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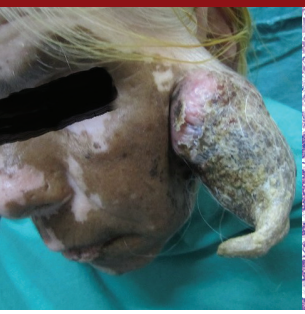
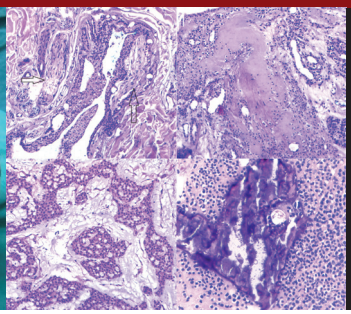


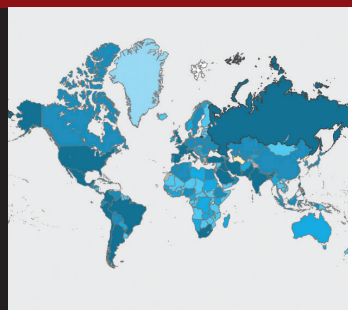
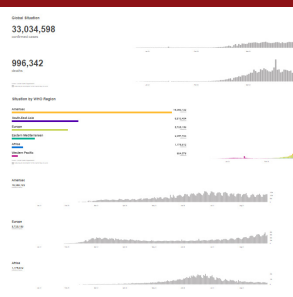

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Aims and Scope

Cyprus Journal of Medical Sciences (Cyprus J Med Sci) is the scientific, peer reviewed, open access international publication organ of Cyprus Turkish Medical Association. The journal is published three times a year, in April, August, and December. As of 2020, the journal has become a quarterly publication, publishing in March, June, September, and December. The journal's publication language is English.

The aim of the journal is to publish original research papers of the highest scientific and clinical value in all medical fields. Cyprus Journal of Medical Sciences also publishes reviews, rare case report and letters to the editors.

The target audience of the journal includes healthcare professionals physicians, and researchers who are interested or working in in all fields of medicine.

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

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Instruction to Authors

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

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3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Background/Aims, Material and Methods, Results and Conclusion). Please check Table I below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of five keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

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

Manuscript Types
Original Articles: This is the most important type of article since it provides new information based on original research. Acceptance of original papers will be

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based upon the originality and importance of the investigation. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. An original article can be signed by maximum 6 authors unless it is a multi-center study or that it required extensive labour. Please check Table I for the limitations for Original Articles.

Clinical Trials

Cyprus Journal of Medical Sciences adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below.

- Clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.
- To have their manuscript evaluated in the journal, author should register their research to a public registry at or before the time of first patient enrollment.
- Based on most up to date ICMJE recommendations, Cyprus Journal of Medical Sciences accepts public registries that include minimum acceptable 24-item trial registration dataset.
- Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.
- For further details, please check ICMJE Clinical Trial Policy at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Data Sharing

As of I January 2019, a data sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

- Whether individual deidentified participant data will be shared
- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Cyprus Journal of Medical Sciences;

- Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.
- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Clinical trial and data sharing policy of the journal will be valid for the articles submitted from I February 2020.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	35	6	5 or total of 10 images
Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

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Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Invited brief editorial comments on selected articles are published in The Cyprus Journal of Medical Sciences. Editorials should not be longer than 1000 words excluding references. Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The subheadings of the review articles should be planned by the authors. However, each review article should include an "Introduction" and a "Conclusion" section. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion with an unstructured abstract. Please check Table 1 for the limitations for Case Reports.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends
Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References
Both in-text citations and the references must be prepared according to the Vancouver style.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Yazıcı A. The efficacy of endoscopic ventilation tube insertion in pediatric populations. Cyprus J Med Sci 2019; 4(2): 73-6.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

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

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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

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Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIEID/cid.htm.

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Contents

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Original Article

DOI: 10.5152/cjms.2020.864

LGBT+ Individuals' Sexual and Mental Health: A Comparison with Hetereosexual Group

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Cite this article as: Boyacıoğlu NE, Dinç H, Özcan NK, Şahin AB. LGBT+ Individuals' Sexual and Mental Health: A Comparison with Hetereosexual Group. Cyprus J Med Sci 2020; 5(1): 189-95.

BACKGROUND/AIMS
Although lesbian, gay, bisexual, and transgender (LGBT+) individuals experience many sexual and mental health problems, these problems are neglected by health professionals. We designed this study to determine the sexual and mental health problems of LGBT+ individuals by conducting a comparison with heterosexual individuals.

MATERIAL and METHODS
This cross-sectional, descriptive, and comparative study design was conducted between August 2015 and October 2015; it involved 210 LGBT+ subjects and 226 heterosexual subjects. Data were collected using online surveys, including an information form (35 questions) and the Turkish adaptation of a standard General Health Questionnaire (GHQ-12 questions). The GSQ-12 is a screening device for identifying minor psychiatric disorders in the general population. Descriptive statistics, independent sample t-test, and Spearman and Pearson's correlation test were used for data analyses.

RESULTS
Compared to the control group subjects, more LGBT+ subjects indulged in sexual activities for money and/or drugs; in addition, the prevalence of sexually transmitted diseases (STDs), experiences of abuse, and sexual problems was higher in LGBT+ subjects. There was no difference between the groups in terms of mental health status.

CONCLUSION
While there was a difference in the sexual health parameters between the groups, there was no difference in their mental health status.

Keywords: LGBT, mental health, sexual health

INTRODUCTION

Lesbian, gay, bisexual, transgender, transsexual, queer, questioning, intersex, inter-gender, asexual, ally and beyond (LGBT+) is a term that encompasses all groups and identities defined as "sexual minorities" (1). For the most part of history, even in the definitions given by the scientific community, homosexuality was defined using negative terms, such as sexual identity disorder, illness, and perversion. The removal of homosexuality from the classification as a disease was performed in steps. In 1952, the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association described homosexuality as a sociopathic personality disorder, while in the DSM-II (1968), it was classified as a sexual deviation. With the effect of dissenting views rising in the 1970s, the homosexuality category left its place to the sexual orientation disorder in 1973 in the DSM-II and this category, in turn, left its place to the category of ego dystonic homosexuality category in 1980 in the DSM-III. Finally, in the DSM-III-R (1987), homosexuality was no longer defined as a mental disorder. However, there are still traces of such negative references in clinical practice (2, 3).

The historical process in the definition of transsexuality is similar to that of homosexuality. Initially, the definition of transsexuality was included in the DSM-III and evaluated in the DSM-IV in the category of sexual identity disorders. Finally,

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the word "disorder" was removed and redefined as "gender dysphoria" and separated from the paraphilias and sexual dysfunctions category. In time, psychiatry continues to make changes related to the definition of "sexual orientation" and "gender identity", still causing the individual to be stigmatized. In Turkey, in the diagnosis and identification of diseases, mental health specialists consider the DSM criteria (2, 3).

In the literature, the term LGBT is used instead of the term homosexuality. The reason for this is that the term homosexuality only brings sexuality to mind and disease diagnosis is perceived as categorization. Moreover, the term homosexuality was abandoned because it only included gay and lesbian individuals. Thus, the term "LGBT" was then used in Western societies (1).

Although not classified as having a disorder, LGBT+ individuals in Turkey are the target of prejudice and discrimination in many societies; they are ostracized and stigmatized by these societies. This situation causes sexual and psychological health problems in the LGBT+ individuals (4-6).

In our country, LGBT+ individuals had experiences similar to those worldwide. LGBT+ individuals started to form small groups outside the public dominion to come together with individuals going through the same experiences so that they could share problems and seek solutions. However, the process of organizing (or creating) a society in Turkey started only 120 years previously for LGBT+ individuals. They took the first step by becoming visible through the establishment of two associations in the metropolises of Turkey, Istanbul, and Ankara. Thereafter, LGBT+ associations were established in many other cities. Today, there are nine non-governmental organizations in Turkey established by LGBT+ individuals (6).

In most studies performed on LGBT+ individuals, the basis of the problems was stated to be discrimination, lack of social support, health inequalities, and minority stress arising from the fact that this group is neglected by health professionals (7-11).

The results of studies examining the sexual and mental health of LGBT+ individuals are varied. Some studies state that having a different sexual identity affects an individual's sexual and mental life negatively; while some state that the sexual and mental health of the group is no different from those of their heterosexual counterparts (9).

Few studies have assessed the needs and priorities of LGBT+ individuals, especially those regarding the provision of their health-related service needs. These research data are very important since they represent a study in Turkey that evaluated both the sexual and mental health and provides the opportunity to compare these data to those of heterosexual individuals. We believe that our results can bridge the knowledge gap on the subject, present a clear picture of the existing situation, and help establish regulations on the issue.

Main Points:

- These results give data on LGBT individuals' sexual health in Turkey.
- These results give data on LGBT individuals' mental health in Turkey.
- This data enables to compare sexual and mental health outcomes for LGBT individuals and heterosexual individuals.

This study aimed to determine the sexual and mental health problems of LGBT+ individuals by conducting a comparison with heterosexual individuals.

The following research questions were addressed by this study:

1. Is the adult LGBT+ population of Turkey more likely to experience sexual problems than the non-LGBT+ adult population?
2. Is the adult LGBT+ population of Turkey more likely to experience mental health problems than the non-LGBT+ adult population?

MATERIALS AND METHODS

Research Design

This cross-sectional, descriptive, and comparative study design was conducted from August 2015 to October 2015.

Participants

The sample included 210 LGBT+ and 226 heterosexual individuals. We did not use any sample calculation method to determine the sample because there are few associations operating in Turkey and only three of these associations share our work with its members. The average number of members of these associations is 600 (Istanbul LGBTI Solidarity Association: 50 members, Lambda Istanbul: 250 members and KaoS GL: 250 members).

As per the inclusion criteria, individuals aged >18 years who belonged to the LGBT+ community in Turkey, were able to understand questions about sexual and mental health, and could report her/his opinions were included. Those adults in personal and occupational mail groups in Turkey who did not identify themselves as LGBT+, were able to understand questions about sexual and mental health, and could report her/his opinions were included as controls.

Instruments

Data were collected using online self-reported questionnaires consisting of an information form (35 questions) and the Turkish version of the General Health Questionnaire-12 (GHQ-12) (12 questions). In the first part of the questionnaire, detailed information regarding the study aim and contact information of the researchers were provided.

Information Form

For both the LGBT+ and the control group, six questions regarding the socio-demographic information, three questions evaluating their habits (smoking, alcohol, substance), twenty questions regarding sexuality (sexual orientation, gender identity, masturbation, age of first sexual experience) and sexual health (sexually transmitted diseases [STD], condom use, sexual health problems, and help seeking behavior), and six questions regarding abuse (physical, emotional, economical, and sexual abuse, childhood physical and sexual abuse) were asked.

The responses were to be given by choosing from multiple choices.

The General Health Questionnaire (GHQ-12)

GSA was used as a first-step screening test in social studies to determine the mental state of individuals without any psychiatric or physical problems. The scale was also preferred in this study because of its short and comprehensible use in social studies. The Turkish validity and reliability study of the GHQ-12 was performed in 1996 by Kilic (12). It contained 12 questions in four fields, including depression, anxiety, obsessively observed behavior, and hypochondriasis. Each GHQ-12 item was formulated as a statement about symptoms experienced during "the last weeks" (rather than "recently" as in the original questionnaire), with four response options, six of which were positively phrased and six of which were negatively phrased. Each item was answered by choosing from among 4 choices, ranging from "less than usual (0 point)", "no more than usual (0 point)", "rather more than usual (1 point)", and "much more than usual (1 point)". We mainly used a bimodal scoring method, whereby "less than usual" and "no more than usual" were both worth zero points and "rather more than usual" and "much more than usual" were worth one 1 point each. Accordingly, the lowest possible score was 0, while the highest possible score was 12.

