstract is not required. The main text should include titles or related topics to further organize the content. The manuscript could be of up to 2500 words (excluding references list and abstract) and could be supported with up to 25 references.

4. Editorial: Special articles are written by editor or editorial board members. An abstract is not usually included in editorials.

5. Letter to the Editor: These are letters which include different views, experiments and questions of the readers about the manuscript and should preferably be related to articles previously published in the Journal or views expressed in the journal. These should be short and decisive observations. They should not be preliminary observations that need a later paper for validation. The letter could have up to 1000 words and a maximum of 15 references.

Please contact the Editor at tip.dergi@mku.edu.tr for sending this type of papers.

Submission Files

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b) Full Manuscript File: This is the blinded manuscript file that will be presented to the reviewers. The main text of the article, beginning from Abstract till references list (including tables, figures or diagrams) should be in this file. The file must not contain any mention of the authors' names or initials or the institution at which the study was done, ethical committee or acknowledgements. Manuscripts not in compliance with the Journal's blinding policy might be returned to the corresponding author. Please, use only Microsoft Word Document files. Do not zip the files. The name of the institution or hospital

which will reveal the place where the study was conducted should be blinded as "... University" or "... Hospital".

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Short title

You should add a running title not exceeding 40 characters to be placed at the header of the inner pages.

c) Title Page File: Only descriptive parts of the manuscript should be included in this file. General information about the article and authors is presented on the title page file and it should include the article title in English, author information, email address of each (all) author, ORCID iDs, any disclaimers, sources of support, conflict of interest declaration, ethical committee information, contact information of the corresponding author, acknowledgement and authorship contribution. This file will not be shared with reviewers.

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ORCID iD information of all authors is required by the TR Index.

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Conflict of Interest declaration. A conflict of interest can occur when you (or your employer or sponsor) have a financial, commercial, legal, or professional relationship with other organizations, or with the people working with them, that could influence your research.

Some authors claim, the influence of the pharmaceutical industry on medical research has been a major cause for concern. In contrast to this viewpoint, some authors emphasize the importance of pharmaceutical industry-physician interactions for the development of novel treatments and argued that moral outrage over industry malfeasance had unjustifiably led many to overemphasize the problems created by financial conflicts of interest.

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Acknowledgement

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Authorship contribution: please indicate which part of the article each author contributed .

Article Format

The submitted file must be in Microsoft Word Document format.

The page size must be 210 mm × 297 mm (A4 size). All margins must be

set to 2.5 cm. If you are using Microsoft Word 2007 or later, you can easily set the margin by choosing "Normal" setting from Margins menu within Layout tab. The text layout should consist of single column.

Do not capitalize diseases or syndromes unless they include a name or proper noun. Note that the words "syndrome" and "disease" are never capitalized; for example, Down syndrome, Hodgkin disease.

The authors should turn off automatic hyphenation. Do not use hyphens with common prefixes unless the word looks confusing when closed up or unless the prefix precedes a proper noun, some other capitalized word, or an abbreviation. Common prefixes that should be "closed up" include ante, anti, hi, co, contra, counter, de, extra, infra, inter, intra, micro, mid, neo, non, over, post, pre, pro, pseudo, re, semi, sub, super, supra, trans, tri, ultra, un, and under.

Use italics sparingly for emphasis in the text.

Spell out Greek letters or use the "Insert, Symbol" feature in Microsoft Word. Do not create your own symbols.

Do not use italics for common expressions, such asin vivo, in utero, en face, aide-mémoire, or in situ.

Use bold type sparingly in text because it competes with headings for the reader's attention.

Always use numerals for statistics, ages, and measurements (including time, for example, 3 weeks). For other uses, spell out numbers from one to nine only.

Spell out abbreviations at first mention in the manuscript, with the abbreviation following in parentheses (except for units of measure, which are always abbreviated following numerals).

Manuscripts including tables, references list and figure legends, must be typewritten with a Unicode font (e.g., Times New Roman, Arial, etc.) that is available both for Windows and Mac Os operating systems. Please avoid using a mixture of fonts or non-Unicode fonts that do not support accented characters. The recommended font size is 12 points, but it may be adjusted for entries in a table. Authors should use true superscripts and subscripts and not "raised/lowered" characters. For symbols, please use the standard "Symbol" fonts on Windows or Macintosh.

Use the TAB key once for paragraph indents, not consecutive spaces. The pages should be numbered consecutively, beginning with the first page of the blinded article file. The pages should include title and abstract in English, the main text, tables, figures or diagrams-if exists- and reference list.

The title of the article should be centered at the top of the main text page, with the abstract below, and followed by Keywords. The capital letter of the first word of title should start with upper case letter. Please avoid capitalizing all letters of the title and conjunctions. The title, abstract, and keywords should be present in English and must be organized respectively. In order to start the Introduction section in a new page, a page break could be inserted at the end of Keywords.

While figure legends should be placed below the figures themselves, table captions should be placed above each table. Characters in figures, photographs, and tables should be uncapitalized in principal.

It would be appropriate to place the figures, tables and photographs at the end of the main text. Please, insert them at the end of main text at appropriate sizes, and order.

Figures and Figure Legends

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You must add the related image file on your computer and add the picture width to 16 cm. Since the need to upload each image (photo, X-ray, BT, MR or other images) is eliminated, please do not upload it to the system during submission. Place only at the end of full text and blind text.

The sections (i.e., Introduction, Method, Case, Results, Discussion, and Conclusion) and their subheadings should not be numbered. Paragraphs might be aligned left or justified, but this situation should be consistent throughout the article. Please, use single return after each paragraph. All headings should be typed on a separate line, not run in with the text. There should be no additional spacing before or after lines. Headings and subheadings should not be numbered, and their depth should not exceed three levels. You should not use the "Endnotes" or "Footnotes" feature for your references and remove any Word specific codes. When 'Magic Citations' inserts citations, or formats your manuscript in Microsoft Word, it uses "fields", which you can typically recognize as boxes that turn grey when the insertion point is placed inside one of them. Here is how to remove the fields in a Microsoft Word document:

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INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2024;15(51)

Reviewer Guide

Dear Reviewer,

Thank you for agreeing to conduct a peer review which will help us decide whether a manuscript is to be published in this journal.

Peer-review is a critical part of the functioning of the scientific community, of quality control, and the self-corrective nature of science. Participating in peer review of scientific publications can be viewed as a responsibility, a burden, and an opportunity all at the same time. Nonetheless, peer review remains a critical component of our profession that helps to ensure the quality, originality, and reliability of scientific findings and claims. Peer review is requested of a colleague with specific interest and expertise in the topic relevant to the manuscript submitted to The Journal. Yet despite the importance of this process in upholding rigorous scientific standards and the integrity of the journal, few if any reviewers receive any formal training or instruction in how to provide a quality manuscript review. This document serves to orient and guide individuals asked to provide peer review for This journal in the process and responsibilities of review and reviewer. In doing so, the hope is to increase scientific quality of the manuscripts and contribution to the medical scientific community.

Process of peer review in The Journal

The journal utilizes a standard online site https://dergipark.org.tr), supported by TUBİTAK, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to The Journal, the Journal Manager and editorial staff review the submission to assure all required components as outlined in the Guide for Authors are included. The manuscript is then assigned to one of the Co-Editors (either the Editor in Chief or an Associate) Editor who directs and oversees the peer-review process. The Co-Editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. Selection of these reviewers is a key step in the peer review process, as this represents a critical component in ensuring quality of manuscript review and in the overall quality of the Journal. Specifically, the selection of a reviewer with expertise in the topic of the manuscript to be reviewed and without any conflict of interest improves both the timeliness and quality of the review. As such, the designation of an area of interest or expertise by the reviewer (entered at the time of registration into the system (and updated in the change details section of the website, in the subsection areas of expertise) is critical for this component of the process. Reviews are chosen to a great extent from members of the advisory board.

Once the reviewers are selected by the editor, an email is sent requesting the review; 30 days is provided to choose to review (or not review) the manuscript. A lack of response to this request leads to the reviewer being uninvited. Statistics on individual reviewers are maintained and reviewed by the journal editors, including the number of reviews requested (and those accepted, uninvited, and refused). These data help in the process of evaluating the overall quality of a reviewer and are used in the selection of future editorial board members.Before Accepting

Please consider the following:

Does the article you are being asked to review match your expertise?

If you receive a manuscript that covers a topic that does not sufficiently match your area of expertise, please notify the editor as soon as possible. Please feel free to recommend alternate reviewer.

Do you have time to review the paper?

Finished reviews of an article should be completed within four weeks. If you do not think you can complete the review within this time frame, please let the editor know and if possible, suggest an alternate reviewer. If you have agreed to review a paper but will no longer be able to finish the work before the deadline, please contact the editor as soon as possible.

Are there any potential conflicts of interests?

While conflicts of interest will not disqualify you from reviewing the manuscript, it is important to disclose all conflicts of interest to the editors before reviewing. If you have any questions about potential conflicts of interests, please do not hesitate to contact the receiving editorial office.

Finally: Educate yourself on the peer review process through the international guides on how to conduct a good review

Some resources;

https://violentmetaphors.com/2013/12/13/how-to-become-good-at-peer-review-a-guide-for-young-scientists/

https://www.theguardian.com/higher-education-network/blog/2013/sep/27/peer-review-10-tips-research-paper

https://www.degruyter.com/document/doi/10.7556/jaoa.2013.070/html

https://scholar.google.com.tr/scholar?hl=tr&q=good+peer+review&btnG=&lr=

(https://www.google.com.tr/search?num=50&btnG=Ara&q=how+to+write+a+good+peer+review).

Respond to the invitation as soon as you can – delay in your decision slows down the review process, whether you agree to review or not.

General criteria for a peer review

There are a number of general criteria that make for a quality review of a scientific manuscript, and a number of responsibilities that come with being a peer reviewer that further enhances the review process.

The peer reviewer is responsible for critically reading and evaluating a manuscript in their specialty field, and then providing respectful, constructive,

and honest feedback to authors about their submission. It is appropriate for the Peer Reviewer to discuss the strengths and weaknesses of the article, ways to improve the strength and quality of the work, and evaluate the relevance and originality of the manuscript.

Timely – Given the time sensitive nature of many scientific manuscripts, the rapid return of a solicited peer review minimizes the timeline between submission and decision (which helps the authors with resubmission if the manuscript is rejected and helps the journal with a shorter time from submission to publication if accepted). Thus, the reviewer plays a very important role in ensuring expeditious dissemination of data. Peer reviews that cannot be completed on time should not be accepted by the reviewer; every effort should be made to complete those accepted within the time allotted for review.

Fair – A reviewer has a responsibility to both The Journal and the author to provide a review that is thoughtful and complete. While the immediate goal of peer review is providing a decision regarding the suitability for publication in the journal, an additional goal is to provide the author comments that will ultimately improve the science and manuscript and providing it the best chance for publication in a peer-reviewed journal. For manuscripts eventually accepted for publication, quality peer review will ensure that the highest quality science is ultimately published (and will weed out unsound papers). Peer reviews requested in areas outside of the area of expertise of a reviewer should not be accepted; in that case, the review process is facilitated by the reviewer recommending those who could provide a quality review.

Collegial – It is rare for any manuscript to be reviewed without comments or criticisms. However, the responsibility of the reviewers is to provide these critiques constructively and objectively, and in a fashion, that is collegial and respectful. Consider each manuscript as one that was written by a valued colleague when drafting a peer review. Importantly, review the manuscript as you would like your own manuscript reviewed.

Clear – The goal of peer review is to provide an advisory recommendation to the editors as to the suitability of a manuscript for publication in The Journal. As such, the responsibility of the reviewer is to provide a clear signal to the editor regarding the appropriateness and priority for publication of a manuscript. The reviewer is expected to provide comments and criticisms to the editor that clearly justifies their recommendation for disposition of the manuscript. It is also critical that the comments to the editor are consistent with those made to the author (such that the comments of the reviewer justify the recommendation regarding the disposition of the manuscript).

Comprehensive – A quality review will include a number of considerations, and may be specific to the manuscript being reviewed. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. A reviewer is expected to comment on the strengths and weaknesses or limitations of the study. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

Considerations for a quality peer review of a manuscript

Structure

Is the article clearly laid out? Are all the key elements present: abstract, introduction, methodology, results, conclusions?

Consider each element in turn:

Title: Does it clearly describe the article? This will be used for medical database searches, so it shouldn't try to be "cute".

Abstract: Does it reflect the content of the article? Are the data consistent with the results reported in the manuscript?

Introduction: Does it describe what the author hoped to achieve accurately, and clearly state the problem being investigated? Normally, the introduction is two or three paragraphs long. It should summarize relevant research to provide context, and explain what findings of others, if any, are being challenged or extended. It should describe the experiment, hypothesis; general experimental design or method.

Methodology: Does the author accurately explain how the data were collected? Is the design suitable for answering the question posed? Is there sufficient information present for you to replicate the research? Does the article identify the procedures followed? Are these ordered in a meaningful way? If the methods are new, are they explained in detail? Was the sampling appropriate? Have the equipment and materials been adequately described? Does the article make it clear what type of data was recorded; has the author been precise in describing measurements?

Results: This is where the author should explain in words, tables and figures what was discovered in the research. It should be clearly laid out and in a logical sequence. You will need to consider if the appropriate analysis been conducted. Are the statistics correct? If you are not comfortable with statistics, advise the editor when you submit your report and recommend review by a statistical editor. Any interpretation should not be included in this section.

Conclusion/Discussion: Are the claims in this section supported by the results, do they seem reasonable? Have the authors indicated how the results relate to expectations and to earlier research? Does the article support or contradict previous theories? Does the conclusion explain how the research has moved the body of scientific knowledge forward?

Language: If an article is poorly written due to grammatical errors, while it may make it more difficult to understand the science, you do not need to correct the language. You may wish to bring it to the attention of the editor, however, and we can refer the authors to an language editing service if you feel the paper may be worth publishing.

Finally, on balance, when considering the whole article, do the figures and tables inform the reader, are they an important part of the story? Do the figures describe the data accurately? Are they consistent (are the bars in the charts the same width, are the scales on the axis logical)? Are the legends appropriate?

Previous Research

If the article builds upon previous research, does it reference that work appropriately? Are there any important works that have been omitted? Are the references accurate and up to date?

Reviewer's Suggestions

Once accepted, the reviewer has 4 weeks to complete the review (details of the components of a review are described in more detail below), which is submitted through The Journal site. Failure to complete the review during this time period leads to a reminder email.

It is the responsibility of the reviewer to provide a recommendation to the editor for the disposition of the manuscript. Importantly, the recommendation of the reviewer is advisory to the editor, as it is ultimately the decision of the editor as to the final disposition of the manuscript.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made.

The recommendations can be categorized into 6 groups.

Accept Submission (without modification)

Minor Revision (Revisions Required): Accept with minor modification (but manuscript requires modifications to improve its quality)

Major Revision (Resubmit for Review): Major modifications required, manuscript is unique, but requires extensive revision and reevaluation prior to potential acceptance

Resubmit Elsewhere: manuscript is unique, but out of the journal scope.

Decline Submission: manuscript is of low quality or low interest to the readership)

The reviewer has two types of comments that can be provided – one to the authors, and one to the editors. It is strongly encouraged that the reviewer utilizes the comments to the editor to provide confidential comments regarding the manuscript under consideration. These comments help assure that the editor understands the true recommendation of the reviewer and provides key assistance to the Editor in determining a manuscript's ultimate disposition. In addition, completing the manuscript rating form is helpful in supporting a reviewer's recommendation for the disposition of a manuscript, and assists the Editor in justifying the final decision.

Review of the reviewer

The editor evaluates the quality of a review upon its receipt. Utilizing the criteria defining a quality review (timely, fair, collegial, clear, and comprehensive), a reviewer is evaluated and scored (from 0-5) on their review. This statistic, in combination with a separate statistic regarding the timeliness of the review, is helpful in assigning subsequent reviews to a reviewer. Reviewers with low scoring or late reviews are not considered highly for subsequent reviews.

Why be a reviewer?

Reviewing requires the investment of time and a certain skillset. Before you decide if you want to become a reviewer, we recommend that you read more about the peer review process and conducting a review.

A reviewer may directly benefit from the peer review process by learning from the work of others prior to publication. Reviewer's insights may also lead to future research ideas, improvements in their own study design and manuscript preparation. In addition, The Council of Higher education supports peer reviewing financially within the context of academic refunds.

As a reviewer, you can;

Establish your expertise in the field and expand your knowledge.

Improve your reputation and increase your exposure to key figures in the field.

Stay up to date with the latest literature, and have advanced access to research results.