TABLE 1. Socio-demographic characteristics and habits of the subjects

	LGBT group (210) n (%)	Control group (226) n (%)	Chi-Square	P
Marital Status				
Married	13 (6.2)	69 (30.5)	46.70	0.001
Single	191 (91)	148 (65.5)		
Single (divorced, widowed)	6 (2.9)	7 (3.1)		
Education				
Primary	1 (0.5)	2 (0.9)	31.87	0.001
Secondary – high school	75 (35.8)	31 (13.7)		
University	134 (63.8)	193 (85.4)		
Status of employment				
Regular	75 (35.7)	137 (60.6)	27.29	0.001
Irregular	85 (40.5)	59 (26.1)		
Unemployed/student	50 (23.8)	30 (13.3)		
Smoking (during last month)				
Regular use	125 (59.5)	96 (42,5)	19.69	0.001
Sometimes	29 (13.8)	30 (13.3)		
Not use	56 (26.7)	100 (44.2)		
Drug use (during one year)				
Not use	149 (71)	197 (87.2)	17.57	0.001
Use	51 (29)	29 (22.8)		
Alcohol use				
Regular use	35 (16.7)	24 (10.6)	14.58	0.002
Sometimes	155 (73.8)	152 (67.3)		
Not use	20 (9.5)	50 (22.1)		

Those who scored <2 points were classified as having negative psychological health status, those who scored 2–3 points were classified as having mid-level psychological health status, and those scored >4 points were classified as having a highly positive psychological health status. The Cronbach alpha coefficient of the scale in the current study was 0.75.

Procedure

The questionnaire was prepared for the study that was planned as an online survey, and the announcement was made on the Web pages of a few associations where LGBT+ individuals were members as well as via in mail groups belonging to LGBT+ groups. For heterosexual individuals, the aim of the study was explained and announcements were made in certain personal and occupational mail groups to achieve participation through the snowball method.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc.; Chicago, IL, USA). In addition to descriptive statistics (mean, percentage, frequency), independent sample t-test and chi-square were used to compare the groups. Statistical significance was determined at $p \leq 0.05$.

Ethical Considerations

Ethical permission was obtained from the ethics board of the Medipol University before the study was initiated (Protocol Number: 10840098-604.01.01-E.1884). The study was carried out in accordance with the principles of the Helsinki Declaration, and approval was obtained at the beginning of the survey to enroll participants using the digital approach. Participants who were willing to participate in the study completed the questionnaires after providing consent.

RESULTS

Socio-Demographic and Other Characteristics

The average age of the LGBT+ individuals was 24.31 (SD=6.44), and the average age of the control group was 27.51 (SD=6.24). There was a significant difference in the age of the two groups ($t= 6.47$, $p<0.001$).

Among the LGBT+ individuals, 38.1% (n=80) stated their sexual orientation as bisexual, 59% (n=124) as homosexual, and 2.9% (n=6) as heterosexual; all the controls reported being heterosexual.

Among the LGBT+ individuals, 41% (n=80) stated their gender identity as male, 35.2% (n=74) as female, 6.7% (n=14) as trans male, and 3.3% (n=7) as trans female. Total 5.7% (n=12) stated that they did not feel a part of any gender, and 8.1% (n=17) did not respond to this question.

LGBT+ individuals were found to marry less, receive less education, work with less regularity (more unemployment); they used more tobacco, alcohol, and illicit drugs than heterosexual subjects (Table 1).

Characteristics Regarding Sexuality and Sexual Health

LGBT+ individuals were found to masturbate more, have more STDs, enter more sexual relations for money/drugs, and experience more sexual problems than the controls. In the matter of

taking professional help for sexual problems, no statistical differences were found between the groups (Table 2).

Total 10.4% of the LGBT+ individuals (n=22) and 19% (n=45) of the control group never had sexual relations. Among the LGBT+ individuals who previously had sexual relationships, 9% (n=19) had experienced gonorrhea, 8.1% (n=17) had genital warts, 1.4% (n=3) were HIV positive, and 1% (n=2) had hepatitis. Among heterosexual individuals, 4% (n=9) had genital warts, and 0.4% (n=1) experienced gonorrhea. Some of those who experienced STDs but did not define the type stated that they did not want to name the disease or did not know the name of the disease. The sexual problems encountered are listed in (Table 3); the most widely experienced problem in both the groups was that of interest and desire. The average age at the time of first sexual experience in the LGBT+ individuals was 16.31 years (SD=3.50) and that in the controls was 19.63 (SD=3.76). LGBT+ individuals had their first sexual experience earlier (t=8.54, p<0.001).

TABLE 2. Sexuality and sexual health-related characteristics

	LGBT group (210) n (%)	Control group (226) n (%)	Chi-Square	P
Masturbation				
Yes	192 (91.4)	169 (74.8)	66.73	0.001
No	18 (8.6)	57 (25.2)		
Ideas on masturbation				
Positive	151 (71.9)	167 (73.9)	1.61	0.445
Negative	16 (7.6)	22 (9.7)		
Neutral	43 (20.5)	37 (16.4)		
Use of condom				
Yes	68 (37.5)	73 (40.8)	10.42	0.015
No	55 (29.3)	68 (37.5)		
Sometimes	61 (33.2)	40 (21.7)		
Sexually transmitted diseases				
Yes	45 (24.4)	16 (8.6)	33.12	0.001
No	143 (75.6)	165 (91.4)		
Sex for money or drug				
Yes	18 (8.6)	3 (1.3)	300.7	0.001
No	192 (91.4)	223 (98.7)		
Problem of sexual life				
Yes	95 (50.5)	53 (29.4)	25.09	0.001
No	93 (49.5)	127 (80.6)		
Professional support for sexual problems				
Yes	5 (26.6)	5 (27.7)	5.02	0.081
No	183 (73.4)	175 (72.3)		

TABLE 3. Sexual problems

	LGBT group (188) n (%)	Control group (181) n (%)
Had no sexual dysfunction	89 (47.3)	126 (69.5)
Loss of libido	32 (17)	22 (12.1)
Difficulty in arousal	10 (5.3)	1 (0.6)
Vaginismus	1 (0.59	1 (0.6)
Pain during intercourse	2 (1.1)	3 (1.7)
Difficulty in orgasm	10 (5.3)	8 (4.4)
Difficulty keeping an erection	9 (4.8)	5 (2.8)
Premature/difficulty ejaculation	10 (5.3)	11 (6.1)
Avoiding due to the anal intercourse	11 (5.9)	0 (0)
Avoiding due to the STI	4 (2.2)	0 (0)
Other	10 (5.3)	4 (2.2)

STI: Sexually transmitted infections

Abuse Experience and General Health Status

The LGBT+ group was exposed to more physical and sexual abuse during childhood and to more physical and emotional

TABLE 4. Distribution of abuse and health aspects

	LGBT group (210) n (%)	Control group (226) n (%)	Chi-Square	p
Physical Violence				
Yes (partner)	31 (14.8)	20 (8.8)	19.37	0.001
Yes (except partner)	63 (30)	36 (15.9)		
No	116 (55.2)	170 (75.2)		
Psychological Violence				
Yes (partner)	41 (19.5)	34 (15)	57.06	0.001
Yes (except partner)	112 (53.3)	52 (23)		
No	57 (27.2)	140 (62)		
Economical Violence				
Yes (partner)	12 (5.7)	13 (5.8)	2.36	0.306
Yes (except partner)	37 (17.6)	28 (12.4)		
No	161 (76.7)	185 (81.8)		
Forced sex				
Yes (partner)	18 (8.5)	8 (3.5)	17.04	0.001
Yes (except partner)	22 (10.5)	6 (2.7)		
No	170 (81)	212 (93.8)		
Physical Abuse in childhood				
Yes (family)	40 (19)	22 (9.7)	16.72	0.001
Yes (except family)	40 (19)	24 (10.6)		
No	130 (62)	180 (79.7)		
Sexual Abuse in childhood				
Yes (family)	9 (4.3)	2 (0.9)	30.55	0.001
Yes (except family)	57 (27.1)	21 (9.3)		
No	144 (68.6)	203 (89.8)		
General Health Status				
Low	90 (42.9)	103 (45.6)	2.80	0.246
Mid	39 (18.6)	52 (23)		
High	81 (38.5)	71 (31.4)		

LGBT: lesbian, gay, bisexual, and transgender

abuse as adults; they were also forced more into sexual relationships than the controls. Although LGBT group had higher (negative psychological health) GSQ scores, there was no statistically significant difference between the groups (Table 4).

DISCUSSION

Discussion of the Socio-Demographic and Other Characteristics

Fewer LGBT+ individuals got married; they received less education, worked less regularly (more unemployment), and used more tobacco, alcohol, and illicit drugs than the controls. These differences in the demographic data were evaluated as results of the social problems experienced by LGBT+ individuals, such as stigmatization and discrimination.

In the present study, the use of tobacco and alcohol was more prevalent in LGBT individuals. The prevalence of smoking among LGBT+ individuals varies between 26.47% and 61% (13, 14), that of alcohol use varies between 65% and 84% (15, 16), and that of illicit drug use varies between 9.7% and 53.3% (17, 18). The reported rates vary in a very large range. The same wide perspective applies to the habits of heterosexual individuals. It is very difficult to make comparisons regarding the use of alcohol, tobacco, and drugs. Many factors, such as the age group, race, employment status, income level, and region of residence affect the alcohol, tobacco, and drug use; the multitude of influencing factors make the comparison challenging (13-15, 19, 20). However, the generally reported alcohol, tobacco, and drug use rates for LGBT+ individuals are higher than those for the population as a whole. This situation is believed to be a negative coping method used to deal with problems arising because of sexual orientation or gender identity differences.

Discussion of Characteristics Regarding Sexuality and Sexual Health

There is no direct relationship between STDs and sexual orientation-gender identity. Sexually transmitted infections may infect anyone, and the clinical symptoms do not vary as per the sexual orientation. Suggestions for avoiding STDs do not differ for LGBT+ individuals, and the determining factor in infection is the cause rather than the person. Risks are high for anyone who engages in unprotected sex (21). LGBT+ individuals experience more STDs, enter more sexual relations for money/drugs, and use condoms more frequently. These differences may be attributable to the inclusion of LGBT+ sex workers in our sample. These individuals are more aware about condom use after experiencing an STD. Studies show that the rate of HIV positivity is higher among LGBT+ individuals (18, 22-24). However, in these studies, risk factors, such as young age, homelessness, frequent changing of sexual partners, and predilection for risky behavior were more stressed than the factor of belonging to the LGBT+ community.

The prevalence of sexual dysfunction among LGBT+ groups was 42.5%–79% (7, 8, 25-27). When the high rates of childhood sexual abuse and STDs among LGBT+ individuals are considered, these rates are not surprising (8, 9). In a recent systematical review, studies examining sexual health problems in LGBT+ individuals were stated to be lacking and the existing studies are criticized for not including heterosexual control groups (9). Thus, the existing studies should be carefully interpreted.

Problems endemic to LGBT+ individuals who are exposed to discrimination in every field of life are unknown or are examined sufficiently by health care workers. Sexual problems are among the most important problems health issues that they experience. In the present study, the most widely experienced problem in both the groups was that of sexual interest and desire. This result is similar to that reported in the literature (8, 25-27).

Discussion of the Findings Regarding Abuse Experience and General Health Status

The finding that the LGBT+ group underwent more abuse of every kind in every phase of their lives (childhood, adulthood, marriage, work life, social life etc.) compared to the control group is consistent with several previous reports. For example, in a national study conducted by Andersen and Blosnich (28) in the USA, where the greatest numbers of studies on the subject have been conducted, LGBT+ individuals were found to be exposed to 60% more childhood abuse (physical, sexual, emotional) compared to heterosexual subjects. Similarly, in a study where the peer bullying experienced by heterosexual and LGBT+ individuals during childhood in Australia were compared, LGBT+ individuals were found to be exposed to more peer bullying (29).

A systematical review by Rothman et al. (30) in the USA that examined 75 studies found that lesbian and bisexual women were sexually attacked more often during adulthood and during their entire lifetime than heterosexual individuals (30). In another study on 1243 LGB individuals in the USA, sexual minorities were reportedly exposed to more abuse during both, childhood and adulthood (31). In addition, most studies that have investigated the abuse of LGBT individuals in the literature focus on spousal violence, with high reported abuse rates (32-35). In a study on LGBT+ individuals in Turkey, they were exposed to violence because of their sexual orientation; 23% were exposed to physical violence, 87% to social violence, and 50% to violence from people they did not know (36). According to another study conducted in Turkey, the rate of people exposed to familial violence because of their sexual orientation and/or gender identity was 6.6%, while the rate of those who received death threats from their families was 3.2% (4).