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* In accordance with the principles of double-blind review, the information regarding the approval of the center where the study was conducted and the approval of the ethics committee were removed from the article after we reviewed it and will be added again during the copyediting following the end of the review. There is no need for our reviewers to make an examination in this respect.

* Before all studies are sent to the reviewer, while they are in the pre-control stage, they are subjected to "Similarity Check" with iThenticate Crosscheck software and if they are above the tolerable level, the author is requested to make the necessary corrections.

* We ask the authors to use a dot as a decimal separator throughout the article, including the Turkish and English abstracts, so this is not an error.

* Therefore, we would like to inform you that there is **no need for you to request any correction regarding the use of a dot as a decimal separator or not, whether the approval of the ethics committee** has been obtained.

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The Journal requires and encourages the authors and the individuals involved in the evaluation process of the submitted manuscripts to disclose any existing or potential conflicts of interest, including financial, consultant, and institutional. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

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

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Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts submitted to another journal for evaluation but rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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Individuals listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org).

The ICMJE recommends that authorship be based on the following four criteria:

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

2. Drafting the work or revising it critically for valuable intellectual content;

3. Final approval of the version to be published; AND

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

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for

other specific parts of the work. Besides, authors should have confidence in the integrity of the contributions of their co-authors.

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Smoking increases chronic postsurgical pain in patients undergoing open abdominal hysterectomy

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Abstract

Objectives: Smoking cause severe postoperative complications. Cotinine is the end product of nicotine in the urine. Our primary hypothesis was that women with high preoperative urinary cotinine levels have more postsurgical chronic/acute pain is tested, and secondarily, that high cotinine levels are associated with more opioid consumption.

Method: 158 patients undergoing open abdominal hysterectomy were divided into three groups according to the cotinine level. 1) Low Cotinine group <10ng/dl (no exposure), 2) Intermediate Cotinine group =10-500ng/dl (exposure), 3) High Cotinine group >500ng/dl (smoker). In postoperative 3 months, postsurgical chronic pain, allodynia score, pain limiting daily activity, Brief Pain Inventory, SF 12 form, Douleur Neuropathique en 4 (DN4) questions test, and Sleep interference test were assessed. Visual Analogue Scale (VAS), morphine consumption, rescue analgesic consumption, and complications were recorded during postoperative 48 hours.

Results: The postsurgical chronic pain scores at the three months($p<0,007$), the postoperative pain scores and opioid consumption were significantly higher in the high cotinine group. High cotinine group had significantly worst HADS, SF 12 PCS, allodynia, and sleep interference test scores.

Conclusion: Smoking and tobacco smoke exposure are associated with high postsurgical chronic pain, and also postoperative acute pain with more opioid consumption.

Keywords: Cotinine, Pain, Smoke

INTRODUCTION

Approximately 20 of every 100 women in the world undergo hysterectomy operation at once in their lifetime (1). It is the second most common operation in women after caesarean section. Thus, accurate determination of the risk factors related to the female patient undergoing hysterectomy and effective management of the perioperative process will affect the lives of millions of women (2). After hysterectomy, acute and surgery-related chronic pain are the leading major problems. Although pain pathophysiology and treatment are well known today, 30-75% of the patients, who underwent hysterectomy, complain about severe pain in acute period and 20-50% about postsurgical chronic pain on the 3rd month (3, 4).

Chronic postsurgical pain is the pain that continues for three months after the surgery and not related to the out-of-surgery reasons. It has high incidence after some surgery types other than hysterectomy, such as 5-65% for thoracic surgery, 50-85% for mastectomy, 30-50%, for cardiac surgery, and 50-85% for amputation. The importance of this pain is that it seriously decreases the quality of life of the patient and causes socioeconomic problems (5).

It is known that approximately 15% of the female population in the world consumes cigarette and other 15% are exposed to tobacco smoke (6, 7). Such high smoking rates in women and the presence of intense pain after hysterectomy draw attention to the relationship between smoking and pain in the perioperative period. However, the relationship

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between pain and nicotine, which is the primary metabolite in cigarettes, is extremely complex. Despite there are studies claiming that nicotine has an antinociceptive effect that reduces acute and chronic pain in the postoperative period, there are some studies supporting the opposite (8-11). Studies that are conducted without measuring the level of cotinine, which is a biomarker of smoking in the body, have opposite results. Probably, the reasons are that the last nicotine exposure time of the patients before the surgery is not known, and the duration and amount of smoking are not equal (12).

Measurement of the amount of cotinine, which is a nicotine metabolite, in the body during the perioperative process is a more objective method than being informed with questionnaires. Today, it is known that nicotine primarily transforms into six separate metabolites in the body and is present in the urine as cotinine at a rate of 70-80% (13). Therefore, in the current study we tested the primary hypothesis that women with high preoperative urinary cotinine levels have more postsurgical chronic pain, and secondarily that high cotinine levels are associated with acute pain and more opioid consumption in the postoperative period.

METHOD

This prospective observational, double blinded study was conducted at the Hospital. The study approval was taken from the University Hospital Ethics Committee (number 181, 22/11/2017), and written consent was obtained from all the patients. The trial was registered with the Clinical Trials number NCT04274673.

We enrolled 158 American Society of Anesthesiologists Physical Status I-II women between 18 and 70 years old, who are scheduled for open abdominal hysterectomy under general anesthesia over the course of a year. The study was restricted to women undergoing open abdominal hysterectomies with a pfannenstiel approach (transverse incision through the external sheath of the recti muscles, about one inch above the pubes) who were able to operate a patient-controlled analgesia (PCA) device.

We excluded women with pre-existing chronic pain at any site requiring opioid analgesia; significant hepatic (ALT or AST >2 times normal) or renal (serum creatinine >2 mg/dl) impairment; allergy to study drugs; emergency or urgent procedures; who had a history of psychiatric diseases (major depressive disorder, bipolar disorder, schizophrenia, etc.)

Anesthesia Protocol

The patients participated in the study were premedicated with 0.15mg/kg intravenous (IV) midazolam. Routine monitoring (ECG, systolic, diastolic, mean noninvasive blood pressure, oxygen saturation) was performed after the patients were taken on the operating table. The first urine sample (10cc) was taken to evaluate the cotinine level of the patients to whom a foley catheter was attached. The cotinine level was measured via immunoassay by using the Immulite 2000 XPI Immun assay device (Siemens, US). According to these values, patients were divided into three groups, and the first group was evaluated as <10ng/dl (low cotinine), second as 10-500 ng/dl (intermediate cotinine), and third as >500ng/dl (high cotinine).

After 3 min 100% O2 administration with mask, anesthesia was induced with propofol (2mg/kg IV); intubation was facilitated by rocuronium (0.6 mg/kg IV); and anesthesia was maintained by sevoflurane in combination with nitrous oxide 50% in oxygen. Fentanyl 2µg/kg intravenously, was given 3-5 min before the surgical incision. After endotracheal intubation, lungs of the patients were mechanically ventilated to maintain end expiratory PCO2 between 34 and 36 mmHg. A Pfannenstiel technique was used in each operation, and the same surgeon conducted all the operations in the study. All patients received 0.03 mg/kg morphine IV 30 min before the skin closure. At the end of the surgery, IV 0.01 mg/kg atropine and 0.05 mg/kg neostigmine were administered to all the patients in order to remove the myorelaxant effect when respiration started.

After return of spontaneous ventilation and tracheal extubation, patients were transferred to the post anesthesia care unit (PACU). There, during postoperative 48 hours patients were connected to a patient-controlled analgesia (PCA) device programmed to provide 2 mg intravenous bolus injections of morphine at a lockout interval of 15 min with a maximum 4-hour limit of 24 mg. The PCA device was discontinued when women made no demands for morphine in the preceding 4-hour interval or at a maximum of 24 hours after surgery. 1 g acetaminophen IV was applied to the patients for 48 hours three times a day. When pain scores exceeded 5 cm on a 10-cm Visual Analog Scale, 75 mg diclofenac intramuscular IM was given as a rescue analgesic.

If the heart rate was <50 beats/minute, 0.5 mg atropine sulfate intravenous was given. When patients sustained nausea or vomiting lasting longer than 5 min, 4 mg ondansetron IV was given.

Measurements

All postoperative measurements were conducted by a researcher who was blinded to processes in the operation period. Heart rate (HR), systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation (SpO2), respiratory rate (RR), complications, antiemetic consumptions and sedation were assessed upon arrival on the PACU (0.h), 1, 4, 8, 12, 16, 20, 24, 32, 40, 48 hours thereafter. Sedation was

assessed using the Ramsey sedation scale and postoperative side effects (respiratory depression (RR<10min), headache, bradycardia (HR <50min), hypotension, and nausea-vomiting were recorded. First flatus, initial ambulation, and first oral intake of solid food were recorded.

Before operation all the patients were educated about how to decide VAS value on a 10 cm ruler: 0 cm was designated as no pain, and 10 cm as the worst imaginable pain. Postoperative pain was separately assessed with patients resting in bed and while sitting. Pain, opioid use in each measurement time, cumulative morphine consumption, PCA demand/supply, and rescue analgesic were recorded in the same measurement times specified above. At the end of the postoperative 48th hour, pain management was assessed as 1=unsatisfied, 2=slightly satisfied, 3=mostly satisfied, 4=completely satisfied. Furthermore, Hospital Anxiety and Depression Surveys were evaluated before discharge from the hospital. The Hospital Anxiety and Depression Scale (HADS) was constructed to allow a rapid and separate measure of depression and generalized anxiety in hospital. This scale has 14 questions, seven of them related to depression and the rest to anxiety. Six questions are coded from 0 to 3, and conversely eight questions are coded from 3 to 0.

An investigator blinded to group assignment evaluated all of the patients three months after the discharge day. Chronic postsurgical pain was evaluated as acute postoperative pain with VAS score at rest. Allodynia test was applied to all the patients and they were asked to provide the appropriate value in the form of VAS. In addition, the patients were asked to what extent their pain limits their daily activities according to VAS. Three months after discharge day, patients completed Douleur Neuropathique en 4 (DN4), Sleep Interference questionnaires, and SF-12 Health survey were assessed. SF-12 consists of two components (physical and mental) and assess the perceived health-related quality of life of the patient. Sleep Interference scores range from 0 (no interference) to 10 (complete interference). DN4 score ≥ 4 indicate that the pain is likely to be neuropathic in origin. Short brief pain inventory was assessed for the severity of the chronic pain and its impact on the functioning of the patient.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Mac version 21 (SPSS Inc. Chicago, IL, USA) software program was used to assess the study data. Homogeneity of data was conducted according to the Levene's test and data were evaluated as homogeneous if p is >0.05. The Shapiro-Wilk normality test was used to evaluate whether the data comply with normality distribution. If p> 0.05, data complied with the normal distribution, and if p<0.05, data did not comply with normal distribution. The data conforming to normal distribution were compared with the One-Way ANOVA test and the results were given as mean ± SD. The Kruskal Wallis test was used to compare the data that did not conform to normal distribution, and the results were given as median±min-max (minimum-maximum). Nominal variables were examined by using the Chi-Square test of Pearson or Chi-Square test of Fisher. For all the tests, p value less than 0.05 at the confidence interval of 95% was considered as statistically significant.

RESULTS

In the study, 158 consenting patients, who fulfilled the entry criteria, were included. The patients were divided into three groups according to the level of urine cotinine taken after induction. Cotinine level of 96 patients was found as <10 ng/dl (Low Cotinine), of 38 patients as between 11 and 500 ng/dl (Intermediate Cotinine), and of 24 patients as >500 ng/dl (High Cotinine).

The three groups were comparable with respect to ASA physical status, age, body weight, and duration of surgery (Table 1).

Table 1. Demographics and baseline characteristics (n=158)

	Low Cotinine	Intermediate Cotinine	High Cotinine	p
	(n=96)	(n=38)	(n=24)	
ASA physical status I II	 29(30.2) 67(69.8)	 8(21.1) 30(78.9)	 5(20.8) 19(79.2)	>0.05
Age (year)	49.0(28-68)	47.5(37-72)	48.5(41-68)	>0.05
Weight (kg)	72.0(50-110)	71.0(52-105)	72.0(58-105)	>0.05
Duration of surgery	85.0(55-180)	85.0(50-140)	80.0(60-150)	>0.05

Kruskal Wallis Test was used and represented as percentage and median (min-max).

During the initial 48 hours after the surgery, systolic, diastolic, mean blood pressure, and Ramsey sedation scale values were found to be similar between three groups. During the same time period in all the measurement times, oxygen saturation values were higher in Low Cotinine and Intermediate Cotinine group than the High Cotinine group. Heart rate was found higher in the patients in High Cotinine group when compared to the patients in other groups.

At all the measurement times, oxygen saturations of the High Cotinine group were higher than the other groups. Moreover, except the measurement at the 8th hour, all the other oxygen saturation measurements in the postoperative 48th hour in Low Cotinine group were higher than

Intermediate Cotinine group. Except 32nd hour and 40th hour, respiratory rate values were higher in High Cotinine group in all the measurement times when compared with the Low Cotinine group and Intermediate Cotinine group.

Except the 1st hour, VAS scores while laying were higher in High Cotinine group than Low Cotinine group ($p<0.005$) in all the measurement times during postoperative 48 hours. Similar to these results, VAS scores on the 8th, 20th, 24th, 32nd, 40th, and 48th hours in High Cotinine group were higher than Intermediate Cotinine group (Figure 1).

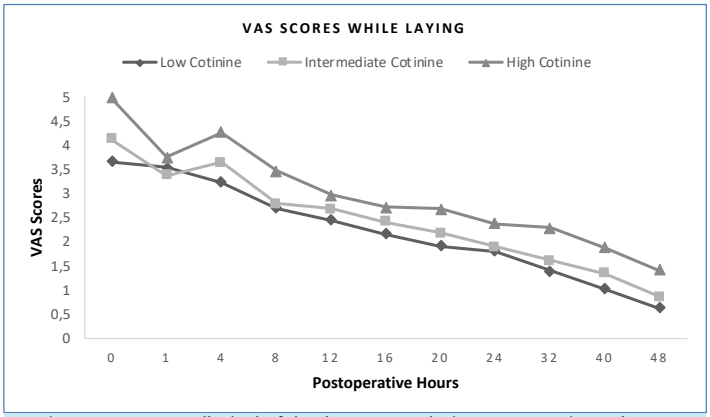

Figure 1. VAS scores (laying) of the three groups during postoperative 48 hours.

Except the 1st hour, VAS scores while sitting during postoperative 48 hours were higher in all the measurements in High Cotinine group than Low Cotinine group. Similarly, VAS scores while sitting at 8th, 32nd, and 40th hours were higher in High Cotinine group than Low Cotinine group. VAS scores while sitting at the 4th and 12th hours were higher in Intermediate Cotinine group than the Low Cotinine group (Figure 2).

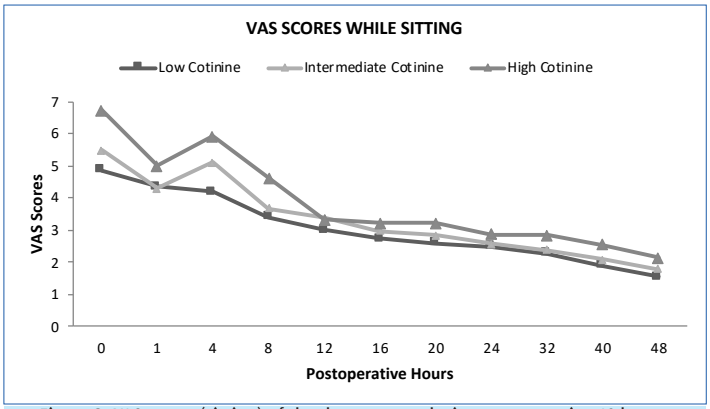

Figure 2. VAS scores (sitting) of the three groups during postoperative 48 hours.

PCA demand/delivery amounts of the patients in the High Cotinine group during postoperative 48 hours were higher than the patients in the Low Cotinine group and Intermediate Cotinine group in all the measurement times except the 0th hour.

Except for the first measurement time in the first 48 postoperative hours, the morphine consumption of the High Cotinine group was higher than the other groups. Only at the 4th hour measurement, the morphine consumption of the Intermediate Cotinine group was higher than the Low Cotinine group (Figure 3).

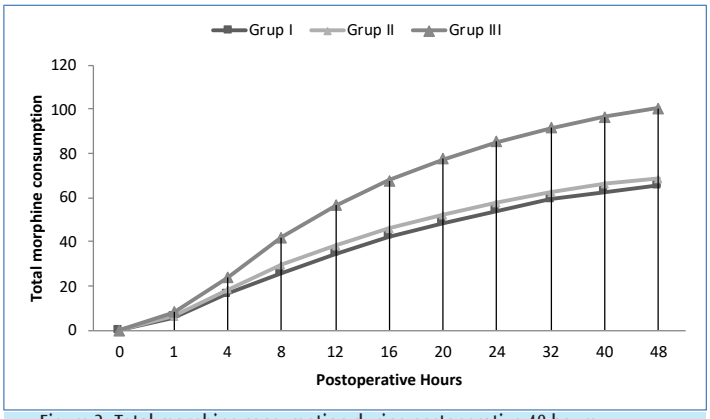

Figure 3. Total morphine consumption during postoperative 48 hours.

On the postoperative 0th, 4th, and 8th hours, additional analgesic consumption of High Cotinine was higher than other groups. In the same measurement times, additional analgesic consumption of the Intermediate Cotinine group was higher than Low Cotinine group.

During postoperative 48 hours, High Cotinine group PCA demand values were higher than other groups in all the measurements excluding the 0th hour. Intermediate Cotinine group PCA demand values were higher than the Low Cotinine group excluding the first two measurements. Similarly, PCA delivery values were similar excluding the last three measurement times.

The most common side effect during the postoperative period was postoperative nausea-vomiting. The rates decreased in time and were found as 61% on the 0th hour, 50% on the 1st hour, 32% on the 4th hour, 17% on the 8th hour, 6% on the 12th hour, 4% on the 16th hour, 1% on the 20th hour, and 0.6% on the 24th hour. In addition, bradycardia was observed for five times in three patients, and hypotension was observed in two different measurements in one patient.

The first flatus time of the patients in the High Cotinine group was longer than the patients in the other group. In addition, the first flatus time of the Intermediate Cotinine group was longer than the Low Cotinine group. First ambulation time were longest in the High Cotinine group. First oral intake time of all the three groups were similar.

Hospital anxiety and depression scores of the patients in the High Cotinine group and Intermediate Cotinine group were higher than the Low Cotinine group. The patients in the High Cotinine group and Intermediate Cotinine group had higher 3-month allodynia and VAS values that limit daily activity

when compared to the patients in the Low Cotinine group ($p<0.05$). SF-12 evaluation is divided into two as physical (SF12-PCS) and mental (SF12-MCS). Only SF12-PCS value of the High Cotinine group was lower than the other groups. However, there was no difference between the SF12-MCS values of all the three groups. Examination findings of 10% of the patients in the Low Cotinine group, 23% in the Intermediate Cotinine group, and 37% in the High Cotinine group were found to be positive in terms of allodynia. Allodynia VAS values of the High Cotinine group were higher than the Low Cotinine group. When the patients were evaluated in terms of pain that limit their daily activities, the rates were 10% in the Low Cotinine group, 23% in the Intermediate Cotinine group, and 33% in the High Cotinine group. VAS values limiting the daily activities of the High Cotinine group was higher than the Low Cotinine group (Table 2).

Table 2. Summary of the other parameters during hospital stay and at the third month.

Parameters				p		
	Low Cotinine	Intermediate Cotinine	High Cotinine	I-II	I-III	II-III
	(n=96)	(n=38)	(n=24)			
First flatus	21.0 (16-30)	23.0 (16-28)	25.5 (20-30)	0.009	<0.001	0.003
First Ambulation	7.0 (6-9)	7.0 (6-10)	7.5 (6-15)	0.075	<0.001	0.042
First oral intake	7.0 (6-17)	7.0 (6-9)	7.0 (6-8.5)	0.446	0.636	0.853
HADS (Anxiety)	4.0 (1-13)	6.0 (2-15)	8.0 (2-17)	<0.001	<0.001	0.065
HADS (Depression)	4.0 (1-14)	5.0 (1-18)	6.0 (2-12)	0.015	0.001	0.272
Allodynia (VAS)	0.0 (0-3)	0.0 (0-3)	0.0 (0-3)	0.037	0.001	0.253
Daily activity (VAS)	0.0 (0-4)	0.0 (0-4)	0.0 (0-4)	0.034	0.002	0.376
SF-12 PCS	60.16687 (22.86056-66.34308)	58.24415 (25.56015-64.63784)	48.56010 (22.25612-61.88461)	0.056	<0.001	0.009
SF-12 MCS	45.63875 (25.93175-54.96308)	45.71335 (35.37748-57.93845)	44.69428 (33.72698-50.88624)	0.735	0.223	0.133

Kruskal Wallis Test was used and represented as median (min-max)

Low Cotinine group was the completely satisfied patient group with pain management during the postoperative period (27%, 7%, 0%, respectively). None of the patients described this situation as unsatisfied (Table 3).

Table 3. Patient satisfaction with pain treatment

Patient satisfaction with pain treatment	Low Cotinine		Intermediate Cotinine		High Cotinine		p1	p2	p3
	%	(n)	%	(n)	%	(n)			
Slightly satisfied	3.1	(3)	13.2	(5)	50	(12)	p >0,05	0.001	0.001
Mostly satisfied	69.8	(67)	78.9	(30)	50	(12)	p >0,05		
Completely satisfied	27.1	(26)	7.9	(3)	0	(0,0)	0.001	0.001	p >0,05

Chi Square test was used and presented as percentage. p1: group I, II, p2: group I, III, p3: group II, III

In the sleep interference tests performed to understand the pain-induced sleep patterns of the patients, the highest values belonged to the High Cotinine group. There was no difference between the groups in terms of the DN4 test. No difference was found between the three groups to which brief pain inventory test was applied.

DISCUSSION

In the current study, there was a clear relevance between high urine cotinine level and postsurgical chronic pain in the patients undergoing open abdominal hysterectomy. Posturgical chronic pain scores were found to be higher on the third month in the patients with high cotinine levels due to smoking or tobacco smoke exposure than those with lower cotinine levels. In addition, situations related to life quality like pain-related sleep disturbances and limitation in the daily activities were more common in the patients with high cotinine levels. The results of the current study are broadly consistent with the previous studies in the literature (10, 14).

In a study evaluating the relation between smoking and postoperative third month pain, it was pointed out that the pain scores were higher in the active smokers than non-smokers and patients who quitted smoking. In the present study, sample size (n=239) was high, however, the included operation groups were different. It is well known that the incidence of postsurgical chronic pain is varied according to the type of surgery. Unlike this study, we included only the patients underwent open abdominal hysterectomy (10). In a multi-center study conducted on the patients who underwent operation, it was observed that non-smoking patients had less back and leg pain when they were evaluated one year later (11). Although direct cotinine levels were not determined in these studies, long-term results were generally consistent with the results of the present study. In case cotinine levels were determined in the patients, who were active smokers or exposed to tobacco smoke and included in these studies, it would naturally be high. A study with a large sample size (4429) was arranged in a cross-sectional design in which the participants, who did not have to undergo operation, were included. Patients with high plasma cotinine levels in the third month (cotinine level>10ng/ mg) had higher chronic pain levels when compared to the group with lower values (the unadjusted odds ratio 1.65 vs 1.04) (14).

The relationship between pain and smoking is quite complex. The first study evaluating the effect of nicotine on pain stated that nicotine reduces pain by releasing endogenous opioids. Also, it showed that smoking increased the β-endorphine level. In addition, nicotine activates the nicotinic acetylcholine receptors (nAChRs) that are present in the central nervous system, autonomic ganglions, neuromuscular junction and in various tissues. Especially, it antagonizes the α4β2 sub-type of these receptor groups and causes antinociceptive effect. Due to prolonged nicotine exposure, cholinergic and opioid systems are also affected. Continuous nicotine exposure is known to cause tolerance and reduce pain inhibition by causing changes in the endogenous opioid system (15).

Acute pain related to a previous surgery has great importantance in the development of chronic or persistent pain. It is known that the process of acute pain occurs at both molecular and cellular levels. Prolongation of neurogenic inflammation, peripheral and central sensitization affect the transmission and processing of pain. As a result, the sensitization process of pain changes. In case inflammation is not treated, inflammatory and algogenic mediators, which are persistent in the environment, cause permanent changes in the nociceptors by causing sensitization (16, 17). Due to all these reasons, effective management of acute postoperative pain is quite important in the development of chronic pain.

In a study related to the effects of smoking on postoperative analgesia and pain were investigated in 80 patients who underwent lower extremity surgery. The patients were divided into two groups as people smoking at least 20 cigarettes a day and people who never smoked. Postoperative 24-hour VAS scores and analgesic consumption were found to be higher in the smoking group. Although no difference was observed in the mean arterial pressure values in the group with high scores, peak heart rate values were found to be high, as in the present study (18). In the patients who underwent hepatectomy, in which both urine and plasma cotinine values were examined, analgesic consumption and pain scores were higher in the smoking patients (19). In the present study, high VAS scores and morphine PCA consumption were found in the patients with high urinary cotinine values in the acute postoperative period.

Anxiety and depression symptoms tend to be more common and severe in smokers (20). Similarly, anxiety and depression tendency of smokers is higher (21). Also, according to the fear avoidance model, fear and anxiety accompanying pain also facilitates the continuation and chronicity of pain (22). As expected, in the current study, anxiety and depression scale results were found to be higher in the patients with high cotinine levels.

The relationship between pain, smoking, and the quality of life was investigated in the patients with chronic pain complaints. The mood, enjoying work/life, and quality of sleep were lower in the smokers when compared to the non-smokers (23). Many studies supporting this situation also specify that smoking decreases the quality of sleep (24, 25). Several studies also state that smokers tend to delay falling asleep, prolonged sleep, daytime sleepiness, and depression when compared to the non-smokers (25). Similarly, in the

current study, patients with high cotinine levels had higher postsurgical chronic pain and lower quality of sleep. The results of the studies investigating the effects of smoking on the quality of life were similar to the results of the present study (26-29).

It was shown that smoking decreases the quality of life and as the number of smoking increases, this situation becomes more significant (26). In the present study, similar negative results in the patients with the increasing rate of urine cotinine were determined.

A methodological strength of the current study is measuring the level of urine cotinine of each patient. The reason is that cotinine, which is the main metabolite of nicotine, is a biomarker that clearly reveals smoking or tobacco smoke exposure. The determination of the amount of this in serum, urine, and saliva is a much more objective method than the questionnaires that are conducted by asking the patients and it saves us from the problems that may occur due to social desirability bias. Cotinine reacts with cytochrome p450 in the body and nicotine iminium ion is formed. It is converted into cotinine via aldehyde oxidase. Cotinine is partially secreted from the kidneys. There are various methods to determine the cotinine level (blood, urine, saliva etc.) (30, 31).

Cotinine is practically easily obtainable, rather than its pharmacokinetic properties recommended for the body fluid to be worked (32). In the present study, the amount of cotinine taken from the urine immediately after the first foley catheter inserted before surgery was studied. Also, the half life of cotinine is similar in different body fluids. Cotinin starts to decrease in the body on the fourth day and disappears at least on the seventh day (33).

Limitations of the study

The study has limitations. Only the female patients who underwent hysterectomy surgery were included in the current study. Women perceive pain more densely and thus, they tend to consume more analgesics (34). In case patients of both genders were included in the study, pain scores and associated opioid consumption of male patients would have been lower. Smoking is a type of addiction and smokers also tend to use opioids due to addiction, apart from pain (35). The same postoperative opioid consumption would have been less in a group of non-smoking patients or the patients exposed to tobacco smoke. Urine cut-off values of cotinine has distinctions in the literature (36). The general opinion is that patients having 500ng/dl cotinine values are regular smokers and having 10ng/dl are not exposed to tobacco smoke too much. In the study, the patients were categorized as <10ng/dl (non-smoking), 10-500 ng/dl (irregularly smoking or exposed to smoking), or <500ng/dl (continuously smoking). In the studies, differences in the cotinine levels depending on races are shown. In this regard, different results can be obtained when the study is conducted at different geographical regions and on different races (37, 38).

CONCLUSION

In the present study, it was found that tobacco smoke exposure increased pain and consequently, the analgesic consumption in acute and chronic periods, depending on the high cotinine level. In addition, it should not be neglected that the quality of life of the patients exposed to tobacco smoke in the chronic period is deteriorated due to pain.

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 22/11/2017 and number 181, and Helsinki Declaration rules were followed to conduct this study.

Thesis

This study was prepared by rearrangement of the specialty thesis by Sümeyra Gökdemir in 2019 entitled as “To investigate the effect of urinary cotinine level on postoperative acute and chronic pain in patients undergoing open abdominal hysterectomy”.

Authorship Contributions

Concept: OK, SG, ST, Design: OK, SG, SH, Supervising: OK, SG, SU, OÖ, SH, Financing and equipment: OK, SG, SH, ST, OÖ, Data collection and entry: OK, SG, SU, Analysis and interpretation: OK, SG, SU, Literature search: OK, SG, SU, ST Writing: OK, SG, SU, Critical review: OK, SG, SU, ST, SH, OÖ

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ORIGINAL RESEARCH

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Curcumin synergistically augments the chemotherapeutic activity of doxorubicin in prostate cancer cells

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Abstract

Objective: Prostate cancer is one of the most commonly diagnosed cancer types in men and many people die every year due to recurring or acquiring aggressive forms of prostate cancer. Numerous chemotherapeutics, such as paclitaxel and doxorubicin are commonly used in the treatment of prostate cancer. However, acquired resistance to chemotherapeutics and broad systemic side effects substantially limit their usage. Curcumin is one of the most examined phytochemicals of the herbal remedy turmeric. Herein, we aimed to investigate the synergistic capability of curcumin on doxorubicin in prostate cancer cells.

Method: The human adenocarcinoma cell line LNCaP was used in cell culture studies. Cell viability was examined by WST-1 assay. The protein expression levels of Beclin1, p62/SQSTM1, LC3-I/II, Hrd1, gp78, polyubiquitin, PERK, eIF2a, phospho-(Ser51) eIF2a, IRE1a, XBP-1s, PARP-1, caspase-3, AR, PSA, c-Myc, E-cadherin, N-cadherin and VEGF-A were investigated by immunoblotting assay.

Results: Our data indicated that co-administration of curcumin with doxorubicin significantly improved the cytotoxic effect of doxorubicin in LNCaP cells. Also, the combination of curcumin and doxorubicin reduced the autophagic flux and remarkably induced endoplasmic reticulum-associated-degradation (ERAD) and unfolded protein response (UPR) signaling. Also, activation of apoptotic proteins PARP-1 and caspase-3 were strongly enhanced by combined treatment in a dose-dependent manner. Moreover, combined treatment markedly decreased levels of AR, PSA, c-Myc and VEGF-A proteins. Additionally, the epithelial-mesenchymal transition (EMT) was reduced by decreasing N-cadherin and increasing E-cadherin protein levels.

Conclusion: Present data strongly suggest that curcumin synergistically improves the anti-cancer features of doxorubicin in prostate cancer cells. This study will be an important guide for testing the effects of the combined treatment of curcumin and doxorubicin in xenograft animal models with prostate tumors.

Keywords: Autophagy, Curcumin, Doxorubicin, ER-associated degradation, Prostate cancer, Unfolded Protein Response

INTRODUCTION

Cancer is one of the most important health problems and many people die every year due to prostate cancer, which is one of the most diagnosed cancer types in men (1). Family history, age, ethnicity and metabolic disorders like obesity are significant risk factors for prostate cancer. Despite surgery, radiation therapy, cryotherapy, chemotherapy and hormonal therapy being the main treatment options for prostate cancer androgen deprivation therapy is one of the most commonly used treatment approaches against aggressive prostate cancer because of the overactivation of androgen receptor signaling (2-4). Moreover, numerous chemotherapeutics, such as docetaxel, paclitaxel and doxorubicin (DOXO) are commonly used in the treatment of prostate cancer either alone or in combination. However, acquired resistance to chemotherapeutics and also their broad spectrum of systemic side effects substantially limit their therapeutic usage. Accumulated evidence has shown that combined therapies may improve the therapeutic benefits of chemotherapeutics by reducing drug resistance and minimizing side effects compared to monotherapy (5).

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Numerous bioactive phytochemicals purified from natural products are widely used as therapeutic and chemo-preventive agents for chronic diseases and various types of cancers. These agents are potentially able to suppress carcinogenesis (6,7). Curcumin (CRC) is one of the most examined phytochemicals of the herbal remedy turmeric (*Curcuma longa)*. It has a variety of biochemical activities, including antiseptic, anti-viral anti-inflammatory, antioxidant and antitumor properties (8). Moreover, there are many clinical trials associated with the therapeutic utilization of CRC, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, psoriasis, Alzheimer's disease, colon cancer and prostate cancer as well (9). The anticancer effects of CRC on androgen-sensitive prostate cancer cell lines have been shown in several studies. It has been reported that CRC dose-dependently suppressed cell growth, survival and proliferation and induced autophagy in LNCaP cells (10,11). Additionally, there are many studies investigating the synergistic effect of combining CRC with many traditional chemotherapeutics and agents in numerous cancers (12). Herein, we efforted the mechanistically investigate the mode of action of the possible booster effect of CRC on DOXO in prostate cancer.