Both national and international data point to the seriousness of the issue. However, regardless of group, care should be given to comparing data on violence. Some studies focus on certain types of violence encountered by LGBT individuals (34, 35), while some only evaluate a certain group of LGBT+ individuals (such as only gay or lesbian people) (31-33). Some studies have focused on spouse violence, while others have evaluated social violence (29) or made evaluations pertaining to different time periods (lifelong, previous 5 years, and previous 1 year).

In this study, 45.6% LGBT individuals had poor general health status. However, no meaningful difference was found on comparison to the heterosexual group. In a study by Yalcinoglu and Onal (3) in Turkey on 210 homosexual/bisexual males, this rate was higher than that in our study (65.3%). Most studies on LGBT+ individuals have focused on the relationship between discrimination and negative health outcomes. Two different systematical reviews performed in this context have shown that discrimination is related to low mental health status (37, 38).

In many studies performed on LGBT+ individuals, the rates of many mental problems, such as depression and suicide (39-41); nicotine, alcohol, and substance use (40, 41); sexual activity under the influence of alcohol or substances (42); anxiety disorders (40); schizophrenia/psychotic disorders (40); eating disorders (43); and PTSD (44, 45) were higher than those in heterosexual individuals.

Although there is much evidence showing that LGBT+ individuals have worse health status than heterosexual individuals, the present results do not support this statement. Most of the people who participated in the study were related to LGBT+ associations and may have created a selection bias. LGBT+ individuals who faced negative attitudes from the society, such as discrimination and exclusion, have come together to raise their own awareness, become organized, and seek their rights. This may have led to better maintenance of their social and psychological health as compared to that of those who remained outside this process.

LGBT+ individuals who are at a distinct disadvantage compared to heterosexuals had lower marriage rates, received less education, worked less regularly (higher unemployment rate), and used more tobacco, alcohol, and illicit drugs than heterosexual individuals. With regard to sexual health, LGBT+ individuals experienced more STDs, entered more sexual relations for money/drugs, encountered more sexual problems, and had higher exposure to more abuse during childhood and adulthood; however, their health status was not inferior to that of heterosexual individuals despite the above-mentioned negative aspects. Many previous studies have reported poorer health status of LGBT individuals, and the contradictory results of our study are believed to be attributed to the fact that our sample comprised LGBT+ individuals who were receiving support from civil society organizations formed to defend their rights.

Clinical Implication

This study may raise awareness on the questioning of the widespread heterosexist approach that accepts heterosexuality as the only acceptable, healthy, and right sexual orientation, with LGBT+ groups being one of the disadvantaged groups with regard to health. It can also remove barriers to healthcare professionals in offering sexual and mental health care without prejudice and objective service to LGBT individuals.

Study Limitations

The current study presents some limitations; therefore, the results should be interpreted cautiously. A Web-based survey was used for sample selection; consequently, only volunteers with internet access were able to participate. Sexual orientation minority status was based on self-identified sexual orientation only.

The sexual function disorders of the participants were determined via self-reporting; this may have resulted in over reporting. The mental health of the participants was determined through a valid and reliable scale; however, no evaluation was performed by a clinician.

In the study, the LGBT+ community individuals were evaluated as a group. Each letter in the abbreviation represents a different population; therefore, care should be taken while interpreting the study results. A significant difference between the groups in terms of age is another limitation of the study.

Ethics Committee Approval Ethical permission was obtained from Medipol University The Ethics Board before the study began (Protocol Number: 10840098-604.01.01-E.1884).

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

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Original Article

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Configuration of Palliative Care Clinics and Integration with Home Health Care Services: Current Practice in Turkey

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BACKGROUND/AIMS
The establishment of palliative care clinics (PCCs) and the integration between PCCs and home health care are important for both patient comfort and disease-related cost reduction. We aimed to analyze PCC distribution and structure of state hospitals along with human resources, and to evaluate the integration of PCCs with home health care services in Turkey.

MATERIAL and METHODS
Data of PCCs started between January 2015 and February 2017 were analyzed in this study with the help of data obtained from the Turkish Ministry of Health.

RESULTS
PCCs are available in 28.9% of state hospitals active in Turkey. Of the total 2957 staff working in PCCs, 77.6% are health care professionals, with 9.9% being doctors. Home health care service (HHCS) units are available in 76.3% of hospitals with PCCs. Service was offered to 48,953 patients in PCCs, 5.7% of whom were transferred to HHCS in an integrational manner.

CONCLUSION
Integration between PCCs and HHCS remains at an inadequate level. We believe that the benefits of integration should be observed by patients, relatives, and health personnel, thereby increasing awareness and accelerating integration. In addition, we believe that hospital information management systems can be used for this purpose and software programs can be developed to accelerate integration between these 2 units.

Keywords: Coordination, home health care, health professionals, integration, palliative care

INTRODUCTION

Palliative care is the comprehensive and integrated care of patients and their families who are facing problems related to life-threatening diseases. It used to be a care philosophy of approach organized and structured at a high level with multidisciplinary health care providers (1). In palliative care units, symptom control is targetted rather than treating the primary disease to enhance the patient's quality of life. In addition to the symptom control of the primary disease, the physical, social, psychological, and moral requirements of the patients are focused

The need for palliative care has increased worldwide owing to prolonged life expectancies and an increasing aging population, as well as an increase in the frequency of noninfectious diseases and cancer. Approximately 40 million people need palliative care annually (2). According to estimations, worldwide, 377 of 100,000 individuals older than the age of 15 years and 63 100,000 individuals younger than 15 years will need palliative care at the end of their life (1). However, only 14% of the people worldwide in need of palliative care are able to obtain it (2).

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In 2011, it was stated that advanced integration of palliative care services with the primary services was available in only 20 (8.5%) out of 234 countries. Only limited and insolated palliative care services are available in 75 countries (31.6%), and no palliative care services are available in 98 countries (42%) (3). In 2011, 136 (58%) out of 234 countries implemented palliative care services in 1 or more hospitals (1). To integrate evidence-based, cost effective, and equitable palliative care services to health services at every level, palliative care policies to support extensive consolidation of health systems have to be developed, empowered, and applied (4).

At the beginning of the 1990s, it was noticed that there was a need for a palliative care program in Turkey, but it could not go beyond providing pain management to cancer patients. A 5-year national cancer control program, including palliative care, was declared in 2009, and palliative care was acknowledged as medical discipline through the "Palya Turk" project in 2010 (5). The legislation for the opening of palliative care clinics (PCCs) in Turkey was issued in 2014. PCC bed capacity was planned to be half of the bed capacity of the intensive care unit available in the same hospital, with such planning limited to the state hospitals (6). Palliative care and home health care services (HHCS) became integrated services, and the cooperation of these 2 disciplines was essential. After completing treatment of the patients in PCCs, their follow-up period is managed at home by HHCS units for their medical, psychological, and social needs to provide the maximum possibility of achievement of better quality of life. Legislative studies have been made for this goal and HHCSs, which began in 2011 has was integrated with PCC in 2015 (6).

The aims of the current study were to analyze PCC distribution and locations within the structure of state hospitals in Turkey, along with human resources, and to evaluate the integration of PCCs with HHCSs.

MATERIAL and METHODS

Data of PCCs between January 2015 and February 2017 were analyzed in this study. Written consent of the T.R. Ministry of Health was provided to acquire and use data for this study. Therefore, ethics committee approval was not required. The appropriate forms have been officially submitted to all hospitals linked to the Ministry that have registered PCCs within their structure. The roles of the hospitals having PCCs, the number of beds in these clinics, the number of qualitative beds, the number of health care professionals, and the integration of the PCC with HHCSs were questioned using the prepared form. Forms were completed by the appropriate individuals in charge. The database from the Ministry and all acquired data were compared to determine correctitude of the information. After evaluation, any inconsistencies were eliminated.

Main Points:

- PCCs are available in 28.9% of the hospitals in Turkey, and 76.3% of the hospitals with a PCC has an HHCS unit. There are 2429 beds in PCCs, 63.3% of which are qualitative.
- Integration between PCCs and HHCS remains at an inadequate level.
- The benefits of integration should be observed by patients, relatives, and health personnel, thereby increasing awareness and accelerating integration.
- Hospital information management systems can be used for the purpose of integration and software programs can be developed to accelerate integration between PCCs and HHCS units. Future studies are also needed in order to analyze the effect of integration between PCCs and HHCSs on morbidity and mortality.

Statistical Analysis

SPSS software (version 24.0; IBM SPSS Corp.; Armonk, NY, USA) was used for descriptive statistical analysis of the data.

Definitions

Role of the Hospital and Classification

The role of the state hospitals and their classification are defined with a circular (7). According to this classification:

(1) Group A-I General Hospitals: Treatment institutions with general beds that are authorized to provide training in a minimum of 5 medical specialities completed training personnel are grouped accordingly, and where third level treatment and rehabilitation service are given, training and research activities are conducted, and specialists are trained and fellowships are given.

(2) Group A-II General Hospitals: General hospitals that do not have active training and research in the provinces, with a health center or the province linked to those centers.

(3) Group B General Hospitals: General hospitals thoseare located in the provinces, other than the A-I and A-II hospitals, which are located or in the improved districts.

(4) Group C General Hospitals: Hospitals that are active in the improved districts or the districts linked to the centers improved within the content of health region planning regarding health services offered, with specialists providing care in the 4 main specialities (internal diseases, general surgery, gynecology and obstetrics, and pediatrics). In addition, specialists are available at least in 2 other specialties and with at least a first step intensive care unit and first level emergency service.

(5) Group D General Hospitals: Hospitals having at least 1 specialist, including a primary care physician (family doctor) and active in the districts linked to the improved districts and those having at least 25 patient beds.

(6) Group E General Hospitals: Hospitals having fewer than 25 patient beds and those where diagnosis and treatment services are offered along with health services at the first step given in the same structure.

Qualitative Bed

Defines the bed where a bath and toilet are located inside the room, and a television, telephone, dining table, and companion sofa bed are provided.

RESULTS

According to our study, among all government hospitals (8) 27% of PCCs are located in Group B hospitals, 24% in Group C hospitals, 21% in Group A-II hospitals, and 19% in Group A-I hospitals. PCCs are not available in Group E hospitals. PCCs are available in 28.9% of state hospitals active countrywide (Table 1). There are 2429 patient beds in PCCs countrywide, and 63.3% of the beds in PCCs are qualitative (Table 2). There are 2957 total staff working in PCCs, 77.6% of whom are health care professionals. Of these, 9.9% are doctors (Table 3). HHCS units are available in 76.3% (n=152) of the hospitals with PCCs (Table 4). This service is offered to 48,953 patients in PCCs, and 5.7% (n=2837) of these patients are transferred to HHCSs (Table 5).

DISCUSSION

PCCs are available in 28.9% of the hospitals in Turkey, and 76.3% of the hospitals with a PCC has an HHCS unit. There are 2429 beds in PCCs, 63.3% of which are qualitative. This constitutes 1.8% of all public beds A total of 5.7% of patients are transferred to HHCSs from PCCs. There are 0.61 nurses per palliative care bed and 1.14 doctors per PCC.

TABLE 1. Distribution of State Hospitals and Palliative Care Clinics in 2017 According to the Role of the Hospitals

Hospital Role	Hospital (*), n	Palliative Care Clinic, n (%)	Rate of Availability of Palliative Care Clinic Within the Structure, %
A1	86	38 (19%)	44.2%
A2	107	41 (21%)	38.3%
B	123	54 (27%)	43.9%
C	163	48 (24%)	29.4%
D	123	18 (9%)	14.6%
E	86	0	0
Total	688	199	28.9%

*: (8)

TABLE 2. Bed and Qualitative Bed Situation in Palliative Care Clinics

	Number of Recently Activated PCCs, n	Number of beds in PCCs, n	Number of Qualitative Beds and Rate, n (%)
2015	98	1.294	757 (58.5%)
2016	79	865	559 (64.6%)
2017 (January-February)	22	270	222 (82.2%)
Total	199	2.429	1.538 (63.3%)

In our study, the number of beds in PCCs was increased by 1.87, whereas the number of qualitative beds was increased by 2.03. Although PCCs are generally available in Group A-I, A-II, and B hospitals located in the province centers, they are rapidly expanding to Group C and D hospitals located in districts as well. Policies of the Ministry are considered to be effective in light of such rapid expansion and increases. The number of beds recommended for hospice and palliative care in Europe is 80 to 100 per 1,000,000 population (9, 10).