DOXO, an anthracycline antibiotic, is extensively used in the treatment protocols of numerous cancers, including breast cancer, leukemia, soft tissue sarcoma and prostate cancer. It prevents the growth of cancer cells by inhibiting nucleic acid synthesis and blocking topoisomerase II enzyme activity (13). While it is highly effective on cancer cells, it targets not only cancer cells but also many other organs like the heart, brain, liver and kidney as well. Therefore, their usage is limited due to their potential cytotoxic effects and the possibility of developing acquired drug resistance. Combined applications of phytochemicals with chemotherapeutic agents offer an excellent alternative option for minimizing the dose ranges used and reducing the systemic cytotoxic effects (14). In 2016, Klippstein et al. reported that the combined treatment of CRC and DOXO has a synergistic effect on metastatic androgen-independent prostate cancer cells through the induction of apoptotic cell death (15). However, detailed studies on the molecular modeling of coadministration of DOXO and CRC on prostate cancer cells were not included in this report.

Herein, we aimed to investigate the possible synergistic effect of CRC on DOXO in non-metastatic prostate cancer cells using a human androgen-sensitive prostate adenocarcinoma cell line LNCaP, which is well-mimic prostate cancer *in vitro*. Firstly, we tested the effect of co-treatment of CRC and DOXO on the viability of LNCaP cells. To understand the molecular mechanism of action of co-administration, we examined its effects on autophagy and endoplasmic reticulum (ER)-associated degradation (ERAD), two primary protein quality control mechanisms in mammalian cells, on the unfolded protein response (UPR) signal, which is involved in the regulation of ER capacity and coordination of ER stress responses, by immunoblotting. Additionally, we examined the cell-death-associated proteins caspase-3 and Poly [ADP-ribose] polymerase 1 (PARP-1), proto-oncogene protein c-Myc, angiogenic factor vascular endothelial factor A (VEGF-A), E-cadherin and N-cadherin which are epithelial-mesenchymal transition markers (EMT) and also prostate tumorigenesis associated proteins, androgen receptor (AR) and prostate-specific antigen (PSA). Present data suggest that co-administration of CRC with DOXO strongly enhanced the anticancer properties of DOXO in prostate cancer cells. The combination of chemotherapeutic agents with CRC could be a promising and powerful strategy to treat prostate cancer.

METHOD

Materials

Fetal bovine serum (FBS), tissue culture media and other cell culture supplements were obtained from Capricorn Scientific (Ebsdorfergrund, Germany). Cell culture plastic materials were obtained from Sarsdeth. Monoclonal rabbit anti-Hrd1 (#14773)(1:3000) and polyclonal rabbit anti-eIF2α (#9722)(1:2500), anti-phospho-eIF2α (Ser51) (#9721) (1:2500), anti-p62/SQSTM1 (#5114)(1:2000), anti-Beclin-1 (#3495)(1:1500), anti-LC3-I/II (#12741)(1:3000) (#2895) and anti-caspase-3 (#9692)(1:1000) were purchased from Cell Signaling Technology (Beverly, MA, USA). Polyclonal rabbit anti-PARP-1 (13371-1-AP)(1:2000), anti-gp78 (16675-1-AP) (1:3000), anti-XBP-1s (#24868-1-AP)(1:2000), anti-ubiquitin (#10201-2-AP)(1:1000), PERK (#24390-1-AP)(1:3500), anti-IRE1α (#27528-1-AP)(1:3000), anti-E-cadherin (20874-1-AP), anti-N-cadherin (22018-1-AP), anti-AR (22089-1-AP)(1:2500), anti-c-Myc (10828-1-AP) and mouse monoclonal anti-PSA (60338-1-Ig) were obtained from Proteintech (Wuhan, China). Polyclonal rabbit anti-VEGF-A (E-AB-53277) was purchased from Elabscience. Mouse monoclonal anti-beta-actin antibody (#A5316)(1:10000) was obtained from Sigma Aldrich. HRP-conjugated goat anti-mouse (#31430)(1:5000) or goat anti-rabbit (#31460)(1:5000) IgG (H+L) was purchased from Pierce (Thermo Fisher Scientific, DE). Curcumin was provided from Sigma-Aldrich (USA) (#C1386)

Cell culture

Human androgen-sensitive prostate adenocarcinoma cell line, LNCaP (CRL-1740TM) was obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute 1640 (RPMI 1640) (Capricorn Scientific, Ebsdorfergrund, Germany) media enriched with 10% FBS, 5 mg ml−1 penicillin/streptomycin and 2 mM L-glutamine (Capricorn Scientific, Ebsdorfergrund, Germany) and were kept in a humidified atmosphere of 5% CO2 and 95% air at a constant temperature of 37 °C. All

compounds were prepared in 1000-fold (1000X) concentration and applied to the cells.

Cell viability assay

Cells were seeded into a 96-well plate (7500 cells/well) and 24 hours later treated with agents for 48 hours. Following the WST-1 assay (Takara Bio Inc., Kusatsu, Shiga, Japan) was performed according to the manufacturer's instructions. The absorbance was determined at 450nm with 600nm set as the reference wavelength by microplate spectrophotometer (BioTek, Epoch 2, USA). Cell viability rates were presented in the graph as a % fold change. IC50 was calculated by GraphPad Prism 7 software (GraphPad Software, La Jolla CA, USA, www.graphpad.com).

Protein isolation and immunoblotting

Cells were lysed within RIPA buffer and then centrifugated at 14.000 rpm for 20 min at 4°C. The supernatant was collected and total protein ingredients were defined by bicinchoninic acid (BCA) protein assay (Thermo Fisher Scientific, DE). 20-30 µg protein was used in immunoblotting studies. Samples were denatured in 4x Laemmli buffer (Bio-Rad Laboratories, Hercules, California, USA) at 70°C for 15 min and proteins were electrophoretically separated on hand-cast polyacrylamide gels and transferred to Immobilon®-P polyvinylidene difluoride (PVDF) membrane (Bio-Rad Laboratories, Hercules, California, USA). The membrane was blocked with 5% nonfat dry milk in Phosphate-buffered saline (PBS) containing 0.1% Tween (PBS–Tween) for 1 h at room temperature and then incubated with primary antibody and secondary antibodies, respectively. Target proteins were visualized by clarity enhanced chemiluminescence western blotting substrate (Bio-Rad Laboratories, Hercules, California, USA) in ChemiDoc XRS+ (Bio-Rad Laboratories, Hercules, California, USA). Densitometric analysis of protein bands was carried out by ImageJ software (National Institutes of Health, USA).

Statistical analysis

Data were presented as means ± standard deviation. The statistical significance of differences between groups was determined by a two-tailed equal variance Student's t-test or One-way ANOVA with a minimum of 95% confidence interval by GraphPad Prism 7. The significant level was set at 5% ($p<0.05$) for all tests.

RESULTS

Curcumin enhances the anti-cancer activity of doxorubicin on LNCaP cells

Firstly, we evaluated the effect of DOXO and CRC on cell viability of LNCaP cells carried out the WST-1 based cell viability assay. LNCaP cells were treated with 1, 2.5, 5, 7.5, 10, 12.5 and 15mM DOXO or 2.5, 5, 10, 25, 50, 100, 250, 500, 1000 and 2000nM CRC for 48 hours. Our results revealed that DOXO and CRC treatment significantly decreased the cell viability of LNCaP cells in a dose-dependent manner (Figure 1a, b). We calculated IC50 values for DOXO and CRC, 10.652mM and 0.369nM, respectively. According to these findings, we decided to study with doses of 5, 10 and 20nM of CRC, where 10mM DOXO and CRC had low effects on the viability of LNCaP cells.

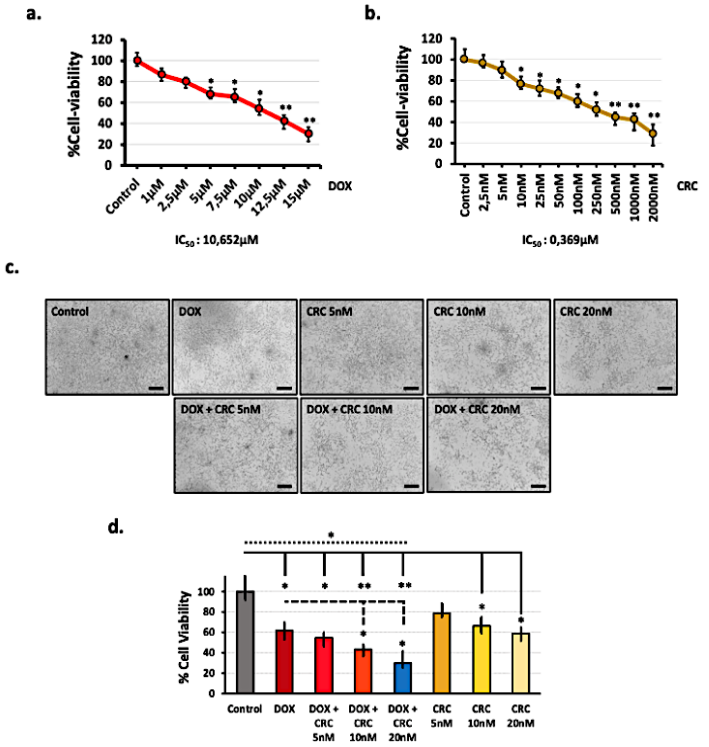

Figure 1. The testing of the effect of curcumin and doxorubicin on cell viability LNCaP cells were treated with (a) 1, 2.5, 5, 7.5, 10, 12.5 and 15mM DOXO or (b) 2.5, 5, 10, 25, 50, 100, 250, 500, 1000 and 2000nM CRC for 48 hours and then cell viability examined by WST-1 assay. IC50 values were calculated by GraphPad Prism 7 software. (c) Cells were treated with vehicle or 10µM DOXO, 5, 10 and 20nM CRC or their combination for 48 hours. The following cells were photographed by an inverted microscope. 4x Scale bar: 5 µm, 20x Scale bar: 10 µm. (d) Cell viability was analyzed by WST-1 assay. Three independent biological and three technical repeats per experiment were used. Statistical significance among the groups was analyzed by Student's t-test or one-way ANOVA and Tukey's tests. (*$p<0.05$, **$p<0.001$).

To examine the improvement effect of CRC on DOXO-induced cell death, LNCaP cells were treated with 10mM DOXO, 5, 10 and 20nM CRC and the combined administration of CRC and DOXO as indicated doses for 48 hours. Microscopic examination results indicated that alone DOXO and CRC decreased the viability of LNCaP cells compared to the control group. Moreover, we observed that the co-administration of CRC and DOXO more efficiently reduced the viability of LNCaP cells in a dose-dependent manner (Figure 1c). Next, to quantify the %cell viability, we carried out the WST -1-based cell viability assay. Our data indicated that 10mM DOXO reduced the viability of LNCaP cells by 60%. Also, 5, 10 and

20nM CRC treatment decreased the cell viability by 22, 35 and 40%, respectively. Co-administration of 10mM DOXO and 5, 10 and 20nM CRC more strongly reduced the % cell viability by 62, 46 and 35%, respectively (Figure 1d).

Co-administration of curcumin with doxorubicin diminishes the autophagic flux in LNCaP cells

CRC and chemotherapeutic drugs are known to have potent effects on autophagic flow. Therefore, we evaluated the effects of co-administration on autophagy. Firstly, we evaluated the morphological alterations of LNCaP cells depending on the CRC, DOXO or co-administration of CRC and DOXO by microscopic examination. We observed that DOXO treatment generated the vacuole-like cellular formation on LNCaP cells. CRC also induced the vacuole-like structures in a dose-dependent manner (Figure 2a). Co-administration more strongly increased the vacuole formation and caused the shrinking cell form. Also, it formed the gathering around the nucleus in the cells (Figure 2a).

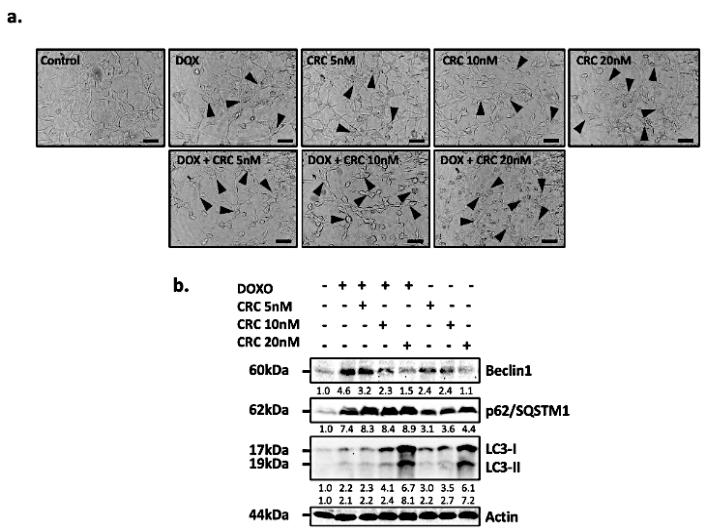

Figure 2. Evaluation of the effect of curcumin and doxorubicin on autophagy proteins in LNCaP cells. Cells were treated with vehicle or 10μM DOXO, 5, 10 and 20nM CRC or their combination for 24 hours. (a) Cells were photographed by an inverted microscope. Vacuolar structures are indicated by arrows. Scale bar: 25 μm. (b) The expression level of Beclin1, p62/SQSTM1 and LC3-I/II levels were analyzed by immunoblotting. Beta-actin was used as a loading control

We examined the impacts of the co-administration of CRC and DOXO on autophagy. To this aim, we treated the cells with 10μM DOXO, 5, 10 and 20nM CRC or their combinations for 24 hours and then the levels of critical autophagy proteins, including Beclin1, p62/sequestosome-1 (SQSTM1) and microtubule-associated protein 1A/1B-light chain 3 (LC3-I/II) were analyzed by immunoblotting studies. Our data showed that DOXO treatment increased the Beclin1, p62/SQSTM1 and LC3-I/II levels compared to the control group. Alone CRC application also elevated the levels of the p62/SQSTM1 and LC3-I/II, whereas Beclin1 was downregulated in a dose-dependent manner (Figure 2b). Combined treatment of CRC with DOXO remarkably increased the p62/SQSTM1 and LC3-I/II levels in a dose-dependent manner. Also, Beclin1 levels were decreased by co-treatment (Figure 2b).

Combined treatment of curcumin with doxorubicin induced the ERAD and UPR signaling in LNCaP cells

To test the possible booster effect of co-administration of CRC with DOXO on ERAD and UPR signaling, we evaluated the state of polyubiquitination, hydroxymethyl glutaryl-coenzyme A reductase degradation protein 1 (Hrd1) and glycoprotein 78 (gp78) which are ERAD E3 ligase enzymes and Inositol-requiring enzyme 1α (IRE1a) and Protein Kinase RNA-like ER Kinase (PERK) branches of UPR proteins, including eukaryotic initiation factor 2α (eIF2a), phosphorylated at serine 51 position eIF2a, PERK, X-box Binding Protein-1 (XBP-1s) and IRE1a by immunoblotting. Our results indicated that DOXO treatment increased the polyubiquitination levels whereas gp78 and Hrd1 levels did not affect compared to the control (Figure 3). CRC treatment markedly elevated the polyubiquitination levels at 10 and 20nM doses. 5nM CRC administration did not affect the polyubiquitination. Similar to these results, Hrd1 and gp78 levels were increased by 10 and 20nM CRC in a dose-dependent manner. However, 5nM CRC treatment did not affect the Hrd1 and gp78 levels and also similar results were obtained by 10mM DOXO administration (Figure 3). Co-administration of CRC with DOXO more strongly increased the steady-state level of polyubiquitination compared to alone CRC and DOXO treatment in a dose-dependent manner. Moreover, Hrd1 and gp78 levels were remarkably increased by the combined treatment of CRC and DOXO (Figure 3).

Additionally, we evaluated the effects of co-treatment of CRC with DOXO on PERK and IRE1a branches of UPR signaling. Alone CRC or DOXO treatment increased the PERK and phosphorylated eIF2a levels whereas total eIF2a levels were not affected compared to the control group. Co-administration more strongly increased the phosphorylated eIF2a and PERK levels and also total eIF2a levels were decreased in a dose-dependent manner (Figure 3b). IRE1a level was not affected by DOXO whereas the level of downstream effector protein of IRE1a, XBP-1s was increased. CRC treatment gradually increased the IRE1a and XBP-1s levels in a dose-dependent manner (Figure 3b). Co-administration of CRC with DOXO more strongly increased the PERK, phosphorylated eIF2a, IRE1a and XBP-1s levels (Figure 3b). Overall, these results indicated that co-administration of CRC with DOXO more efficiently induced the IRE1a and PERK branches of UPR signaling in LNCaP cells.

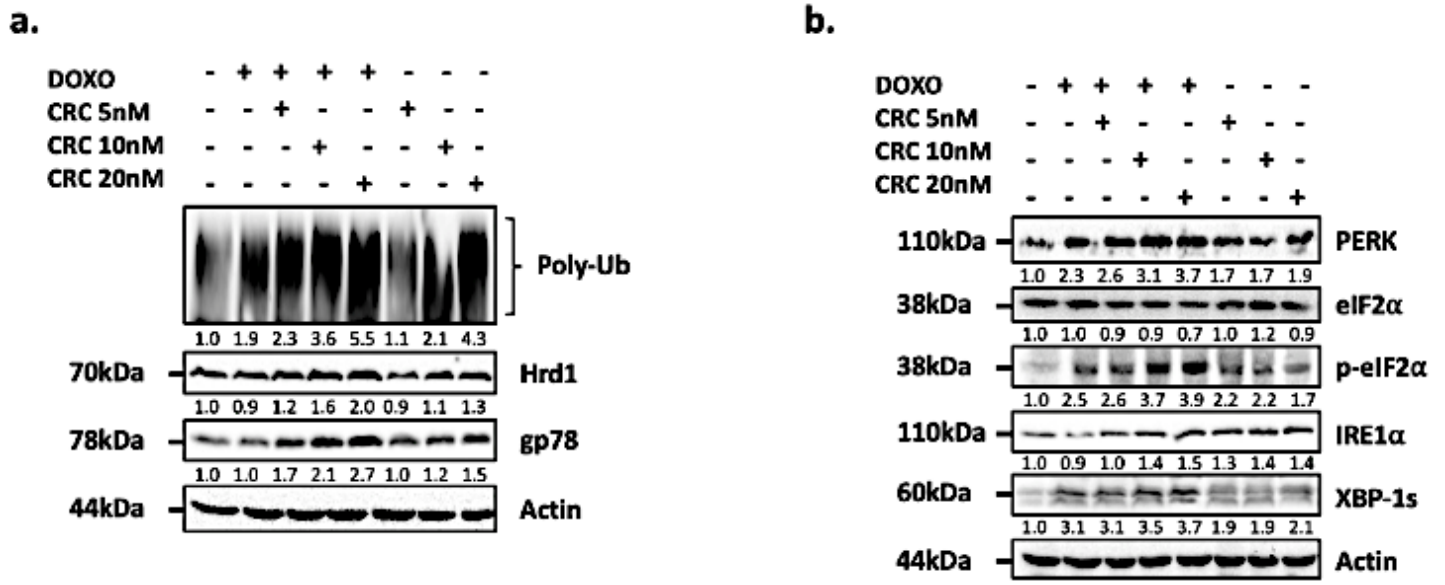

Figure 3. Assessment of the effect of curcumin and doxorubicin on ERAD and UPR proteins in LNCaP cells . Cells were treated with vehicle or 10μM DOXO, 5, 10 and 20nM CRC or their combination for 24 hours. The expression level of (a) ERAD components, including poly-Ub, Hrd1 and gp78 levels and (b) UPR signaling proteins, eIF2α, p-eIF2α, PERK, IRE1α and XBP-1s were analyzed by immunoblotting. Beta-actin was used as a loading control.

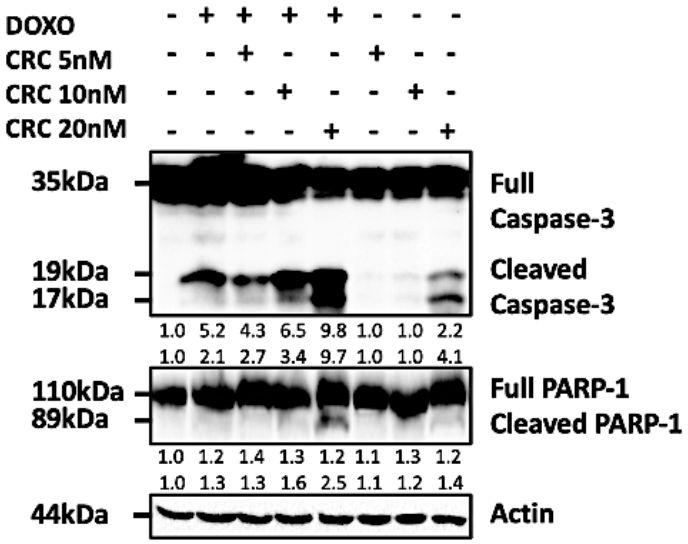

Figure 4. Evaluation of the effect of curcumin and doxorubicin on cell-death-related proteins in LNCaP cells . Cells were treated with vehicle or 10μM DOXO, 5, 10 and 20nM CRC or their combination for 24 hours. The expression levels of full and cleaved caspase-3 and PARP-1 were analyzed by immunoblotting. Beta-actin was used as a loading control.

Curcumin enhances the doxorubicin-induced caspase-3 and PARP-1 activation in LNCaP cells

It is known that caspase enzymes and PARP-1 activation play a key role in programmed cell death (16). Also, chemotherapeutics strongly stimulate the activation of these enzymes (17). Thus, we examined the booster effect of CRC on DOXO-induced caspase-3 and PARP-1 activation. 10μM DOXO treatment slightly generated the 89kDa cleavage fragment of PARP-1 and it strongly induced the 19kDa cleavage fragment of caspase-3 compared to the control group (Figure 4). Moreover, alone CRC treatment weakly induced the PARP-1 activation at 10 and 20nM doses. 5nM CRC did not activate caspase-3 and PARP-1 compared to the control group. Despite 10nM CRC treatment slightly induced the cleavage of caspase-3, 20nM CRC markedly increased the caspase-3 activation (Figure 4). Co-administration of CRC and DOXO remarkedly induced cleavage of caspase-3 and PARP-1 in a dose-dependent manner compared to alone DOXO or CRC as indicated doses (Figure 4). These results indicated that co-administration of CRC with DOXO more strongly induced cleavage of caspase-3 and PARP-1 activation in LNCaP cells.

Co-administration of curcumin with doxorubicin strongly reduced the tumorigenic protein levels in LNCaP cells

We tested the effect of co-administration of CRC and DOXO on tumorigenic protein levels, including PSA, AR, c-Myc, VEGF-A and the EMT-related proteins E-cadherin and N-cadherin by immunoblotting. We found that only CRC or DOXO administration reduced AR, PSA, c-Myc, N-cadherin and VEGF-A levels compared to the control group. E-cadherin levels were increased by CRC or DOXO treatment (Figure 5). Co-treatment of CRC with DOXO more strongly decreased the PSA, AR, c-Myc, N-cadherin and VEGF-A levels, whereas E-cadherin was increased in a dose-dependent manner (Figure 5). These results suggested that CRC and DOXO alone treatment reduced the tumorigenic protein levels and co-treatment more effectively reduced the PSA, AR, c-Myc and VEGF-A levels. Moreover, EMT-related proteins N-cadherin more strongly decreased with co-administration whereas E-cadherin was induced by the co-administration of CRC and DOXO.

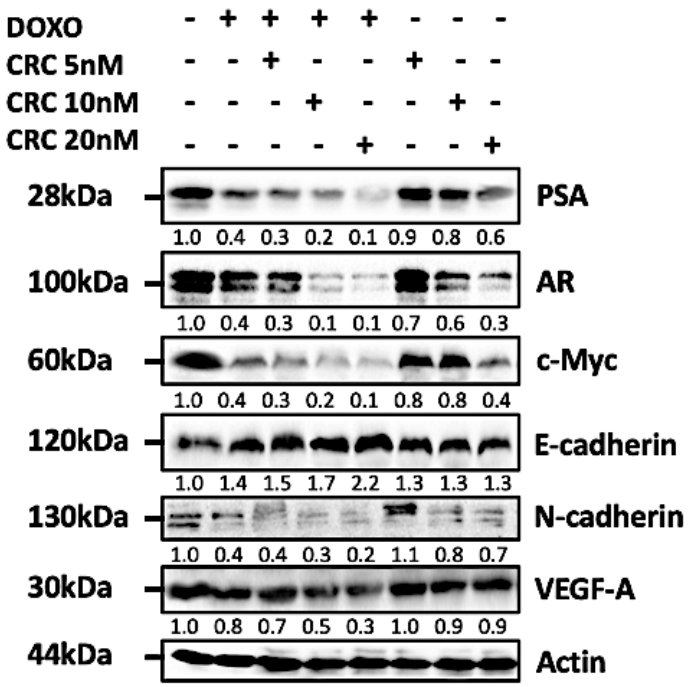

Figure 5. Evaluation of the effect of curcumin and doxorubicin on prostate cancer tumorigenesis-related proteins in LNCaP cells . Cells were treated with vehicle or 10µM DOXO, 5, 10 and 20nM CRC or their combination for 24 hours. The expression levels of PSA, AR, c-Myc, E-cadherin, N-cadherin and VEGF-A were analyzed by immunoblotting. Beta-actin was used as a loading control.

DISCUSSION

Since ancient times, natural compounds have been extensively used as medicinal remedies in different cultures owing to their antioxidant, anti-inflammatory and antimicrobial properties (18). Most of the chemotherapeutics with strong anti-cancer properties were discovered after further characterization of the active ingredients in natural products. Today, studies focusing on plant-derived agents are continuing intensively (19).

CRC, a polyphenol, is the active ingredient of turmeric (*Curcuma longa Linn*) and has diverse biochemical activities, including neuroprotective, anti-inflammatory, anti-proliferative, anti-angiogenic, antioxidant, antiviral and anti-tumorigenic effects (20). Studies have shown that caspase-related apoptosis is induced by CRC administration in androgen-dependent and castration-resistant prostate cancer cells (21,22). CRC and its analogues have been extensively studied for their anticancer properties, including prostate cancer (20). In addition, there have been many ongoing and finalized phase studies related to the effectiveness of CRC on various types of cancers for the last 20 years (23). Furthermore, *in vitro* studies demonstrated that CRC can potentiate the cytotoxic effects of chemotherapeutic drugs, including tamoxifen, cisplatin, vincristine, daunorubicin and DOXO (24-26). Also, multi-drug administrations clinically have been used such as combined administration of DOX with other chemotherapeutics, including cyclophosphamide, 5-fluorouracil, docetaxel, vinblastine and bleomycin (27-29). Moreover, Klippstein et al. reported that the combinatory administration of CRC nanocapsule and DOXO has a synergistic effect on metastatic androgen independent prostate cancer cells, PC3 and DU145 through the induction of apoptotic cell death (15). Moreover, recent studies have reported that CRC administration may reduce the adverse effects of DOX (30). Based on these studies, we aimed to mechanistically investigate the possible booster effect of CRC on DOXO in human androgen-dependent prostatic adenocarcinoma LNCaP cells.

Firstly, we evaluated the impacts of co-administration of CRC with DOXO on cell viability, we found that combined treatment more strongly reduced the viability of LNCaP cells (Figure 1a, b). It was also determined that co-administration increased the cytotoxic effect and decreased the IC50 value. These results suggest that CRC raised the anti-tumorigenic ability of DOXO by elevating the susceptibility of LNCaP cells to DOXO treatment (Figure 1a, b). Our results supported the results of Klippstein et al., on androgen-independent metastatic prostate cancer cells (15).

Autophagy is an evolutionarily conserved mechanism that delicately regulates the cell content, including long-lived and unfolded proteins and damaged organelles. Today, the role of autophagy in cancer is enigmatic and it may work as a tumor support or suppressor depending on the status of the cancer cells (31). Autophagy involves the formation of the double-membrane vesicle degradation through lysosomes, which consists of sequential steps, including membrane nucleation, phagophore expansion, formation of autophagosome and fusion with lysosomes. The formation of the double-membrane vesicle is a complex process in which a large number of autophagy-related proteins (Atg) work in tandem (32). Therefore, many proteins need to be studied simultaneously in the cellular-level monitoring of autophagy, which has multiple steps (33). For this aim, we examined the effect of co-administration on Beclin1 protein levels, p62/SQSTM1 turnover and LC3-I to LC3-II conversion by immunoblotting. Beclin1 is a key regulator of autophagy which plays a role in the initiation of autophagy through interaction with lipid kinase complex and coordinates the membrane trafficking (34). The ubiquitin receptor protein, p62/SQSTM1 directly binds to the LC3 proteins and is degraded by autophagy. The steady-state level of p62/SQSTM1 increases or decreases depending on the autophagic activity in the cells. Therefore, it is often used to monitor the autophagic flux (35). During autophagy, the cytosolic form of LC3, LC3-I, is modified with phosphatidylethanolamine and it covers to the LC3-II, which is recruited to autophagosomal membranes

and degraded during the fusion of the autophagosome with the lysosome (36). Our data indicated that either alone DOXO or CRC treatment increased the steady-state level of p62/SQSTM1 compared to the control group. Also, LC3-I and LC3-II levels were increased by CRC and DOXO treatment. Combination of DOXO and 5 nM CRC enhanced the Beclin1 levels whereas 10nM and 20nM CRC administration reduced the Beclin1 levels in a dose-dependent manner (Figure 2b). Considering that autophagy is a physiological mechanism, it can be thought that LNCaP cells respond through the reorganization of autophagy against 5nM CRC-mediated reduced autophagic activity by increasing Beclin1 levels. Co-administration of CRC and DOXO increased the accumulation of p62/SQSTM1 and increment of LC3-I and LC3-II levels stronger than either alone CRC or DOXO treatment whereas Beclin1 was decreased in a dose-dependent manner (Figure 2b). Collectively, these results suggested that CRC and DOXO alone reduced the autophagic flux in LNCaP cells while co-administration more strongly reduced autophagic activity. Additionally, microscopic examination results also support these findings (Figure 2a).

ERAD is another important protein quality control mechanism in mammalian cells. The ER is an important centre for the synthesis of one-third of the cellular proteome. Therefore, it hosts advanced protein quality control mechanisms. ERAD is a sophisticated mechanism that selectively recognizes misfolded, unfolded and incorrectly oligomerized proteins and directs them to proteosome-mediated degradation. Moreover, ERAD also controls the endogenous levels of physiologically important proteins (37). Besides, ubiquitination, a posttranslational modification, is the molecular marking required for directing proteins to degradation (38). We found that DOXO treatment did not affect the levels of E3 ubiquitin ligase enzymes (Hrd1 and gp78), whereas poly-ubiquitination slightly increased by DOXO. CRC treatment increased the Hrd1, gp78 and poly-ubiquitination levels in a dose-dependent manner. Co-administration remarkably increased the levels of E3 ligase enzymes and poly-ubiquitination state (Figure 3a). These data indicated that co-administration strongly induced the ERAD-mediated protein turnover in LNCaP cells.

It is known that the unfolded protein response (UPR) signaling plays a pivotal role in improving the capacity of the ER and re-establishing impaired ER homeostasis (39,40). The UPR signaling is regulated through ER membrane-localized three transmembrane proteins, IRE1α, PERK and ATF6 (41). We found that either DOXO or CRC treatment induced the IRE1α and PERK branches of UPR. Our data indicated that CRC markedly increased the IRE1α and its effector protein XBP-1s levels in a dose-dependent manner. PERK protein levels and phosphorylation of eIF2 were increased by CRC treatment. Similar to these results, DOXO administration induced phosphorylated eIF2α, PERK and XBP-1s levels. Co-administration of DOXO with CRC more strongly increased the levels of PERK and IRE1α signaling proteins in a dose-dependent manner (Figure 3b). The severe ER stress signaling can induce programmed cell death in cells by increasing the levels of pro-apoptotic proteins, such as C/EBP-homologous protein (CHOP) by causing overstimulation of the UPR (42,43). Our results suggest that the potentiating effect of CRC on DOXO is through potentiation of DOXO-induced cell death due to overstimulation of the UPR in prostate cancer cells.