According to our data, 30.4 beds are currently serving each 1,000,000 population countrywide, which is far below the recommendation. PCCs are available in 28.9% of the state hospitals, a rate that has to be increased. In addition, we believe that the target may come closer together if private and university hospitals were included in the planning. A total of 2957 personnel currently work in PCCs countrywide, of whom 77.6% are health personnel. Of these, 9.9% are doctors and 65% are nurses. The recommendation according to international standards is 1 nurse per bed (9, 10). Currently in Turkey, our study found the number of nurses per bed is 0.61, which is quite low.

The integration of palliative care with home care and having transfers made in harmony will assure that patients receive the proper health and care service easily (1, 11). Such integration and harmony would also provide support to the health economy through the economical use of resources (6). According to our study, 76.3% of PCCs countrywide are integrated with HHCs. However, the rate of patients transferred to HHCs is very low at 5.7%. Factors causing this situation must be examined first and the integration setup should be reevaluated. PCCs receive most of their patients from intensive care clinics. Along with an increase in the number of beds in PCCs, the tendency for increase for beds in intensive care units, especially in state hospitals, is expected to drop. However, this expectation was not reflected as of 2017 (Figure 1). It is believed that an increase in the number of intensive care beds continues, as the palliative care field had just started in 2015 and needs in this field are very high. Studies conducted in this field are necessary, as PCCs will affect occupation rates and the number of admission dates of intensive care beds.

Implementation of palliative care services have an important role, especially in the management of end-of-life patients. As HHCs run by state hospitals attached to the Ministry of Health cover the entire population free of charge, this is an important development in the field of social medicine. Implementations aligned with health policies are rapidly extended countrywide. Although both units are localized in the same hospital, integration between PCCs and HHCSs remains at an inadequate level.

TABLE 3. Number of the Health Care Professionals working in Palliative Care Clinics in Turkey, February 2017

Healthcare Professionals						
Medical Doctor	**Nurse**	**Psychologist**	**Social Worker**	**Physiotherapist**	**Dietician**	**Total**
228	1,492	149	127	150	150	2,296
Other Personnel						
Spiritual Care Staff	**Clinical Support**		**Other**			
67	91		503			661

TABLE 4. Integration of Palliative Care Clinics with Home Health Care Services

	Recently Activated PCCs, n	Hospitals with PCC and HHCS Units, n (%)
2015	98	75 (76.5%)
2016	79	58 (73.4%)
2017 (January-February)	22	19 (86.3%)
Total	199	152 (76.3%)

HHCS, home health care services; PCC, palliative care clinics.

TABLE 5. Rate of the Patients Transferred to Home Health Care Services from Palliative Care Clinics in Turkey

	Number of Patients (n)	Number and Rate of Patients Transferred to HHCS Units, n (%)
2015	8,815	452 (5.1%)
2016	31,958	1,952 (5.9%)
2017 (January-February)	8,180	433 (5.2%)
Total	48,953	2,837 (5.7%)

HHCS, home health care services

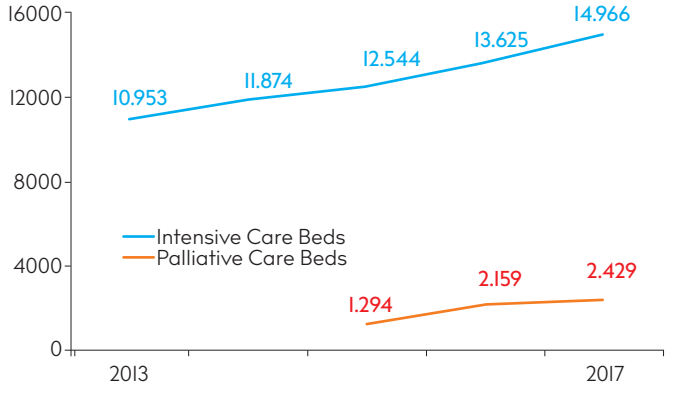

FIGURE 1. Increase Tendency of the Number of Intensive Care Beds and Palliative Care Beds

We believe that benefits of such integration would be observed by the patients, their relatives, and health care professionals, increasing awareness and accelerating integration in long-term implementations. If short-term positive feedback is expected concerning the satisfactory quantitative interaction between PCCs and HHCSs, some applications are provided and should be developed. These applications must be independent of demand of patients and reference of health care professionals. We believe hospital information management systems can be used for this purpose and that software programs can be developed to help accelerate the integration between these two units. We also believe that there is a need for future studies analyzing the effect of integration between PCCs and HHCSs on morbidity and mortality.

Ethics Committee Approval: Written consent of the T.R. Ministry of Health was provided to acquire and use data for this study, therefore local ethics committee approval was not recieved. Written consent was obtained from the Ministry of Health by official correspondence (number 32693313–622.03)

Informed Consent: Written consent was obtained from the Ministry of Health by official correspondence.

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Original Article

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Is Autonomic Function Impaired in Patients with Pseudoexfoliation Syndrome?

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BACKGROUND/AIMS
Pseudoexfoliative syndrome is an aging disease that progresses primarily with the accumulation of fibrillary materials in the eye and in some organs other than the eye, particularly in the heart. Accumulation of this substance in the heart is closely related to morbidity and mortality. This study aimed to evaluate the heart rate recovery index (HRR-I), which is a predictor of autonomic dysfunction.

MATERIAL and METHODS
A total of 253 patients diagnosed with PEX in the ophthalmology outpatient clinic between March 2018 and May 2019 were included in the study. The control group consisted of 238 participants who were diagnosed as non-PEX and had no disease. After routine physical and blood examinations, both groups underwent routine electrocardiograms, transthoracic echocardiograms, and treadmill exercise test (TET). Heart rates of the study and control groups were recorded at the beginning, peak exercise, first, second, and third recovery levels of TET. Heart rate recovery index (HRR-I) values of the first, second, and third minutes were subtracted from the peak level HR values and compared.

RESULTS
In the study group, first-minute HRR-I value (20.93±5.93 ms vs. 32.11±5.43 ms, t=21.74 and p<0.01), second-minute HRR-I value (38.83±6.99 ms vs. 51.65±7.12 ms, t=20.12 and p<0.01), and third-minute HRR-I value (62.76±9.56 ms vs. 77.21±12.22 ms, t=14.64 and p<0.01) were found to be lower than in the other group.

CONCLUSION
There were significantly lower HRR-I values at every recovery stage of the TET. These findings revealed that the autonomic balance is impaired in patients with PEX and that the risk of sudden cardiac death increases.

Keywords: Risk, death, sudden, cardiac, exfoliation syndrome

INTRODUCTION

The pseudoexfoliative syndrome (PEX) can manifest itself by the accumulation of extracellular fibrillary material in many organs such as the eye and heart. PEX can be easily identified by biomicroscopic examination. White-gray deposition on the pupil edge and in front of the lens is sufficient for diagnosis (1). The substance accumulating in the heart is a risk factor for heart disease and sudden cardiac death. Cardiovascular diseases such as myocardial infarction, arterial hypertension, abdominal aortic aneurysm, heart failure, and coronary artery disease have been shown to be associated with PEX (2). Decreased cardiovascular functions are responsible for most of the mortality and morbidity in PEX patients (3). The incidence of PEX in patients with coronary artery disease and the incidence of atherosclerotic heart disease in patients with PEX have been shown to be higher than in the general population (4). Besides, atherosclerotic heart disease in PEX patients who underwent cataract surgery was again detected at a higher incidence than in the general population (5).

Although HRR-I is a marker that directly reveals the autonomic nervous system functions and is also a reliable predictor of cardiovascular (CV) mortality and morbidity, it is not routinely evaluated in daily clinical practice. HRR-I has been closely associated with morbidity and mortality in CV diseases (6, 7). The autonomic nervous system is one of the most important control mechanisms governing CV functions; therefore, a deterioration in the autonomic nervous system may lead

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to increased CV morbidity and mortality (8, 9). HRR-I is a very important predictor of the effects of vagal activity on the heart, and directly demonstrates the vagal activity (10, 11). In the treadmill exercise test (TET), HRR-I indicates the rate of decrease from the peak level in the heart rate of the cooling phase. HRR-I values can be obtained by extracting the cooling phase heart rates from the HR at the peak level of the TET (12).

The decrease in parasympathetic system activity and an increase in sympathetic system activity are associated with direct ventricular arrhythmias regardless of the disease or even in healthy individuals. As known, sympathetic activity increases and parasympathetic activity decreases during the exercise. Therefore, most arrhythmias and sudden cardiac deaths can occur immediately after severe exercise (13). PEX is directly proportional to age (14). SCD occurs at a higher rate than the subgroup over the age of 35 years, and this occurs after severe exercises (15). Although there was no underlying CV disease in PEX patients, there was a higher incidence of arrhythmias than in the general population. This may indicate that vagal activity may be reduced and sympathetic activity may be increased relatively (16).

Our study aimed to compare the effect of stress testing on HRR-I values in PEX patients and to compare this predictor in the exercise test with a similar control group matched for age and sex.

MATERIALS and METHODS

Study Design

Patients were diagnosed with PEX by biomicroscopy, and by the presence of a white-gray extracellular fibrillary material on the pupil edge or in the anterior capsule and were included as the study group. The control group consisted of patients diagnosed as non-PEX in the ophthalmology outpatient clinic.

Study Population

A total of 253 patients with PEX (199 males, 78.65% and 54 females, 21.35%) were included in the study. The mean age of the study group was 67.37±12.63 years. There was no statistically significant difference between the sex ratio and mean age of the study and control groups. The control group consisted of two hundred eighty-eight (186 males, 78.15% and 42 females, 21.85%) patients who were diagnosed as non-PEX by biomicroscopy in the ophthalmology outpatients clinic. The control group had a mean age of 66.38±11.93 years. Exclusion criteria included having atherosclerotic heart disease and those receiving treatment for any reason; having hypertension or diabetes mellitus; deterioration of the liver, kidney, or thyroid functions in routine blood tests;s having electrolyte disturbances; previously diagnosed with chronic pulmonary obstructive disease and having bronchodilator medication; having anemia; having a systemic disease that affect the CV system; having hypertension and antihypertensive medication; having a history of coronary artery disease, having a body mass index (BMI) over 30 kg/m^2, having a positive effort test, which indicates significant atherosclerotic heart illness; smoking; having a diagnosis of atrial fibrillation or having AF rhythm in superficial electrocardiograms; and patients with orthopedic disorders who were unable to perform TET.

Main Points:

- Pseudoexfoliative syndrome is a disease of old age as it is known.
- With the increasing age, it is expected that autonomic functions deteriorate against the vagal system.
- Advances against the vagal system and in favor of the sympathetic system mean increased cardiovascular mortality.
- Heart rate recovery index is a predictor of parasympathetic activity.
- By using this predictor, high-risk pseudoexfoliative syndrome patients will be selected with a very easy and inexpensive method.

Treadmill Exercise Test

In both groups, after the physical examination, routine blood tests, and routine transthoracic echocardiograms (TTE) and electrocardiograms (ECG) were performed, the TET was performed according to the Bruce Protocol (17). The speed of ECG recordings was at 25 mm/sec and the amplitude of th ECG recordings was at 10 mm/mV. The ECG recordings were taken as basal, peak exercise level, and recovery phases of the TET. HRR-I values were obtained by extracting the HR values of the recovery phases from the peak HR value.

Ethical Approval

All the procedures performed in this study involving human participants were in accordance with the ethical standards of the Turkey Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written permission was obtained from Sincan State Hospital Management Committee (26.08. 2019/22568850-929). Before the study, written informed consent was obtained from all the participants.

Statistical Analysis

SPSS software (Version 20; IBM SPSS Corp.; Armonk, NY, USA) 20.0 was used for the collection and analysis of the data. Measurements were expressed as mean ± standard deviation. Analyzes were performed using the t-test. To compare the values of the two different groups, and to compare the different values of the same group, T-Test Calculator for Independent Two Means and T-Test Calculator for Depended Means were used, respectively. The Z test calculator was used to compare the two population proportions. For correlation involving two values of the same group, the Pearson Correlation Coefficient Calculator was used. For all tests with $p<0.05$, the differences were considered statistically significant.