Next, we evaluated the programmed cell death-related caspase-3 and PARP-1 protein levels. Effector caspases enzymes such as caspase-3, -6, -7 regulate the programmed cell death apoptosis through fragmentation of DNA, blebbing and shrinkage of cells (44). Cysteine–aspartic acid protease, caspase-3 is one of the main executioner proteins of apoptosis and leads to the cleavage of numerous key proteins, including PARP-1 (44,45). Activation of caspase-3 leads to proteolytic cleavage of the full version of caspase-3 and produces 17/19 kDa cleavage caspase-3 form (44,45). Our results indicated that either alone DOXO or CRC administration induced the activation of caspase-3 whereas co-administration remarkably increased the caspase-3 activation in a dose-dependent manner (Figure 4). Also, we tested the level of full (116kDa) and cleavage form (89kDa) of PARP-1 protein, which is a 116 kDa nuclear protein and cleavable through the caspase-3 enzyme (46,47). We found that DOXO or CRC treatment weakly produced the 89kDa fragment of PARP-1 protein, whereas the combination of DOXO and 20nM CRC strongly increased the cleavage form of PARP-1 (Figure 4). These data suggest that CRC improves the anti-cancer properties of DOXO on prostate cancer cells through inducing executioner protein levels.

Lastly, we evaluated the tumorigenic protein levels, including PSA, AR, c-Myc and VEGF-A. We also tested the level of N-cadherin and E-cadherin proteins, which are related to the arrangement of the invasion and migration capability process. Androgen receptor signaling has a crucial role in the progression of prostate cancer. It regulates the transcription of AR target genes, including PSA as an active transcription factor after stimulation of AR with its ligand (48). c-Myc is a well-known oncogene and is a major driver in prostate cancer malignancy. Moreover, a positive correlation has been determined between expression levels of c-Myc and AR in human prostate cancer samples (49). VEGF-A is an important regulator of angiogenesis and it promotes the growth of tumors (50). We observed that either DOXO or CRC treatment importantly decreased the AR, PSA and c-Myc levels compared to the control group. Furthermore, co-administration more strongly reduced the levels of these proteins in a dose-dependent manner (Figure 5). Additionally,

VEGF-A levels were slightly decreased by alone CRC and DOXO whereas co-administration remarkably reduced VEGF-A levels in a dose-dependent manner compared to either alone DOXO or CRC (Figure 5). These data suggest that co-administration more effectively decreases the tumorigenic protein levels in prostate cancer cells.

EMT works as a key mechanism in cancer cells for acquiring mobility and increasing invasiveness/migrative features. Reduction of E-cadherin and elevated level of N-cadherin induces epithelial to mesenchymal transition (51). Our data showed that CRC or DOXO administration increased E-cadherin and decreased N-cadherin levels compared to the control group. Co-administration more potently increased the level of E-cadherin and reduced N-cadherin. Collectively, these results indicated that CRC efficiently evolved the anti-tumorigenic properties of DOXO on prostate cancer cells.

Prostate cancer is one of the main health problems among men worldwide and it causes the death of many people (52). Today, numerous therapies depending on the stage and subtype of prostate cancer, including surgery, cryotherapy, androgen-deprivation therapy and chemotherapy, while the efficacy of the treatments may be limited due to the serious side effects caused by the long-term use of high-dose chemotherapeutics or acquired drug resistance (53). The results of numerous *in vitro* and in vivo experiments show that natural products in treatment protocols can offer a promising approach (19).

The anthracycline DOXO is one of the most commonly used anticancer drugs in clinical practice and has a broad spectrum of use, such as in childhood and adult malignancies, including prostate cancer (54,55). However, accumulated evidence has shown that DOXO could affect non-targeted tissues; thereby, acute and chronic toxicity can develop in these tissues as a side effect (54). Herein, we examined the booster effect of CRC on DOXO on prostate cancer cells through investigating the detailed molecular signaling mechanisms, including autophagy, ERAD, UPR, AR signaling, angiogenic signal and EMT.

Limitations of the study

The present study investigates the possible potentiator effect of CRC on DOXO *in vitro*. The more effective anti-cancer responses demonstrated by the co-administration of CRC with DOXO need to be confirmed in vivo studies.

CONCLUSION

Overall, the present data strongly suggest that CRC potently and synergistically improves the anti-cancer features of DOXO by blocking autophagic flux, inducing ERAD and UPR signaling, activating the executioner proteins caspase-3 and PARP-1 and negatively modulating the AR signaling and EMT mechanism and also decreasing angiogenic factor VEGF-A and protooncogene c-Myc levels.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

This study does not require any ethical permission, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: YE, Design: YE, Supervising: YE, Financing and equipment: YE, Data collection and entry: YE, HKD, DC, Analysis and interpretation: YE, Literature search: YE, HKD, DC, Writing: YE, Critical review: YE, HKD, DC.

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ORIGINAL RESEARCH

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The evaluation of patients applied for septorhinoplasty in terms of body perception, disability, depression and social phobia

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Abstract

Objective: Psychiatric suitability is an important parameter that is evaluated together with anatomical suitability when deciding on rhinoplasty surgery. There is no matter how successful the treatment or surgery is, the results are not satisfactory for individuals with psychiatric symptoms. To make a broader assessment of psychiatric suitability, we aimed to evaluate body perception, disability, depression and social phobia in individuals who underwent for rhinoplasty surgery.
Method: In this study, patients who applied to the Mustafa Kemal University Hospital Otorhinolaryngology outpatient clinic between 1/1/2019 and 1/1/2020 were included. Among the patients, 50 volunteers who applied for complaints of dissatisfaction with the aesthetic appearance of the nose were included in the case group. In the control group, 50 patients who applied to the Otorhinolaryngology outpatient clinic, had any complaints other than nasal deformity and were not planning for any other aesthetic operation were included.
Results: There were no statistically significant differences in terms of body image, disability, depression and social phobia.
Conclusion: It has been confirmed that depression and body image do not show significant changes in patients who will undergo septorhinoplasty, and the information that disability and social phobia are not effective has been brought to the literature. Further studies with larger samples are needed on preoperative psychiatric evaluation.
Keywords: Septorhinoplasty, Body dysmorphic disorder, Depression, Body perception

INTRODUCTION

Aesthetic operations are surgical procedures that have become popular especially in recent years. The variety and number of applications of these procedures, which can be performed in every part of the body with different shapes and purposes, are increasing. According to the data of the American Society of Aesthetic Plastic Surgery, the number of patients who applied for aesthetic anxiety in 2018 and who underwent invasive procedures1,5 million, noninvasive procedures 3,5 million, total were approximately 4.8 million (1). Among these operations, facial aesthetic surgeries, especially septorhinoplasty, are important. In 2018, septorhinoplasty was one of the most common surgical procedures applied to the head and neck region, with an increase of 6.6% compared to that in the previous year(1).

Physical attractiveness has been a highly valued human characteristic across cultures from the past to the present (2). Although it is accepted that the perception of beauty is subjective, studies show that physical attractiveness has common cultural value (3). Considering the importance of being attractive in society, it is not surprising that a person is unhappy about his or her appearance. However, if this dissatisfaction affects a person's psychological and social well-being, it can be considered pathological.

In addition to its respiratory function, the nose is also an important organ in terms of aesthetics since it is located in the midline of the face. It has an important place in the formation of personality perception. Every component of the face is important for overall facial harmony. Nevertheless, the nose, located in the middle of the face, greatly impacts the

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person's overall appearance through its position, shape, and size. Because physical appearance plays a major role in social life and interpersonal communication, it is better understood how important the shape and structure of the nose are (4).

While deciding on the feasibility of septorhinoplasty, another parameter that should be considered together with anatomical suitability is psychiatric suitability(5). With the increase in studies in this area, researchers have observed an increase in the number of people who apply for septorhinoplasty, as these procedures are not sufficient in terms of psychiatric suitability (6).

Body dysmorphic disorder, depression, psychosis and many other psychiatric clinical conditions may cause such a presentation and an unsatisfactory surgical outcome. When the surgical procedure is considered irreversible, the best approach is to detect and prevent such a negativity beforehand. There are many studies in the literature in which preoperative psychiatric evaluation is performed. While body image, depression and several other parameters were evaluated in most of these studies, disability and social phobia were not adequately evaluated. In this study, we aimed to evaluate body image, disability, depression and social phobia in people who underwent septorhinoplasty to perform a broader evaluation to determine psychiatric suitability.

METHOD

Patients who underwent surgery at the Mustafa Kemal University Hospital Otorhinolaryngology Department between 2019 and 2020, one year after the date of ethics committee approval, were included in this study in the preoperative period. By evaluating previous studies in the literature and taking into account the physical capacity of the otorhinolaryngology department, 58 patients were determined for the study. When the exclusion criteria were evaluated, 8 patients were excluded from the study. Among the patients, 33 men 17 women for a total of 50 volunteers, who applied for complaints of dissatisfaction with the aesthetic appearance of the nose included in the case group. In the control group, 33 men and 17 women, for a total of 50 patients, who presented at the Otorhinolaryngology outpatient clinic, had any complaints other than nasal deformity and were not scheduled for any other aesthetic operation were included. By choosing patients who were far from the idea of aesthetic surgery on the nose or any other part of the body in the control group, we aimed to reach the group that was as far away from the pathologies that may be rooted in aesthetic concerns, such as body perception, social phobia, depression, and disability, among the parameters we evaluated. Apart from these patients, being between the ages of 18 and 45 years, volunteering to participate in the study, signing the voluntary consent form, and being able to answer the applied tests were determined as inclusion criteria. The presence of any psychiatric disease diagnosed, age younger than 18 and 45 years or older, mental retardation, metabolic or endocrine disorders that affect cognitive functions were excluded from the study. By including patients over the age of 18 within the inclusion criteria, we aimed to include patients who made their decisions with their free will to participate in the study. Patients older than forty-five years were included among the exclusion criteria to ensure group homogeneity due to anatomical differences from patients aged 18-45 years, where demand is common, and therefore different surgical results and expectations. Since the study included self-evaluation questionnaires, the exclusion criteria included having any psychiatric disorder that could affect this evaluation, mental retardation, or any metabolic or endocrine disease affecting cognitive functions. A total of 58 patients were included in the study group, and 8 patients who met the exclusion criteria were excluded from the study. The patients were asked to complete the study form, which consisted of a sociodemographic data form, the Beck Depression Scale,(7) the Body Image Scale (8), the Functioning Assessment Short Test (9), and the Liebowitz Social Phobia Symptoms Scale (10). Beck Depression Scale was developed by Beck et al. in 1961 and is used to evaluate the emotional, cognitive, somatic, and motivational symptoms observed in patients with depression(7). On this scale, the patient evaluates himself or herself. The purpose of the scale is to objectively determine the degree of depression symptoms in patients. It contains 21 items, and there are 4 options for each item. By summing the scores of the selected options, a depression score between 0 and 63 was obtained. The Beck Depression Scale is not used to diagnose depression but rather to objectively evaluate the degree of depression symptoms. Low scores on the scale indicate fewer depressive symptoms, and higher scores indicate more depressive symptoms. The body perception scale was developed by Secord and Jourard in 1953(8). It aims to measure how satisfied or dissatisfied people are with various parts of their bodies and various functions in their bodies. The scale consists of 40 items that question body parts or functions. Higher scores indicate higher satisfaction levels. The scale consists of 40 items, each related to an organ or part or function of the body. A score of 1 indicates the most negative situation, while maximum score of 5 indicates the most positive situation. A total of 40 questions were scored between 40 and 200. An increase in the total score obtained from the scale indicates that the satisfaction of the person with the body parts or function increases, and a decrease in the score indicates that the satisfaction decreases. The Functioning Assessment Short Test was developed by Rosa et al. to provide a rapid assessment of functionality (9). This scale is a 24-item scale and provides a four-point Likert-type evaluation. It consists of six dimensions: autonomy, occupational functioning, cognitive functioning, financial

matters, interpersonal relationships, and leisure activities. A high score indicates poor functionality. The Liebowitz Social Phobia Symptoms Scale is a Likert-type self-assessment scale developed to evaluate social relationships and performance situations in which individuals with social anxiety disorder exhibit fear or avoidance behavior. The severity of anxiety and avoidance that occurs in various social situations are also questioned. It contains two subscales, the first of which is aimed at measuring the level of anxiety experienced in social environments, and the second is aimed at measuring the severity of avoidance behavior. The self-administered scale consists of a total of 24 items, 11 of which are related to social relations and 13 of which are related to performance. An increase in the score indicates that social anxiety and avoidance are becoming more severe. The scale was developed by Liebowitz in 1987 (10). The study was approved by the Ethics Committee of Mustafa Kemal University Medical Faculty.

Statistical Analysis

The data of the study were evaluated through the SPSS "Statistical Package for Social Sciences (SPSS 23.0)" program. The data were calculated as the mean +/- standard deviation or percent (%). For the statistical analysis, the distributions of the groups were tested by Kolmogorov-Smirnov analysis. Nonparametric tests were used because the variables were not normally distributed ($p<0.05$). The Mann-Whitney U test was used to evaluate differences between two independent nonnormally distributed groups from similar populations. Correlation analysis was performed to determine the direction and degree of relationships between variables, and the Spearman test was used since groups with nonnormal distribution were evaluated. At the 95% confidence interval for statistical significance, $p<0.05$ was accepted.

RESULTS

Sociodemographic data

Of the 50 patients in the case group included in the study, 33 (66%) were male and 17 (34%) were female. The mean age of the patients, whose ages ranged from 18-45 years, was 28±5.707 years. Of the 50 patients in the control group included in the study, 33 (66%) were male and 17 (34%) were female. The mean age of the patients, whose ages ranged from 18-45 years, was 27.54±6.345 years. There is no statistically significant difference was observed between the two groups in terms of age and gender ($p=0.362$). The sociodemographic data of the patients in the case and control groups are given in Table 1.

Applied scales

The Beck Depression Scale, Body Image Scale, Functioning Assessment Short Test and Liebowitz Social Phobia Symptoms Scale data applied to the case and control groups are given in Table 2, Table 3, Table 4 and Table 5, respectively. Correlation analysis was performed by applying the Spearman test to evaluate the relationship between the scales used. Accordingly, moderate negative correlation was observed between the Beck Depression Scale score and the Body Image Scale ($p = 0.001$, $r = -0.452$). There was a positive moderate correlation between the Beck Depression Scale score and the Liebowitz Social Phobia Symptoms Scale ($p = 0.001$, $r = 0.457$) and between the Beck Depression Scale score and the Brief Functioning Assessment Scale ($p <0.001^*$, $r = 0.544$). The detailed content evaluating the correlation between the applied scales is given in Table 6.

Table 1. Sociodemographic data of the case and control groups

	Gender				Mean Age
	Male		Female		
	n	%	n	%	
Case	33	66	17	34	28±5.707
Control	33	66	17	34	27.54±6.345
p= 0.362					

Table 2. Beck Depression Scale data

BDS	n	Mean	Median	Min-Max
Case	50	6.7±5.560	6	0-23
Control	50	8.16±4.278	9.50	0-15
p= 0.065				

Table 3. Body image scale data

BIS	n	Mean	Median	Min-Max
Case	50	158.72±21.711	156.50	104-196
Control	50	153.30±20.549	151.00	111-200
p=0.153				

DISCUSSION

According to the data of the American Society of Aesthetic Plastic Surgery (ASAPS), the number of patients who applied for invasive or noninvasive procedures among patients who applied aesthetic expectations in 2018 was approximately 4.8 million (1). A comparison of this figure with the total number of applications in 1997 revealed that the number of cases increased by 2.5 times (11). These values numerically reflect the significant increase in the number of patients who applied aesthetic expectations.

Physical attractiveness has been a highly valued human characteristic across cultures from the past to the present (2). Although it is accepted that the perception of beauty is subjective, studies show that physical attractiveness has common cultural value (3). However, with increasing

Table 4. Functioning Assessment Short Test data

FAST		n	Mean	Median	Min-Max	p
Case	Autonomy		1.66±2.163	0.50	0-9	0.183
	Occupational Functioning		1.32±2.706	0	0-14	0.322
	Cognitive Functioning		2.44±2.296	2	0-9	0.707
	Financial Issues		1.06±1.766	0	0-6	0.481
	Interpersonal Relationship		1.50±2.501	0	0-8	0.137
	Leisure time		0.98±1.348	0	0-5	0.058
	Total	50	8.96±8.889	7.5	0-45	0.167
Control	Autonomy		0.94±1.300	0	0-5	0.183
	Occupational Functioning		1.96±2.185	1.5	0-7	0.322
	Cognitive Functioning		2.22±2.033	2	0-7	0.707
	Financial Issues		0.98±1.186	0	0-5	0.481
	Interpersonal Relationship		2.48±2.288	2	0-7	0.137
	Leisure time		1.36±1.191	2	0-4	0.058
	Total	50	9.94±6.594	11	0-22	0.167

globalization, common norms in physical attractiveness are emerging worldwide. The noticeable physical features of a popular person in a country can become the general beauty criterion of humanity through digital media, especially social media. In our study, the Beck Depression Scale was used to evaluate depression scores in patients who underwent septorhinoplasty. As indicated in Table 2, no statistically significant relationship was found between the values of the case and control groups according to the Beck Depression Scale data (P=0.065). Taziki et al. investigated 250 aesthetic rhinoplasty patients in terms of body dysmorphic disorder, self-esteem, and depression score and they evaluated depression score with the Beck Depression Scale. When he determined 13 as the cutoff point for the depression score, he found a high value at a rate of 42.2% (12). Bender et al. evaluated 201 rhinoplasty patients in terms of preoperative depression score and body dysmorphic disorder. The author, using the Beck Depression Scale, determined the rate of depression to be 1.7% and found that there was no statistically significant difference(13). Naraghi et al. evaluated the depression scores of patients who were scheduled for aesthetic and functional rhinoplasty surgery preoperatively (14). In the literature, many studies have shown statistically significant and nonsignificant relationships between the depression tendency and patients who requested septorhinoplasty. In our study, we also did not find a statistically significant relationship between the case and control groups regarding depression scores. This may have been caused by our sample size not being large enough. In addition, considering that the Beck Depression Scale is an assessment tool in which the patient evaluates himself, our case group may not have had the competence to analyze and report their situation. The significant and nonsignificant relationship results found between depression and beauty perception found in other studies in the literature reveal the need for studies with larger samples and measurement tools that will define it in more detail.