RESULTS

There were no differences in both groups in terms of socio-demographic findings and baseline clinical findings (Table I)

Considering the BHR, there was no difference in both groups. In the study group, HRs of all the recovery phases were significantly higher than in the control group. Considering the HRR-I values, there were statistically significant differences between the study and control groups (Table 2). This finding suggests that the autonomic function was impaired much more in the study group than in the control group.

TABLE I. Socio-demographic characteristics and basal clinical findings of the Study and Control Groups

Variables	Study Group	Control Group	T or Z-value	p
Age, years	61.72±4.23	61.86±3.24	0.41	0.68
Male, %	71.46	71.62	0.02	0.96
Female, %	28.54	28.38	0.02	0.96
BMI, kg/m^2	26.46±2.69	26.94±2.44	1.63	0.10
Basal SBP, mm Hg	122.34±12.74	121.94±12.53	0.35	0.72
Basal DBP, mm Hg	77.47±8.52	76.38±7.84	1.47	0.14
Basal HR, beat/mn	77.83±6.32	77.32±5.35	0.96	0.33
LV Mass, gram	175.68±32.47	177.61±29.73	-0.68	0.49
Total Cholesterol, mg/dL	168.42±41.57	171.43±38.54	-0.83	0.40
LDL, mg/dL	102.58±22.48	105.82±19.62	-1.69	0.09
Triglycerides, mg/dL	165.38±23.68	167.16±21.84	-0.86	0.38
Hemoglobin, gr/dL	14.63±2.21	14.34±2.52	1.35	0.17
Calcium, mg/dL	9.41±1.01	9.33±0.94	0.90	0.36
Sodium, mEq/L	141.73±2.64	141.93±1.99	-0.94	0.34
Potassium, mEq/L	4.02±0.58	4.12±0.73	-1.68	0.09
Magnesium, mg/dL	1.94±0.26	1.95±0.33	0.37	0.70

Abbr: BMI; Body Mass Index, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, HR; Heart Rate, LV; Left Ventricle

TABLE 2. The comparison of TET values of the study and control groups

Variables	Study Group	Control Group	T-value	p
BHR, b/mn	77.83±4.23	77.32±5.35	1.17	0.24
PHR, b/mn	154.25±6.39	158.88±6.11	8.19	<0.01
First-minute recovery HR, b/mn	133.32±6.31	126.77±6.83	11.04	<0.01
Second-minute recovery HR, b/mn	115.37±7.13	107.22±4.98	14.59	<0.01
Third-minute recovery HR, b/mn	91.48±7.42	76.68±9.37	19.46	<0.01
HRR-I in the first minute, b/mn	20.93+/-5.91	32.11+/-5.43	-21.78	<0.01
HRR-I in the second minute, b/mn	38.88+/-6.99	51.65+/-7.12	-20.05	<0.01
HRR-I in the third minute, b/mn	62.76+/-7.42	77.21+/-9.22	-19.18	<0.01

Abbr: BHR; Basal Heart Rate, PHR; Peak Heart Rate, HR; Heart Rate, HRR-I; Heart Rate Recovery Index

In the study group, the third-minute HR was significantly higher than the basal HR. Besides, in the control group, the third-minute recovery HR was similar to the basal HR. (Table 3). This also suggests that the autonomic functions were impaired much more in the study group than in the control group.

Considering both age and HR, there was a weak, but statistically significant positive correlation in both groups. There were also moderate positive correlations between HRR-I values at each recovery stage of the effort test in both groups (Table 4).

TABLE 3. The comparison of recovery HR values of the study and control groups

Study Group (n=253)		
Variable I	**Variable 2**	**p**
Basal HR	First-minute HR	<0.01
Basal HR	Second-minute HR	<0.01
Basal HR	Third-minute HR	<0.01
Control Group (n=238)		
Basal HR	First-minute HR	<0.01
Basal HR	Second-minute HR	<0.01
Basal HR	Third-minute HR	0.36

Abbr: HR; Heart Rate

TABLE 4. The correlations of the study and control groups

Variable I	Variable 2	Correlation	F-value	p
The Study Group				
Age	HR	Weak Positive	0.22	<0.01
Age	HRR-I in Ist minute	Moderate Positive	0.72	<0.01
Age	HRR-I in 2nd minute	Moderate Positive	0.69	<0.01
Age	HRR-I in 3rd minute	Moderate Positive	0.66	<0.01
The Control Group				
Age	HRR-I in Ist minute	Moderate Positive	0.67	<0.01
Age	HRR-I in 2nd minute	Moderate Positive	0.57	<0.01
Age	HRR-I in 3rd minute	Moderate Positive	0.51	<0.01
Age	HR	Weak Positive	0.28	<0.01

Abbr: HR; Heart Rate, HRR-I; Heart Rate Recovery Index

DISCUSSION

This study had found three interesting findings. The first of these findings was that the third-minute HR value was significantly higher than the basal HR of the study group. In addition, in the control group, there was a similarity between the basal HR and the third-minute recovery HR. The second finding was that there was a statistically significant difference in terms of all the HRR-I values of the recovery phases between both groups. Besides, there were moderate positive correlations between the HRR-I values and the ages of both groups in each recovery stage.

The results of our study showed that the vagal system is less functional in PEX patients than in the non-PEX patients. The delay in HRR-I is directly associated with the decreased vagal activity, and the reduced vagal activity is also characterized by the increased risk of SCD (18).

SCD generally results in patients with structural heart disease. In particular, it occurs immediately after heavy exercises (19). It is known that sympathetic activity increases with an exercise test; the vagal activity is at the recovery phase after the exercise test. It has been documented that an elevated sympathetic response or a reduced vagal response immediately precedes the onset of atrial and ventricular arrhythmias as well as sudden cardiac death (20). Furthermore, delayed HRR was found to be one of the indirect predictors of decreased vagal activity (21). In our

study, we found that there was much more delayed HRR in the study group compared to non-PEX patients.

Many researchers have focused on the association between PEX and CV diseases, searching for underlying events. The first of these was homocysteine. Higher levels of homocysteine were found in patients with PEX than in non-PEX patients (22, 23). In addition, vitamin Bl2, vitamin B6, and folic acid levels were also found to be decreased (24). Although many researchers argued that there were relationships between PEX and other CV diseases, in a recent study, researchers found that only the prevalence of arrhythmias was found to be higher in PEX patients than in non-PEX patients (25).

The underlying mechanisms of arrhythmias in PEX patients have been investigated, and the most commonly considered one was the decreased vagal activity (26). Many indirect methods have been developed to investigate this. One of these is the carotid artery baroreceptor reflex. Compared with non-PEX patients, carotid artery baroreceptor reflex was found to be decreased in PEX patients (27). Some investigators have also found reduced cardio-vagal regulation in PEX patients (28). Most studies on decreased vagal autonomic activity have focused on heart rate recovery. Regardless of the underlying disease, there was a relationship between reduced HRR-I and increased mortality (29).

HRR-I shows the degree of heart rate decrease after exercise (30). At the first-minute recovery phase of the TET, the vagal system plays an important role in decreasing the HR. In addition, at the second and the third-minute recovery phases of the TET, the reducing of the sympathetic system affects the decreasing HR (3l). HRR-I is an independent predictor for all-cause death, regardless of coronary artery disease, left ventricular failure, and low exercise capacity (32). A faster reduction in the first minute is closely associated with a lower risk of mortality (33). It was found that there were relationships between low HRR-I and elevated fasting blood glucose level, elevated triglyceride/HDL ratio, duration of diabetes mellitus, the severity of the endothelial dysfunction, and the history of recent myocardial infarction (MI) (34). The ratio of SCD due to MI is 2 times increased in patients with HRR-I<25 beats/minute in the first minute than in those with HRR-I≥25 beats/minute in the first minute (35).

In conclusion, HRR-I, which has been studied in such a detailed and long-term manner and is an important predictor of all event-related deaths, has never been investigated in PEX patients. We thought that this might be due to the balance disorders in the neurohumoral equilibrium in PEX patients. In our study, HRR-I was found to be lower in the study group than in the control group at each stage, and as a result, it was found that autonomic nervous system balance decreased vagal activity and directly increased sympathetic activity in PEX patients compared to the control group. Therefore, it indicates an increased risk of sudden cardiac death in PEX patients that is higher than in non-PEX patients of the same age and sex.

In our study, the sample size was small. Furthermore, we could not perform 24 hours-Holter monitoring to investigate the ventricular arrhythmias in both groups. In addition, long-term studies should be made to observe the effect of medical therapy on the HRR-I and ventricular arrhythmias induced by the exercise test in patients with PEX. More comprehensive and long-term follow-up studies should be performed to obtain healthier data in PEX patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sincan Dr nafiz Korez State Hospital Management (22568850-929/26.08.2019).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.C.; Design - A.G.; Supervision - A.C.; Resource - A.C., A.G.; Materials - A.C., A.G.; Data Collection and/or Processing - A.G.; Analysis and/or Interpretation - A.C.; Literature Search - A.C.; Writing - A.C., A.G. ; Critical Reviews - A.C.

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Original Article

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The Effect of Exercise and Shortwave Diathermy Treatment on the Quality of Life of Patients with Chronic Low Back Pain

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BACKGROUND/AIMS
This study aimed to determine the effects of back school therapy, a home exercise program, and shortwave diathermy treatment on the quality of life of patients with chronic low back pain.

MATERIAL and METHODS
In this interventional study, we evaluated 90 patients who were admitted to our clinic from 2006 to 2007 and had been followed-up for their low back pain complaints that had been present for at least 6 months. These patients were randomized into 3 groups after being subjected to back school therapy and home exercise programs. Placebo shortwave, continuous shortwave diathermy, and pulsed shortwave diathermy treatments were applied to these three groups, respectively. The Short form 36 (SF-36) was used to evaluate the quality of life of the study groups.

RESULTS
In this study, statistically significant recovery was achieved in all the three groups in terms of physical function, role limitations due to physical problems, and bodily pain criteria. Those who received the diathermy therapy had higher mean scores in terms of all the three criteria mentioned above.

CONCLUSION
Significant improvements were achieved within the study groups in terms of all the above-mentioned criteria, except for "role limitations due to emotional problems", as measured by SF-36. However, we could not find any significant difference between the groups in terms of the quality of life.

Keywords: Chronic low back pain, short form health survey, shortwave diathermy

INTRODUCTION

The Global Burden of Disease studies report that chronic low back pain (CBP) is ranked first among the causes of years lived with disability and sixth among the causes of disability-adjusted years of life (1). The National Institutes of Health Research Task Force defined chronic low back pain as "a back pain problem that has persisted for at least 3 months and has resulted in pain on at least half of the days in the past 6 months" (2). Chronic low back pain is distinguished from acute back pain with regard to the duration and underlying conditions or injuries (3). Lower back pain is a cause of significant disability and severe restriction of routine daily activities. Data from studies demonstrate that more than 84% of all adults experience low back pain in their lives (4-6). CBP, which is evidently a common disorder, is also associated with physical disability and a reduced quality of life (7).

In chronic low back pain patients, numerous interventional physical modalities have been used in addition to physical treatments. Shortwave diathermy is one of such modalities (4). Shortwave diathermy has been used since 1928 for the treatment of low back pain, since high frequency waves (10–100 MHz) cause heat increase in deep tissues (8). Shortwave therapy has been shown to reduce pain and muscle spasm, increase pain threshold, trigger vasodilation, enhance the elasticity of connective tissues, and additionally, it increases joint mobility when applied before exercise therapy (9, 10).

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Various studies have demonstrated that exercise and back school programs are effective in patients with CBP, and these methods positively contribute to the quality of life and also to the emotional state of patients (11-13). In a randomized controlled study, the effect of back school therapy on the quality of life was assessed using the SF-36 survey, and an improvement was reported in all the criteria (13). However, we found only a few studies in the literature that investigated the effects of combined treatment with exercise programs and shortwave diathermy on patients with CBP (14).