Table 5. Liebowitz Social Phobia Symptoms Scale data

LSPSS		n	Mean	Median	Min-Max	p
Case	Fear		42.34±12.775	40.00	24-91	0.364
	Avoidance		39.42±8.896	39.00	24-59	0.926
	Total	50	81.76±19.220	82.50	48-121	0.555
Control	Fear		40.30±10.916	38.50	24-75	0.364
	Avoidance		40.54±10.708	38.00	24-72	0.926
	Total	50	80.84±21.013	77.50	48-147	0.555

Table 6. Correlations between the applied scales

		BDS	BIS	FAST	LSPSS
BDS	r	1.000	-0.452	0.544	0.457
	p		0.001*	<0.001*	0.001*
	n	50	50	50	50
BIS	r	-0.452	1.000	-0.412	-0.177
	p	0.001*		0.003*	0.219
	n	50	50	50	50
FAST	r	0.544	-0.412	1.000	0.179
	p	<0.001*	0.003		0.214
	n	50	50	50	50
LSPSS	r	0.457	-0.177	0.179	1.000
	p	0.001*	0.219	0.214	
	n	50	50	50	50

In her study, Ayaz reported that the body image of patients who underwent aesthetic surgery was significantly lower than that of patients who underwent reconstructive surgery (15). In their study, Amirhosein et al. compared patients who would undergo aesthetic rhinoplasty with patients who would undergo reconstructive surgery. Accordingly, patients who undergo aesthetic rhinoplasty have lower body perceptions and those diagnosed with body dysmorphic disorder are more common in this population (16). In their study, Samadzadeh et al. examined the relationship between mental health and body image in 100 female patients who underwent aesthetic rhinoplasty, both before and after the operation (17). When the patients' body image and mental health were compared before and after the operation, a statistically significant relationship was observed. In our study, no significant relationship was found between the body image of the patients who underwent septorhinoplasty and that of the control group.

Body perception is a complex entity that varies from person to person and is difficult to evaluate. Patients with impaired body perception generally tend not to report their complaints. In particular, young and male patients do not see their complaints as a psychological problem and do not want to report them, considering the possibility of feeling embarrassed and being humiliated by their close circle (18). This complex condition may not have been adequately evaluated with the body image assessment scale alone, or patients may have refrained from expressing their condition. We think that such a result may have emerged when all these situations were combined with our small sample size.

There are studies in the literature evaluating the depression score and body image of patients who will undergo aesthetic surgery. However, studies examining the disability and social phobia status of these patients are insufficient. In our study, when the patients who underwent septorhinoplasty were evaluated for disability and social phobia, no significant relationship was found between them and the control group.

Social phobia and disability can occur simultaneously with many psychiatric diseases. Severe disability can occur, especially in diseases such as body dysmorphic disorder (19). Again, social phobia is among the most common comorbidities in patients with body dysmorphic disorder, along with depression and obsessive-compulsive disorder (20,21). There are not enough studies in the literature to compare the results we found in our study on social phobia and disability. Moreover, evaluating these complex parameters with only the scales we use may not be sufficient. Considering the short follow-up period of the patients, we think that the results we obtained are valuable, but we believe that comprehensive and further studies are necessary.

Correlation analysis was performed by applying the Spearman test to evaluate the relationship between the scales used in our study. The results of evaluating the correlation between the scales applied are given in Table 6. There was a significant relationship between Beck Depression Scale scores and other scale scores, which is consistent with the literature. Liao et al. evaluated body dysmorphic disorder, social anxiety, and depressive symptoms in Chinese medical students. It was determined that social anxiety and depressive symptom levels were greater in participants with impaired body image (22). Aderka et al. studied body image in patients with social anxiety disorder, obsessive compulsive disorder and panic disorder. It was observed that the social anxiety levels of patients positively affect their perception of body image disorders and negatively affect their level of appearance evaluation (23). Ramseyer et al. reported that when women's body likes increase, their depression score decreases (24).

The fact that depressive symptoms are observed more frequently in individuals with impaired body image is consistent with the literature. Body dysmorphic disorder is a disease that can lead to severe disability (19). The negative correlation between the body image scale score and the Functioning Assessment Short Test score is consistent with this finding. As seen in the literature, a significant correlation was observed between depression tendency and body image, disability and social phobia in our study. As seen in our study and in the literature, the fact that the scales used have significant positive and negative correlations with each other can guide the evaluation of possible pathologies. A possible preoperative evaluation predicts that a patient with a distorted body image may also have depressive symptoms, and taking precautions in this regard and performing surgery after appropriate management can ensure that the patient obtains good results from the procedure.

The limited number of patients, the preference for the scales completed by the patients, and the limited postoperative follow-up period can be considered limiting factors of our study. Although there are many studies in the literature with a much smaller sample size than the number of patients in our study, statistically stronger values can be achieved with a larger sample size. More detailed and physician-centered scale evaluations of psychiatric examinations may enable us to reach more accurate results. Additionally, since none of the scales used are diagnostic, comprehensive studies in which patients are examined psychiatrically in more detail may provide clearer results.

CONCLUSION

In our study, when the patients who requested septorhinoplasty were compared with the control group, no statistically significant differences were found in terms of body image, disability, depression or social phobia. It

has been confirmed that depression score and body image do not significantly change in patients who will undergo septorhinoplasty, and the information that disability and social phobia are not effective has been provided in the literature. With these findings, patients who are candidates for aesthetic procedures such as septorhinoplasty can be evaluated in detail preoperatively and provided with satisfactory results. This initiative for the effective use of patient, physician, and shared resources will benefit everyone. However, further studies with larger samples are needed for preoperative psychiatric evaluation.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 30/11/2018 and number 2018/174, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: BG MA, Design: BG MİG, Supervising: BG MİG, Financing and equipment: BG MİG Data collection and entry: BG MİG, Analysis and interpretation: BG MİG ŞO, Literature search: BG MİG, Writing: BG MİG, Critical review: BG MİG ŞO MA.

Thesis

This study was prepared by rearrangement of the doctoral thesis by Dr. Beyza Gülmez, entitled as “Septorinoplasti talebiyle başvuran hastalarin vücut algisi, yeti yitimi, depresyon ve sosyal fobi açisindan değerlendirilmesi”.

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ORIGINAL RESEARCH

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Comparison of diagnostic values of monocyte-lymphocyte ratio, neutrophil-lymphocyte ratio, red cell distribution width-lymphocyte ratio, and systemic inflammatory index in predicting patients with non-dipper hypertension

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Abstract

Objective: Hypertension is related to myocardial ischemia, malignant arrhythmias, and cardiovascular mortality. However, inflammatory biomarkers are an important predictor of cardiovascular events. This study aimed to examine the diagnostic utility of inflammatory biomarkers in determining non-dipper hypertensive individuals and the relative superiority of the biomarkers.

Method: The research was carried out as a retrospective observational study. The patients with hypertension were classified into two groups: non-dipper (n=54) and dipper (n=143). The cut-off value of MLR (monocyte-lymphocyte ratio), NLR (neutrophil-lymphocyte ratio), SII (systemic inflammatory index), and RLR (red cell distribution width-lymphocyte ratio) for predicting non-dipper hypertension was determined using a receiver operating characteristic (ROC) analysis.

Results: A total of 197 patients, comprising 84 females (42.6%) and, 113 males (57.4%) with a median age of 62 (54-69) years, participated in the research. Age, FPG, CRP, WBC, NEU, LYM, MONO, RDW, NLR, MLR, RLR, and SII were higher in the non-dipper group ($p<0.05$). MLR, NLR, RLR, and SII were found to have acceptable diagnostic capabilities in identifying non-dipper hypertension patients (AUC: 0.70-0.76). When ROC analysis was performed to determine the main similarities, it was found that there were no differences between inflammatory indicators ($p>0.05$).When the odds ratios of putative variables were evaluated, it was found that increasing MLR (OR: 7.22; 95%CI: 3.52-14.78; $p<0.001$), NLR (OR: 8.63; 95%CI: 4.19-17.68; $p<0.001$), RLR (OR: 4.29; 95%CI: 2.18-8.54; $p<0.001$), and SII (OR: 6.31; 95%CI: 3.09-12.85; $p<0.001$) were independent predictors for non-dipper positivity.

Conclusion: In hypertensive patients, hematological inflammatory biomarkers MLR, NLR, RLR, and SII are valuable in determining non-dipper hypertension.

Keywords: Non-Dipper hypertension, Monocyte-Lymphocyte Ratio, Neutrophil-Lymphocyte Ratio, RDW-Lymphocyte Ratio, Systemic Inflammatory Index

INTRODUCTION

Hypertension is a prevalent systemic disease worldwide and is the leading potential cause of cardiovascular events (1). Despite many treatment methods, the expected degree of preventing organ damage from hypertension has not been achieved (2). Blood pressure (BP) is greatest in the morning, gradually drops during the day, and reaches its lowest level at night. Dipper hypertension is described when overnight BP lowers by more than 10% relative to daytime readings, while non-dipper hypertension is identified when nighttime BP reduces by less than 10% (3). Hypertension is related to harm to organs such as the cardiovascular system in non-dippers (4). The risk of atherosclerotic events is three times greater in people with non-dipper hypertension than those with dipper hypertension (5).

Inflammation plays a role in the pathogenesis of hypertension (6). Variation in BP is connected with inflammatory indicators. Recent research has revealed that inflammatory biomarkers, such as monocyte-lymphocyte

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ratio (MLR), systemic inflammatory index (SII), and neutrophil-lymphocyte ratio (NLR) are useful for predicting the non-dipper pattern in hypertension (7). RDW-lymphocyte ratio (RLR) was compared with other markers in many diseases (8). The predictive value of RLR in estimating the non-dipper pattern remains unknown.

We aimed to examine the diagnostic utility of inflammatory biomarkers in determining non-dipper hypertensive individuals and the relative superiority of the biomarkers.

METHOD

This retrospective research was carried out between March 2021 and January 2023. Patients diagnosed with hypertension were enrolled in this study. Exclusion criteria were coronary artery disease, hyperthyroidism, hypothyroidism, valve disease, heart failure, renal failure, autoimmune disease, active infection or cancer, using steroids or anticoagulants, hepatic disease, morbidly obese, pulmonary disease, congenital heart disease, hematological disease. This research eliminated participants for whom data were unavailable and whose ambulatory BP monitoring analysis was ineffective. The local ethics committee (Gazi Yasargil Training and Research Hospital) approved the study protocol (No: 2023-371). It complied with the Helsinki Declaration's ethical criteria for human testing (Date: 03/03/2023) (2013). Patients' sociodemographic and clinical data were extracted from archival files. BP measurements of all patients were obtained from ambulatory Holter (Schiller BR-102 plus PWA, Baar, Switzerland) recordings. According to Holter recordings, patients were divided into dipper and non-dipper. Routine blood test results studied before ambulatory Holter BP wore were used. The formula used to calculate body mass index (BMI) was weight divided by height squared. The NLR value, which is the primary outcome variable and was utilized to calculate the reliability evaluation (post-study power) of counts of individuals enrolled in the groups, was by the cross-sectional research design. NLR was 7.34±5.61 in individuals with the non-dipper, whereas it was 3.11±2.36 in individuals with the dipper. The post-study power was 99% based on the disparity in NLR values between the independent group averages. The post-study power was over 80% based on the differences in the secondary outcome variables MLR, RLR, and SII. The skilled and experienced people wore the ambulatory BP device (DMS 300-3A Holter Recorder). Blood measures were obtained every 15 minutes between 07:00 and 23:00, and every 20 minutes between 23:00 and 07:00. Using short time intervals, the period from 10:00 to 22:00 was designated as daytime, while the period from 24:00 to 6:00 was designated as nighttime. Non-dipper hypertension was defined as lowering the mean blood pressure by less than 10% or staying constant. Dipper hypertension was defined as lowering mean systolic and diastolic blood pressure readings by more than 10%. The whole blood count was calculated using an automated hematology analyzer manufactured by Sysmex Corporation (Kobe, Japan). Total leukocyte count and differentiation, hemoglobin, hematocrit, platelet levels, RDW, NLR, MLR, and RLR values were documented as blood parameters. Multiplying the number of platelets by the NLR yields the SII (Platelet x NLR). Additionally, CRP levels were measured utilizing a Mindray Chemistry Analyzer instrument (BS-2000M, China). IBM SPSS software was used for the analysis (version 24.0).

Statistical analysis

The mean standard deviation or median are utilized to represent initial continuous variables (interquartile range). The Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to determine the normality of the variable distribution. Frequencies and percentages were utilized to represent categorical variables. The chi-squared or Fisher's exact test was employed for categorical variables. The Student's t-test or Mann-Whitney U-test was used to evaluate continuous variables. Statistical significance was stated at 0.05 for all tests.

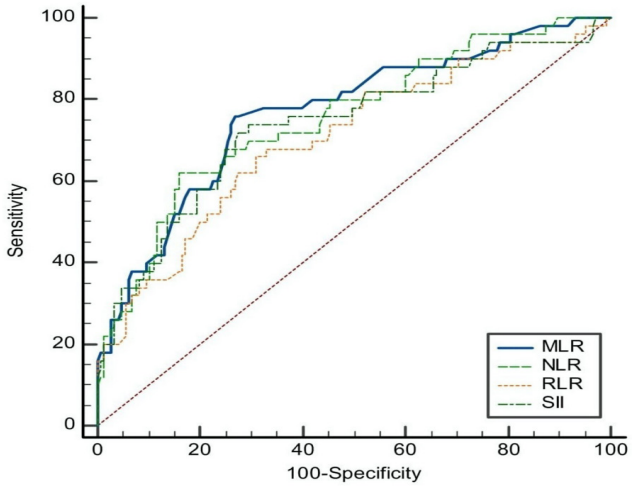

Figure 1. Comparison of the ROC curves for predicting dipper hypertension

RESULTS

A total of 197 patients, comprising 84 females (42.6%) and, 113 males (57.4%) with a median age of 62 (54-69) years, participated in the research. Individuals were classified into two groups: non-dipper (n=54) and dipper (n=143). The patient's clinical characteristics and laboratory results were expressed in Table 1. Age, FPG, CRP, WBC, NEU, LYM, MONO, RDW, NLR, MLR, RLR, and SII were higher in the non-dipper group ($p<0.05$). MLR, NLR, RLR, and SII were found to have the acceptable diagnostic capability in determining non-dipper hypertension (AUC: 0.70-0.76) (Figure 1, Table 2). When ROC

analysis was performed to determine the main similarities, it was found that there were no differences between inflammatory indicators (p>0.05). Put another way, we found that these biomarkers could be utilized interchangeably to predict hypertension in non-dippers (Table 3). When the odds ratios of putative variables were evaluated, it was found that increasing MLR (OR: 7.22; 95%CI: 3.52-14.78; p<0.001), NLR (OR: 8.63; 95%CI: 4.19-17.68; p<0.001), RLR (OR: 4.29; 95%CI: 2.18-8.54; p<0.001), and SII (OR: 6.31; 95%CI: 3.09-12.85; p<0.001) were independent predictors for non-dipper positivity (Table4).

Table 1. Clinical characteristics and laboratory tests of patients.

PARAMETERS	Total (n=197)		Dipper hypertension (n=143)		Non-dipper hypertension (n=54)		p-value*
	n	%	n	%	n	%	
Sex, female	84	42.6	58	40.6	25	46.3	0.43
Diabetes mellitus	86	43.6	62	43.3)	24	44.4	0.91
DL	79	40	55	38.8	24	44.4	0.48
Smoking	68	34.5	45	31.9	23	42.6	0.16
Age (years)	62 (54-69)		61 (53-66)		67 (57-74)		<0.001
BMI, (kg/m2)	31±4.5		31±4.4		30.8±4.9		0.54
FPG (mg/dL)	126.7±40.2		117.2±25.8		154.4±58.3		<0.001
Urea (mg/dL)	34 (29-39)		34 (28-39)		36 (29-49)		0.07
Creatinine (mg/dL)	0.85 (0.73-0.99)		0.83 (0.72-0.98)		0.87 (0.79-1.01)		0.11
Na (mmol/L)	139.14±2.96		139.13±2.98		139.14±2.89		0.98
K (mmol/L)	4.15±0.57		4.11±0.63		4.23±0.44		0.22
ALT (U/L)	20.59±10.51		19.8±9.63		22.4±12.5		0.09
AST (U/L)	21.76±8.95		21.21±8.34		21.24±10.19		0.15
LDL (mg/dl)	137±37		136±39		140±30		0.42
HDL (mg/dl)	39.8±8.4		40.1±8.3		38.6±9.3		0.24
CRP (mg/L)	3.86±3.89		3.21±2.35		5.75±4.96		0.02
WBC (103mcL)	9.82±3.16		9.21±2.51		11.42±2.71		0.001
HGB (g/L)	14.27±1.78		14.28±1.84		14.23±1.59		0.86
HCT (%)	42.33±4.41		42.43±4.48		42.12±4.23		0.56
NEU (103mcL)	6.96±3.25		6.06±2.45		9.59±3.76		<0.001
LYM (103mcL)	2.37±1.51		2.51±1.06		1.97±1.23		0.004
MONO (103mcL)	0.6±0.18		0.55±0.13		0.75±0.26		0.001
RDW (fL)	13.16±0.89		12.83±0.63		14.11±0.94		<0.001
PLT (103mcL)	258.22±72.86		258.38±70.5		257.74±80.06		0.96
NLR	4.29±3.79		3.11±2.36		7.34±5.61		<0.001
MLR	0.33±0.23		0.24±0.13		0.59±0.42		<0.001
RLR	7.38±5.01		6.28±3.08		10.57±7.57		<0.001
SII (PLT*NLR)	1108.19±989.8		779.8±641.53		2060.51±1350.99		<0.001
Systolic BP (mmHg)	110.64±12.50		108.82±12.58		123.48±18.32		<0.001
Diastolic BP (mmHg)	62.36±5.54		60.42±7.84		69.12±8.14		<0.001

* Student's t-test, Chi-Square test (p<0.005 significance). Values are presented as mean ± SD as appropriate. DL: Dyslipidemia, BMI: Body mass index, FPG: Fasting plasma glucose, Na: Sodium, K: Potassium, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TSH: Thyroid-stimulating hormone, fT3: free triiodothyronine, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CRP:C-reactive protein, WBC: White blood cell, HGB: Haemoglobin, HCT: Haematocrit,NEU: Neutrophil, LYM: Lymphocyte, MONO: Monocyte, RDW: Red Cell Distribution Width, PLT: Platelets, NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, RLR: RDW to lymphocyte ratio

Table 2. Diagnostic accuracy of inflammatory biomarkers to predict non-dipper hypertension withcut-off values.

	AUC	Cut-off	Sensitivity %	Specificity %	%95CI	P-value	PPV %	NPV %
MLR	0.76	>0.25	75	73.1	0.70-0.82	<0.001	49.2	88.9
NLR	0.75	>4.53	62.1	83.9	0.67-0.82	<0.001	57.3	85.6
RLR	0.70	>6.85	65	69	0.63-0.76	<0.001	42.3	84.5
SII	0.73	>831.39	72.4	72.6	0.66-0.77	<0.001	47.2	87.2

AUC: Area under the curve, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval, MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, SII: systemic immune inflammation index

Table 3. Pairwise comparison of ROC curves and difference between areas.

	Difference between areas	95% Confidence Interval	P-value
MLR-NLR	0.01	0.056-0.081	0.71
MLR-RLR	0.06	0.021-0.145	0.15
MLR-SII	0.03	0.048-0.105	0.46
NLR-RLR	0.05	0.013-0.112	0.13
NLR-SII	0.02	0.015-0.046	0.34
SII-RLR	0.03	0.042-0.108	0.38

MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, SII: systemic immune inflammation index

Table 4. Multiple regression analysis of inflammatory biomarkers associated with non-dipper hypertension.

	Odds ratio	95% CI	P-value
MLR	7.22	3.52-14.78	<0.001
NLR	8.63	4.19-17.68	<0.001
RLR	4.29	2.18-8.54	<0.001
SII	6.31	3.09-12.85	<0.001

CI: confidence interval, MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, SII: systemic immune inflammation index

DISCUSSION

This study's primary finding is that MLR, RLR, NLR, and SII could be utilized to predict non-dipper patterns in individuals with hypertension. The ambulatory Holter BP, which is most frequently used to determine non-dippers in individuals presenting with hypertension, has a lengthy research duration. In contrast, because they are easily accessible and calculable, inflammatory indices may aid in predicting non-dipper hypertension that can cause major adverse events.

According to previous studies, patients with non-dipper hypertension had a more extensive inflammatory reaction, increased serious end-organ damage, and higher cardiac morbidity and mortality (9). The non-dipper BP pattern had a detrimental impact on cardiovascular risk irrespectively of whether the blood pressure was within or beyond the normal range (10). The harmful impact of non-dipper hypertension could be attributed to endothelial damage. Non-dipper hypertension individuals had lower endothelial progenitor cell counts than dipper hypertension individuals in previous research, which is crucial for endothelial stability and arterial regeneration (11). Numerous chronic disorders, including renal disease, coronary artery disease, hypertension, diabetes, connective tissue disease, and cancer, are related to theinflammatory process (12,13,14). Inflammation is related to BP fluctuation and plays a crucial role in the pathophysiology of hypertension (15). Specifically, high BP fluctuation may promote vascular inflammation (16). In Tanase et al. study, inflammatory cytokines including IL-6, hs-CRP, and TNF-α were related to BP fluctuation (17). In addition, Isayeva et al found that the non-dipper pattern of BP was linked to raised inflammatory markers (18).

The neutrophil-lymphocyte ratio (NLR) is a comprehensive inflammatory indicator that evaluates neutrophils and lymphocytes and indicates a pro-inflammatory state. Liu et al. found that increased NLR levels significantly correlated with a raised risk of developing hypertension (19). In another study, NLR was a surrogate marker for hypertension (20). Belen et al. revealed that NLR values were higher in resistant hypertension than in controlled and normotensive patients (21). NLR was independently associated with LVH in hypertensive patients (22). WANG et al. showed that there was a relationship between NLR and artery stiffness in non-dipper hypertension (23). Likewise, epicardial fat tissue thickness and NLR were higher in newly diagnosed hypertension patients (24). In the Taiwan population, NLR was found as an index for hypertension in males and the elderly (25). In Sun et al. study, higher NLR was associated with in-hospital mortality in hypertensive patients aged over 80 years (26).

Monocytes are a component of innate immunity and mature into macrophage and dendritic cells to maintain homeostasis, especially when the presence of inflammation and infection (27). Monocytosis was employed as a marker for several inflammatory disorders such as being essential in the formation of atherosclerosis in coronary artery disease (28). MLR was identified as an independent risk factor for carotid stenosis in hypertensive patients with ischemic stroke (29). Zhang et al. revealed that MLR was a predictor of chronic kidney disease in hypertensive patients (30). In a study, MLR found a new marker to identify target organ damage in children with primary and secondary hypertension (31). Xiang et al. showed that high MLR values better predict all-cause mortality in resistant hypertensive patients undergoing hemodialysis (32). On the other hand, Yıldırım et al. reported that MLR was not a diagnostic marker of preeclamptic patients (33).

In hypertensive individuals, elevated angiotensin II values may stimulate erythrocyte proliferative progenitors (34). Variation in erythrocyte size in circulation is measured by RDW. RLR is a novel inflammatory marker derived from the ratio of the red cell distribution width to the number of lymphocytes. Tanindi et al. found that higher RDW levels were correlated with non-dipper hypertension (35). Buyukkaya et al. stated that RDW was elevated in non-dipping BP in normotensive and hypertensive patients (36). Sarıkaya et al. observed that RDW values were higher in hypertension individuals with AF (37). In a study, RDW was associated with a higher possibility of adverse outcomes of hypertension (38). On the other hand, Sun et al. emphasized that RDW was not accompanied by an increased risk of all-cause mortality (26).

SII is a novel inflammatory index that thoroughly depicts the equilibrium between the immunological and inflammatory states of the organism. It has been established that a high SII value is connected with adverse consequences in individuals with cardiovascular disease and cancer (39). Akyüz et al. stated that SII was independently higher in non-dipper hypertension individuals (40). Saylik et al. observed that SII values were elevated in newly diagnosed, untreated hypertensive individuals with pronounced daytime BP increases (41). In addition, Çırakoğlu et al. demonstrated a strong association between carotid intima-media thickness and SII in non-dipper hypertension (42). In our study, we found that SII had similar diagnostic power to other parameters.

Limitations of the Study

This was a retrospective investigation at a single center. The study population was small. ECG and echocardiography analyses were not examined. No particular inflammatory markers, such as CRP, IL-6, and TNF-α, were examined to evaluate and compare the accuracy and efficacy of parameters.

CONCLUSION

In this study, MLR, NLR, SII, and RLR had the acceptable diagnostic capability in identifying non-dipper hypertension patients. These biomarkers could be utilized interchangeably to predict hypertension in non-dippers. In this field, large-scale studies are needed to determine the diagnostic importance of hematologic inflammation markers and to determine the limit values in predicting the non-dipper character in hypertensive patients.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Gazi Yaşargil Training and Research Hospital Clinical / Human Research Ethics Committee for this study with date March 3rd, 202 and number 2023-371, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: SG, FK Design: SG, FK, Supervising: SG, FK, Financing and equipment: SG, FK, MZK, Data collection and entry: SG, FK, Analysis and interpretation: SG, FK, Literature search: SG Writing: SG, Critical review: SG, FK, MZK

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CASE REPORT
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Fluvoxamine Induced Priapism: an unusual case report

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Abstract

Antidepressants are usually associated with sexual side effects such as reduced sexual desire, erectile dysfunction or delayed ejaculation, impotence and orgasm problems. In the literature, there are reported cases including increased libido due to fluvoxamine use. But there aren't any case report about priapism due to fluvoxamine. In this case report, it was aimed to discuss the increase in libido and prolonged painful erection that occur during fluvoxamine treatment.
Keywords: Fluvoxamine, Antidepressant, Priapism

INTRODUCTION

Antidepressants have long been used in the treatment of many diseases such as depression, anxiety disorders, obsessive-compulsive disorder (OCD). Sexual dysfunction can be secondary to psychiatric diseases such as depression, but the use of antidepressants can cause sexual side effects. Such as decreased sexual desire, erectile dysfunction, ejaculation, impotence and orgasm problems (1).

In studies interested in sexual adverse effects of antidepressants, researchers are claimed that paroxetine has more sexual side effects and fluvoxamine has less sexual side effects than the other antidepressants (2, 3). Fluvoxamine is a selective serotonin re-uptake inhibitor (SSRI). SSRI group antidepressants like fluvoxamine have a strong inhibition effect on serotonin reuptake. Particularly through the stimulation at 5-HT2 receptors, it is thought to cause libido reduction owing to suppressing the release of dopamine from the nucleus accumbens in the mesolimbic pathway (4). An increase in dopaminergic activity in the nucleus accumbens which is one of the most important formations of the limbic system lead to increased sexual activity (5, 6).

Another side effect of antidepressants is priapism characterized by prolonged and painful erection. Although trazodone is most associated with prolonged erection and priapism; there are some case reports of priapism and prolonged erection due to the use of citalopram, paroxetine, fluoxetine and duloxetine in the literature (7-11).

CASE

Our case is 47 years old male patient. He is teacher, married for 18 years, has two children. He has obsessive thoughts about his wife for 3 years. He found out that his wife had another boyfriend before marriage. He had the idea that he had been betrayed for not having been told before his marriage. Because of this thought he was getting alienated from his wife. He spent most of the day to thinking about that he was being deceived and he was constantly asking to his wife about this.

Besides, there were complaints such as insomnia, unhappiness and malaise. He had sexual aversion. Even though he knew that his wife would not cheat on him, he felt like cheated.

In the psychiatric examination, the patient's clothing was attentive, meticulous; self-care was good; speech speed and pressure was normal. Cognitive functions were normal. The patient's mood was depressive and anxious. The thought process was neat and detailed. He had a full insight. He has never taken any psychiatric treatment. There wasn't any psychiatric disease in his family history. The patient did not report a history of additional medical disease. He was diagnosed with OCD and Fluvoxamine 200 mg / day was given gradually.

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In the interview after one month, he mentioned increased libido and the fact that despite ejaculation, there was painful erection over 6 hours. His complaints have begun after the use of fluvoxamine. Manic symptoms were questioned. Manic or hypomanic findings were not found. The patient was consulted to the urology outpatient clinic to investigate any organic pathology. Urologists did not detect active pathology to explain prolonged and painful erection. As a result, fluvoxamine was gradually stopped. Control was recommended one month later. In the control examination, he said that erection duration was decreased, there was no painful erection and the sexual desire was returned to normal.

DISCUSSION

SSRIs have been approved in the treatment of major depression in their first years of discovery. They are currently used in the treatment of many disorders such as anxiety disorders, panic disorder, social phobia, post-traumatic stress disorder, eating disorders, OCD and premenstrual dysphoric syndrome. Sexual side effects of antidepressants are important negative factors in treatment compliance and treatment continuity of patients. In many studies, different sexual side effects have been reported for antidepressants from different groups (13). These drugs may cause sexual side effects such as reduced sexual desire, erectile dysfunction, ejaculation, lubrication and orgasm problems (1, 12).

In a study involved 4557 depressive patients in France, the frequency of sexual problems reported by the patients was 35%. In the study, 989 (79%) of 1332 people using SSRIs had sexual side effects. The most common side effect was decreased libido (13). In Montejo Gonzales Angel L. et al., 's study involving 344 subjects using fluoxetine, paroxetine, sertraline, fluvoxamine; sexual dysfunction was occurred in 200 (58.14%) of the participants (2, 14).

Although antidepressants are frequently associated with sexual dysfunction; increased sexual behaviors such as prolonged erection, increased libido and priapism can be seen (4).

It was reported that fluvoxamine could rarely increase libido in a post-marketing study in France (15). It is assumed that fluvoxamine has alpha 2 adrenoreceptor antagonist. This antagonism directly and indirectly increases noradrenaline and dopaminergic activity (16). Therefore, the increase in libido associated with fluvoxamine may be related to this. Indeed, in some study, alpha 2 receptor antagonist agent yohimbine has been reported to treat sexual dysfunctions due to antidepressants (17). In addition, some researchers assert that fluvoxamine increases glutamate release in the prelimbic cortex by activating 5-HT3 and sigma receptors (18). This information may also be illustrative for neurobiological aspects of increased libido associated with fluvoxamine. The fact that the effect on 5-HT1, alpha 1 and 5-HT2C receptors minimal can be informative for this increased sexual arousal (4).

Another side effect was prolonged erection in our case. When we looked at the literature, we did not find any cases of prolonged erection due to fluvoxamine use. Although antidepressant most associated with prolonged erection is trazodone, the underlying mechanism is still unclear. Trazodone is thought to cause prolonged erection and priapism by antagonizing 5-HT2A / 5-HT2C and alpha 2 adrenergic receptors (4). Fluvoxamine induced prolonged erection may be associated with alpha receptor blockade. The interaction of fluvoxamine with 5-HT1A, 5-HT2C may help the erection by increasing parasympathetic tone, while inhibiting ejaculation by decreasing sympathetic tone (19). In the peripheral nervous system, it can extend the erection time through reducing sympathetic discharge and increasing parasympathetic discharge (19). Penile erection is activated by the stimulation of 5-HT1B, 5-HT1C, 5-HT1D receptors, whereas it is inhibited by 5-HT1A, 5-HT2 stimulation (20).

CONCLUSION

Although we have explained the possible mechanisms of fluvoxamine-induced increased libido and priapism, prospective large-sample studies are needed. The use of fluvoxamine should also be kept in mind in physicians encountering priapism.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: AT, GBA, Design: AT, GBA, Supervising: AT, GBA, Financing and equipment: AT, GBA, Data collection and entry: AT, GBA, Analysis and interpretation: AT, GBA, Literature search: AT, GBA, Writing: AT, GBA, Critical review: AT, GBA.

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