Therefore, this study aimed to determine the effects of back school therapy, home exercise program, and shortwave diathermy treatment on the quality of life of patients with chronic low back pain.

MATERIAL and METHODS

Study Group

In this interventional study, we evaluated 90 patients who were admitted to our clinic from 2006 to 2007 and had undergone X-ray and MR imaging for their low back pain complaints that had been present for at least 6 months.

Patients aged between 40 and 65 years, suffering from low back pain, which was limited to the lumbar, sacral, or lumbosacral regions, for more than 6 months were included in the study.

Patients with any type of neurological deficit, any type of lumbar or thoracic hernia, cardiovascular disease that would prevent exercise; those who had radicular pain, severe osteoporosis, or osteomalacia; patients with uncontrolled diabetes and hypertension; those with infectious diseases, inflammatory diseases, and a history of malignancy; pregnant patients; and those who had any condition that would prevent the use of the short-term diathermy therapy were excluded from the study. The study was approved by the ethics committee of Dokuz Eylül University, Faculty of Medicine (09/11/2006/247). Patients were informed about the study and a written consent was also obtained.

Treatment

Age, gender, BMI, occupation, and the duration of the low back pain of all the patients were recorded. Patients were randomized to three groups after being subjected to back school therapy and home exercise programs. In the first group (n=30), a placebo shortwave therapy was used while the device was switched off. In the second group (n=30), a continuous shortwave diathermy treatment (Curapuls 419) was applied for 20 minutes every day for 15 days (27.12 MHz frequency and 11.06 m wavelength, 200 W). In the third group (n=30), a pulsed shortwave diathermy treatment (Curapuls 419) was performed for 20 minutes every day for 15 days (27.12 MHz frequency, 11.06 m wavelength, 200 W, 0.3 msec pause). Randomization and evaluation of the treatment practices were performed by a researcher blinded to the study protocol. In the study period, no additional treatment modalities were suggested to the patients.

Main Points:

- Continous or pulsed short wave diathermy treatment is effective on the quality of life if patients with chronic low back pain.

Short-wave diathermy treatment was applied in the outpatient treatment unit of our clinic 5 days a week for a total of 3 weeks (15 sessions). The exercise programs of the all patients were demonstrated and performed under the physician's supervision on the first day. From thereon after, all the patients continued their exercise program at home. The patients were advised to perform the exercises in sets of 10, for the three different times in a day. The patients were given an exercise diary and were asked to note the days when they performed the exercises. Patients were re-evaluated at the end of the 3-week treatment period and were asked to attend a final follow-up 3 months later. Therefore, patients were evaluated three times: before the treatment, at the end of treatment, and 3 months after the treatment.

Measurements

Short form-36 (SF-36) was used to evaluate the quality of life of the patients in the study groups. SF-36 is a questionnaire consisting of questions about general health, physical function, physical role, emotional role, social function, pain, vitality, and mental health that will contribute to the final score, and an additional question regarding the health status, which is not scored. Each question contributes to only one subscale. Possible scores for each subscale range from 0–100. A higher score indicates a higher quality of life (15).

Statistical Analysis

Power analysis was performed using the PASS 11 Home software. The size effect was calculated as 0.414 according to the results of previous studies. Power was adjusted to 0.90 with a type I error of 0.05. The result showed that at least 27 patients will be required in each group.

All the patients' data were imported into SPSS v21. Test for normality was done using Shapiro Wilk test. Comparison between the groups was done with one-way Analysis of Variances (ANOVA) or the Kruskal–Wallis test regarding normality for continuous variables and Chi Square test for categorical variables. Evaluation of repeated measurements was done with the two-way repeated measurements ANOVA for normally distributed variables. For non-normally distributed variables, time-bound changes within the groups were evaluated with the Friedman's test, while the differences between repeated measurements in each of the groups were compared with the Kruskal–Wallis test. For pairwise comparison, the Bonferroni correction method was used. A p value <0.05 were accepted as statistically significant results.

RESULTS

A total of 90 patients (17 males and 73 females) were included into this study, and the mean age was 51.36±6.07 years. These patients were divided into three groups according to the diathermy treatment (placebo, continuous, pulsed; group 1, group 2, group 3; respectively). There was no significant difference between the groups in terms of age, body mass index (BMI), educational status, working status, symptom duration, MRI diagnosis, paracetamol intake, and number of days of exercise. There were significantly more males in group 3 than in the other groups (p=0.044) (Table 1).

TABLE I. Summary of Patients' Characteristics Regarding Treatment Groups

	Group I	Group 2	Group 3	p
N	30	30	30	N.A
Age	51.47±6.50	51.63±6.26	50.97±5.59	0.908
Gender (Male)	3 (10.00%)[a]	4 (13.33%)[a]	10 (33.33%)[b]	0.044
BMI	25.35±3.82	25.42±3.66	25.07±3.26	0.924
Education Status				
Primary	8 (26.67%)	6 (20.00%)	9 (30.00%)	0.794
Secondary	6 (20.00%)	9 (30.00%)	6 (20.00%)	
High school	10 (33.33%)	12 (40.00%)	9 (30.00%)	
University	6 (20.00%)	3 (10.00%)	6 (20.00%)	
Working Position				
Standing	10 (33.33%)	10 (33.33%)	5 (16.67%)	0.257
Housewife	16 (53.33%)	15 (50.00%)	15 (50.00%)	
Sitting	4 (13.33%)	5 (16.67%)	10 (33.33%)	
Symptom Duration (years)	5 (0.5 - 20)	3.5 (1 - 17)	2.25 (0.5 - 30)	0.185
MRI Diagnosis				
Bulging	5 (16.67%)	9 (30.00%)	6 (20.00%)	0.615
Protrusion	9 (30.00%)	9 (30.00%)	14 (46.67%)	
Extrusion	3 (10.00%)	2 (6.67%)	2 (6.67%)	
Spinal Stenosis	1 (3.33%)	2 (6.67%)	0 (0.00%)	
Degeneration	12 (40.00%)	8 (26.67%)	8 (26.67%)	
Paracetamol Intake	0 (0 - 23)	0 (0 - 30)	0 (0 - 9)	0.294
Exercise (Day)	89.5 (10 - 90)	75 (2 - 90)	70 (12 - 90)	0.976

Data given as mean ± standard deviation or median (minimum - maximum) for continuous variables regarding normality and frequency (percentage) for categorical variables
Same letters denote lack of significant difference between groups

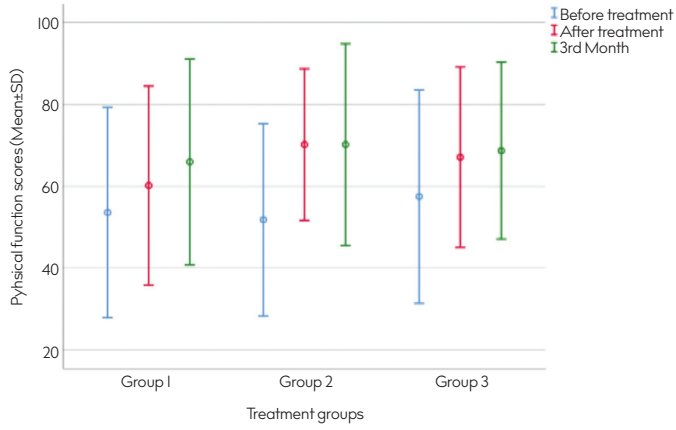

FIGURE I. Isometric flexion strength

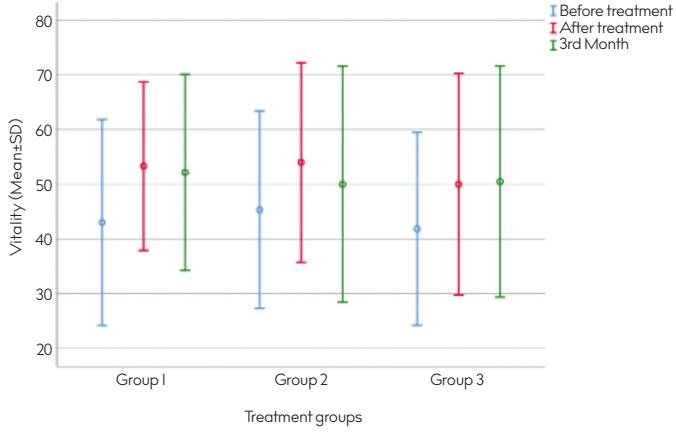

FIGURE 2. Isometric extension strength

Regarding the physical function scores, third month scores were significantly higher than before treatment scores for Group I (p=0.036). There was no significant difference between before and after treatment (p=0.429) and also after treatment and 3rd month scores (p=0.217) for Group I. After treatment and 3rd month scores were significantly higher than the initial scores for Group 2 (p<0.001), while there was no significant difference between after treatment and third month scores (p=0.999). There was no significant difference between the measurements for Group 3 (p=0.067). In addition, there was no significant difference between the groups in terms of an increase in physical function scores (p=0.334) (Table 2) (Figure I).

Regarding the role limitations due to physical problems scores, third month scores were significantly higher than before treatment scores for Group I (p<0.001). On the other hand, there was no significant difference between before and after treatment scores (p=0.526) as well as after treatment and 3rd month scores (p=0.060) for Group I. In Group 2, third month scores were significantly higher than before treatment scores (p=0.004), while there were no significant differences when before and after treatment scores (p=0.364) and after treatment and third month scores (p=0.999) were compared. For group 3, third month scores were significantly higher than before treatment scores (p=0.006), while there was no significant difference between before and after treatment scores (p=0.320) and after treatment and third month scores (p=0.999). There was no significant difference between the groups in terms of an increase in role limitations due to physical problems scores (p=0.183) (Table 2).

Regarding the bodily pain scores, third month scores were significantly higher than before treatment scores for Group I (p=0.015), while there were no significant differences between before and after treatment scores (p=0.184) and after treatment and third month scores (p=0.999) for Group I. In Group 2, after treatment and third month scores were significantly higher than before treatment scores (p<0.001). There was no significant difference between after treatment and third month scores (p=0.999). When Group 3 was evaluated, after treatment and third month scores were found to be significantly higher than before treatment scores for Group 3 (p<0.001). There was no significant difference between after treatment and third month scores (p=0.364). There was also no significant difference between the groups in terms of an increase in bodily pain scores (p=0.126) (Table 2).

Regarding the general health scores, there was no significant difference between the measurements for Group I (p=0.198). On the other hand, after treatment and third month scores were significantly higher than before treatment scores for Group 2

TABLE 2. SF-36 Scores Regarding Treatment Groups and Comparison Results

		Group I (n=30)	Group 2 (n=30)	Group 3 (n=30)	p (Between Groups)
Physical Function	Before	53.61±25.66[a]	51.83±23.43[a]	57.5±26.06	0.334
	After	60.19±24.29[ab]	70.17±18.5[b]	67.09±22.04	
	3rd Month	65.96±25.13[b]	70.17±24.62[b]	68.67±21.57	
p (Within Groups)		0.036	<0.001	0.067	
Role Limitations Due to Physical Problems	Before	0 (0-100)[a]	25 (0-100)[a]	0 (0-100)[a]	0.183
	After	12.5 (0-100)[ab]	50 (0-100)[ab]	29.17 (0-100)[ab]	
	3rd Month	50 (0-100)[b]	75 (0-100)[b]	50 (0-100)[b]	
p (Within Groups)		<0.001	0.004	0.006	
Bodily Pain	Before	41 (12-100)[a]	41 (10-72)[a]	41 (12-74)[a]	0.126
	After	51 (22-84)[ab]	62 (0-84)[b]	56.5 (22-100)[b]	
	3rd Month	51.5 (22-100)[b]	57 (10-100)[b]	52 (10-100)[b]	
p (Within Groups)		0.015	<0.001	<0.001	
General Health	Before	50.43±19.08	51.37±17.43[a]	47.1±12.1	0.788
	After	54.07±18.95	60.23±20.09[b]	52.1±19.87	
	3rd Month	56.67±17.82	59.67±19.21[b]	52.67±20.07	
p (Within Groups)		0.198	0.011	0.283	
Vitality	Before	43.00±18.83[a]	45.33±18.10[a]	41.83±17.64	0.827
	After	53.33±15.44[b]	54.00±18.26[b]	50.00±20.3	
	3rd Month	52.17±17.94[b]	50.00±21.58[ab]	50.50±21.15	
p (Within Groups)		0.010	0.041	0.059	
Social Function	Before	62.5 (0-100)	62.5 (0-100)	50 (12.5-100)[a]	0.334
	After	68.75 (12.5-100)	62.5 (25-100)	62.5 (25-100)[b]	
	3rd Month	62.5 (25-100)	62.5 (12.5-100)	62.5 (25-100)[b]	
p (Within Groups)		0.166	0.051	0.004	
Role Limitations Due to Emotional Problems	Before	0 (0-100)	66.67 (0-100)	0 (0-100)	0.146
	After	50 (0-100)	66.67 (0-100)	33.33 (0-100)	
	3rd Month	66.67 (0-100)	66.67 (0-100)	33.33 (0-100)	
p (Within Groups)		0.136	0.957	0.373	
Mental Health	Before	57.87±16.93	59.07±19.07	51.60±20.05[a]	0.361
	After	60.80±15.35	63.07±19.39	61.47±20.19[b]	
	3rd Month	60.53±17.32	58.00±17.85	58.40±18.33[ab]	
p (Within Groups)		0.999	0.263	0.010	

Data given as mean±standard deviation or median (minimum - maximum) regarding normality
Same letters denote lack of significant difference between repeated measurements.

(p=0.011); however, there was no significant difference between after treatment and third month scores (p=0.999). In Group 3, there were no significant differences between measurements for Group 3 (p=0.283). In addition, there was no significant difference between the groups in terms of the amount of increase in general health scores (p=0.788) (Table 2).

Regarding the vitality scores, after treatment and third month scores were significantly higher than before treatment scores for Group I (p=0.010). There was no significant difference between after treatment and third month scores (p=0.999) for this group. In Group 2, after treatment scores were significantly higher than before treatment scores (p=0.041), while there was no significant difference between before treatment and third month scores (p=0.184). There was no significant difference between the measurements for Group 3 (p=0.059). In addition, there was no significant difference between the groups in terms of the changes in vitality scores (p=0.827) (Table 2), (Figure 2).

Regarding the social function scores, there was no significant difference between measurements for Group I (p=0.166) and Group 2 (p=0.051). After treatment and third month scores were significantly higher than before treatment scores for Group 3 (p=0.004). On the other hand, there was no significant difference between after treatment and third month scores (p=0.999). In addition, there was no significant difference between the

groups in terms of the changes in social function scores (p=0.334) (Table 2).

Regarding the emotional role functioning, no significant differences were found in the comparisons within Group I (p=0.136), Group 2 (p=0.957), and Group 3 (p=0.373), and also in the comparison between the groups (p=0.146).

Regarding the mental health scores, there was no significant difference between the measurements for Group I (p=0.999) and Group 2 (p=0.263). For Group 3, after treatment scores were significantly higher than before treatment scores (p=0.010), while there was no significant difference between before treatment and 3rd month scores (p=0.186). Third month scores were lower than after treatment scores, but this difference was not found to be statistically significant for Group 3 (p=896). In addition, there was no significant differences between the groups in terms of changes in mental health scores (p=0.361) (Table 2).

DISCUSSION

In our study, a statistically significant recovery was achieved in all the three groups in terms of the physical function, role limitations due to physical problems, and bodily pain criteria. All the three groups received back school therapy and home exercise programs, while the first group did not receive the diathermy treatment (placebo). There were significant improvements in all the groups; however, comparisons revealed that there were no significant differences between the groups. Even so, the second and third groups (those that received the diathermy therapy) had higher mean scores in several subscale scores. When within group improvements were evaluated, we found that general health scores were significantly increased in only group 2 (continuous shortwave therapy). There was no significant difference in the vitality criteria in group 3, but there was a significant increase in these criteria in the other groups. On the other hand, there was a significant difference in the social function and mental health scores only in group 3, and no difference was found in the other groups. There was no significant difference in the scores concerning role limitations due to emotional problems in any of the groups.

In a study that evaluated the effects of an exercise program on CBP, improvements in the physical function of the patients were found (16), similar to the findings of our study. However, improvements in role limitations due to physical problems were found in our study whereas, improvements were instead observed in role limitations due to emotional problem in their study (16). Although the authors stated that their study had a significant selection bias that rendered the comparison of the groups quite unfeasible, their findings still showed important benefits with exercise therapy. Furthermore, in a randomized controlled study that evaluated the effect of exercise therapy on the quality of life with the SF-36 questionnaire, significant improvement was shown in all the scores (13). The sample sizes can be a factor that contributes to the differences between the various studies on this topic, but performing exercise therapy under the supervision of a physician or at home (without supervision) may also be a parameter affecting the results. In our study, the exercise programs were demonstrated and performed under a physician's supervision only once. Thereafter, patients were asked to continue their exercise program at home. Although we asked them to keep an exercise diary and to record the time when the exercise was performed, we cannot be absolutely sure that all the exercises were performed in accordance with the demonstration.

In the present study, it was found that there was no difference in terms of the quality of life results in the recipients of the continuous or pulsed shortwave diathermy treatment. In addition, we could not detect a significantly positive effect of the diathermy treatment on the quality of life of patients when compared with placebo. However, in the general health, social function, and mental health scores, no significant change was found in the placebo group, whereas a significant increase was observed in the groups receiving continuous/pulsed diathermy treatment. Several studies have put forth substantial evidence that exercise training can improve the functional ability and quality of life of patients with low back pain (13, 17, 18). However, there were very few studies that assessed the effect of continuous and pulsed shortwave diathermy on patients with CBP (19, 20). Diathermy treatments are mostly used in the treatment of knee osteoarthritis (21). In one of these studies, it was reported that shortwave diathermy treatment had no significant effect on the quality of life in knee osteoarthritis (22). Further clinical studies are needed to evaluate the effect of continuous/pulsed shortwave diathermy on the quality of life of patients with chronic low back pain.

The total sample size in the current study can be considered as adequate for an interventional research; however, the fact that the patients were divided into 3 different groups decreased the sample sizes for each group. This may be seen as a limitation, and future studies may benefit from increasing the patient numbers or dividing the patients into two groups. Another limitation in our study is that there was a higher proportion of females than males (approximately 80%). Furthermore, approximately half of these females were housewives, which may have been a source of bias. In another study similar to ours, it was reported that the whole study group consisted of women, most of them being housewives, and that this situation may be seen as a handicap because housewives are physically less active, resulting in a bias in terms of the perception of the quality of life among the patients (13). This limitation can be overcome by performing long term studies with larger sample sizes. Finally, pain measurements before and after the interventions and at a follow-up visit would have provided a chance to assess the quality of life results with regard to pain levels; however, pain measurements had not been performed in most of the patients and was therefore lacking from the study, which is also a limitation. An important strength of our study is the fact that, to the best of our knowledge, it is the first study to evaluate the effect of shortwave diathermy treatment on the quality of life of patients with CBP.

In conclusion, the SF-36 questionnaire to evaluate patients with CBP, and all scores –except for role limitation due to emotional problem scores– were significantly increased in each group in our study. However, we could not find any significant difference between the 3 groups in terms of the quality of life. In addition, regarding the general health, social function, and mental health scores, there was no significant change in the placebo group, but significant increases were found in the groups receiving

continuous or pulsed diathermy treatment. Further clinical studies with larger sample sizes are needed to evaluate the effect of continuous/pulsed short-wave diathermy on the quality of life of patients with chronic low back pain.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University, Faculty of Medicine (09/11/2006/247).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - S.K.; Design - S.K.; Supervision - S.O.; Resource - S.K., S.O.; Materials - S.K.; Data Collection and/or Processing - S.K.; Analysis and/or Interpretation - S.K.; Literature Search - S.K, S.O, I.S.; Writing - S.K, I.S.; Critical Reviews - S.K.

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Load Distribution in Tooth and Implant–Abutment Identical Cases

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BACKGROUND/AIMS
We sought to compare the biomechanical behavior of dental implants with that of natural teeth under identical situations in accordance with Ante's law.

MATERIAL and METHODS
We used finite element analysis to compare identical cases. We designed different combinations [tooth-supported models (TSMx) and implant-supported models (ISMx)] [TSM0: full-arch dentition, TSMI: 5–7 tooth-supported fixed dental prosthesis (FDP); TSM2: 4–7 tooth-supported FDP; TSM3: 3–7 tooth-supported FDP; ISM0: full-arch dental implant-supported artificial crowns for each tooth; ISMI: 5–7 dental implant-supported FDP; ISM2: 4–7 dental implant-supported FDP; ISM3: and 3–7 dental implant-supported FDP]. We used Cobalt–chromium supported ceramic as the prosthetic material. We used a foodstuff model to apply a 100 N of load for each tooth in the case of mastication.

RESULTS
In general, ISMs showed higher stress values than identical TSMs. The distribution of stress in the cortical bone was similar in identical models regardless of the abutment type. The maximum and minimum principal stress values in the cortical bone increased with the number of missing teeth. The trend in stress values was different between ISMs and TSMs.

CONCLUSION
Within the limitations of this study, stress distribution was similar in both abutment types. However, there was a difference in the magnitude and change in the magnitude of stress values of dental implants and tooth abutments. Our findings reveal that Ante's law may not be suitable as a guideline for dental implant treatment due to the difference in the trends of the maximum and minimum principal stress values.

Keywords: Cortical bone, dental abutments, dental implants, dental models, finite element analysis, mastication

INTRODUCTION

Implantation of partial fixed dental prosthesis (FDP) typically requires splinting of additional abutments to overcome the loss of bone support of the abutment. Ante's law is used as a guide to plan an FDP with an optimal number of abutments (1). In the glossary of prosthodontics, the Ante's law for FDPs states: "in fixed dental prosthodontics, the combined pericemental area of all abutment teeth supporting a fixed dental prosthesis should be equal to or greater than that of the tooth or teeth to be replaced" (2). Based on this, more abutments may be needed as the edentulous span of an FDP increases (1).

In current practice, most people prefer dental implants as replacement for missing teeth (3). The high survival and success rate of dental implants is widely acknowledged (4–9). Application of biomechanical principles is therefore key to sustain these rates (5, 6, 8–12).

Well-known theoretical approaches are often not supported by clinical observations (such as the number of dental implants to be used for FDPs) (13). One common approach is to place a dental implant for each missing tooth (14). From another theoretical perspective, the solution is to place dental implants to support FDP with a central pontic (15). However, there is a lack of consensus on the optimal number of dental implants required to provide adequate support (5, 7, 16).

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Direct clinical evaluation is the most accurate method to analyze the biomechanical effects of dental implant treatment. However, the complexity of the structures involved makes direct clinical evaluation of the biomechanical behavior of intraosseous structures nearly impossible. The potential difficulties for this type of study include possible ethical issues, applicability of methodology, and time required for the procedure. To overcome these limitations, several studies have employed computational, analytical, and experimental models to evaluate the biomechanics of dental implants. These include finite element analysis (FEA), photoelasticity, and the use of strain gauges (11, 17, 18).

FEA involves the use of virtual models to simulate and test the progressive resistance and stress distribution of complex structures. This method enables for the investigation of mechanical problems by dividing the problem into many smaller and simpler elements. This approach creates a mesh of elements and solves the problem using mathematical functions. This allows for the simulation and evaluation of the biomechanical behavior of bone, dental implants, and prosthetic component interfaces, which otherwise would be impossible to analyze *in vitro* or *in vivo* (11, 17).

The purpose of this study was to evaluate the differences in the distribution and magnitude of stress values in dental implants and tooth abutments of an FDP in identical situations. Furthermore, we sought to investigate the optimal number of dental implants in comparison with the identically placed tooth abutments according to Ante's law. The first null hypothesis stated, "the type of abutment (dental implant and tooth abutments) does not affect the magnitude of stress." The second null hypothesis stated, "the type of abutment does not affect the stress distribution in cortical bone in identical situations." Moreover, the third null hypothesis stated, an "an increase in the number of missing teeth does not affect the distribution and magnitude of stress in tooth abutment models." Finally, the fourth null hypothesis stated, "an increase in the number of missing abutments does not affect the distribution and magnitude of stress in dental implant models."

MATERIAL and METHODS

We created, homogenized, meshed, and analyzed three-dimensional (3D) models using a computer (Intel Xeon ® R CPU 3,30 GHz processor, 500 GB hard disk, 14 GB RAM, Windows 7 Ultimate Version Service Pack 1) with Activity 880 (Smart Optics Sensortechnik GmbH, Sinterstrasse 8, D-44795 Bochum, Germany), computed tomography (CT; ILUMA, Orthocad, CBCT, 3M Imtec, OK, USA), Rhinoceros 4.0 (Seattle, WA, USA), 3D-Doctor (Able Software Corp., MA, USA), VRMesh (VirtualGrid, Bellevue, WA, USA), and Algor Fempro (ALGOR, Inc. Pittsburgh, PA, USA).

Main Points:

- The increase in the missing tooth resulted with higher stress values in peripheral bone.
- Dental implants and natural tooth abutments had similar stress distribution behaviour.
- The different stress trends were observed in identical treatment plans with dental implants/natural tooth abutments.
- Ante's law may not be suitable for planing dental implants because of the difference in stress trends. Further studies are recommended.

We constructed a CT data of mandible from a human cadaver using a 3D model of the edentulous mandible with 2-mm cortical bone layer. Then, we transferred the data into the 3D-Doctor and Rhinoceros software in order to generate a 3D finite element model with a 1-mm thick slice.

We scanned dental implants, abutments, and dental gypsum models using Activity 880 in order to construct 3D models of teeth and the dental implant–abutment complex. We used a bone-level dental implant (diameter: 4 mm; length: 10 mm) for all dental implant-supported models (ISMs). Moreover, we scanned the teeth models for reconstruction according to Wheeler standards using the Rhinoceros software. Then, we reformed the abutment teeth in accordance with tooth preparation principles. We designed superstructure models of FDPs with modified ridge-lap pontics using Wheeler standards as a guide. We also designed frameworks of the restorations with a thickness of 0.3 mm and a 3-mm connector width of FDPs. Finally, we used cobalt–chromium-supported ceramic as the prosthetic material for the process.

Models

There were two main model types: teeth-supported models (TSMs) and dental ISMs. We created the first group of models without any missing teeth (TSM0) or dental implants (ISM0). The second group of models comprised of a missing mandibular right first molar and FDPs with supports at the mandibular right second molar and second premolar (teeth-supported, TSM1; dental implant-supported, ISM1). We removed the mandibular right first molar and second premolar and abutments (teeth-supported, TSM2; dental implant-supported, ISM2) at the mandibular right second molar. We then supported the four-unit FDP in the third group of models using the first premolar region. We considered the mandibular right first molar, second premolar, and first premolar missing and the supports of the restoration were at the mandibular right second molar and canine (teeth-supported, TSM3; dental implant-supported, ISM3). In total, we created eight models.

Mesh Creation

We transferred models created in the Rhinoceros software to Fempro while preserving the 3D coordinates. The models were rigidly solid meshed using bricks and tetrahedral elements. In the bricks and tetrahedral solid modeling system, Fempro uses as many as eight nodes in the model. We used seven-, six-, or five-node elements when eight-node elements could not achieve the required detail. All the models were linear, homogeneous, and isotropic. Table 1 displays the properties of the materials used in the study.

Boundary Conditions

We fixed the models at the base and the mesial and distal edges of the mandible with zero degree of freedom.

Loading Conditions

Overall, we applied a force of 700 N to the model by means of

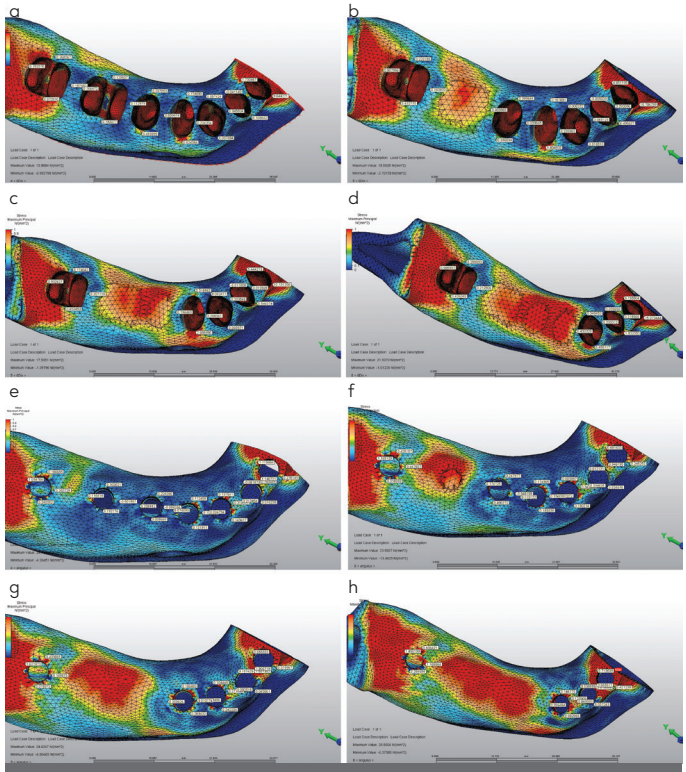

FIGURE 1. a-h. Maximum principal stress analysis in the cortical bone of TSM0 (a), TSMI (b), TSM2 (c), TSM3 (d), ISM0 (e), ISMI (f), ISM2 (g), and ISM3 (h). The red color indicates the highest stress distribution area whereas the blue color indicates the lowest stress distribution area. The highest stress values which were used to compare the models are displayed at the left corner of each model

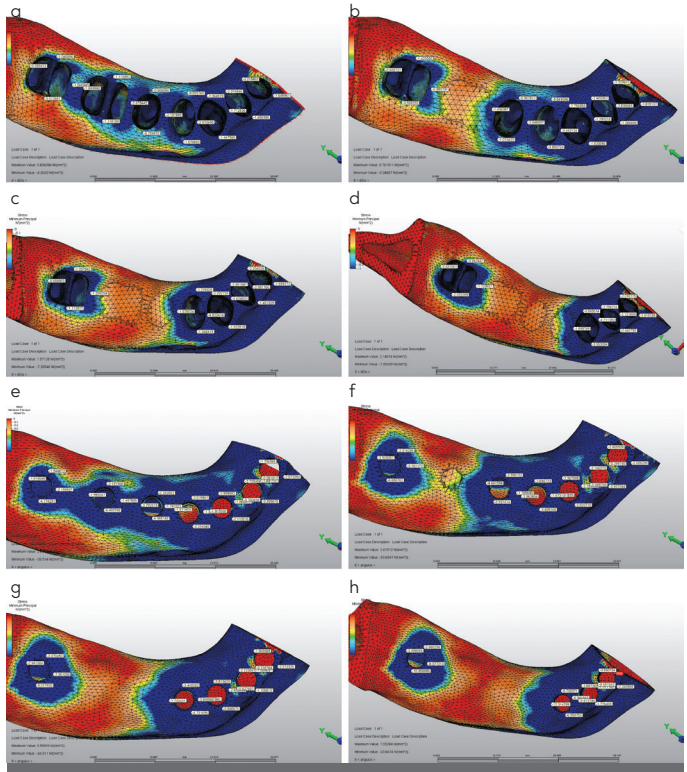

FIGURE 2. a-h. Minimum principal stress analysis in the cortical bone of TSM0 (a), TSMI (b), TSM2 (c), and TSM3 (d), ISM0 (e), ISMI (f), ISM2 (g), and ISM3 (h). The blue color indicates the highest stress distribution area, whereas the red color indicates the lowest stress distribution area. The highest stress values which were used to compare the models are displayed at the left corner of each model

TABLE I. Material properties

Materials	Young modulus (MPa)	Poisson ratio
Feldspathic porcelain	82.800	0.35
Cobalt–Chromium alloy	218.000	0.33
Enamel	82.500	0.33
Dentin	18.600	0.31
Periodontal ligament	170	0.45
Ti-6Al-4V	110.000	0.35
Cortical bone	13.700	0.3
Trabecular bone	1.370	0.3

seven foodstuffs. Each foodstuff applied 100 N of vertical force to each tooth's occlusal surface. We used TSM0 and ISM0 as control groups. We used the highest maximum principal stress values (σmax) and minimum principal stress values (σmin) in the cortical bone for comparison. We also used these values to calculate the ratio between identical situations or similar supporting-abutment types. We considered a more than 10% difference in the values as clinically important. There was no need for any statistical method due to the nature of our study.

RESULTS

Figure 1–3 present the results of FEA. Figure 1–2 demonstrate the maximum and minimum principal stress analysis, respectively. Figure 3 shows a graphical representation of the highest stress values. The positive values in the graphical illustrations reflect the σmax values (Figure 3a), whereas the negative values reflect the σmin values (Figure 3b). The red color in Figure 1 and the blue color in Figure 2 indicate the highest stress distribution area. The left lower corner of each figure displayed the highest stress value of the models. We then used these values to compare the models.

In general, ISMs resulted in higher stress values than TSMs. ISM models had 32%–80% higher σmax stress values and 181%–342% higher σmin values than their corresponding TSMs. The distribution of stress in the cortical bone was similar in identical models regardless of the abutment type. In TSM0 and ISM0, stress was well-distributed. However, the loss of tooth/teeth resulted in more stress concentration at the edentate (pontic) area.

The σmax and σmin values in the cortical bone increased with increase in the number of missing teeth. TSMI, TSM2, and TSM3 showed higher σmax stress values (12%, 26%, and 55%, respectively) (Figure 1b-d) and higher σmin stress values (51%, 21%, and 26%, respectively) (Figure 2b-d) than TSM0 (Figure 1a, 2a). We observed similar σmax and σmin stress values in ISM0 (Figure 1E and 2E), ISMI (Figure 1f, 2f), and ISM2 (Figure 1g, 2g). Meanwhile, ISM3 showed 14% higher σmax stress value (Figure 1h) and 10% lower σmin stress value (Figure 2h) than the others (Figure 2e-g).

DISCUSSION

We rejected the first null hypothesis based on the differences in stress values between the numbers of tooth abutments and dental implants in the different combinations of the posterior

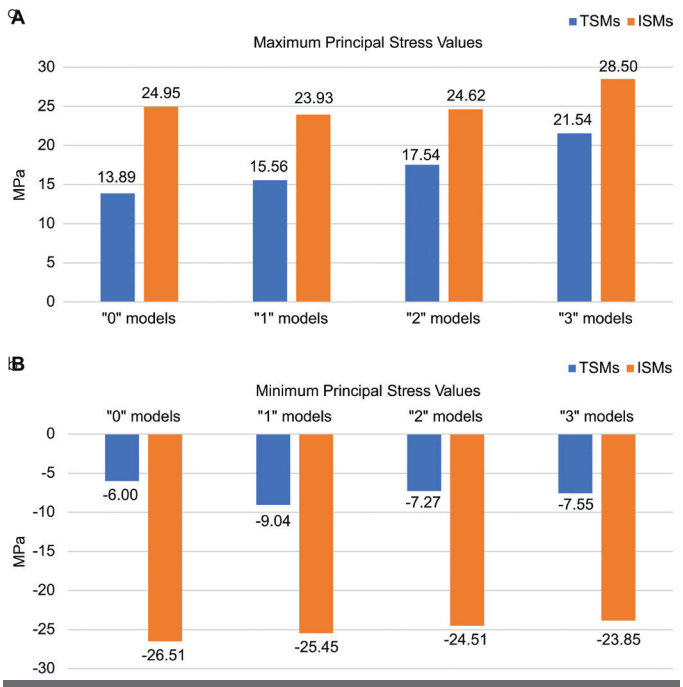

FIGURE 3. a, b. Graphical illustration of the maximum (a) and minimum (b) principal stress values in the cortical bone of TSMs and ISMs. The positive values reflect the σmax values, whereas the negative values reflect the σmin values

edentulism. We accepted the second null hypothesis was accepted based on the similar stress distribution in the identical models. We rejected the third null hypothesis based on the differences between TSMs with respect to stress distribution and levels of σmax and σmin. We partially accepted the fourth null hypothesis based on the similarity of the stress distribution and magnitude of σmax and σmin among ISMs, with the exception of the stress values of ISM3.

According to the results, the magnitude of stress depends not only on the number but also on the type of abutment (tooth or dental implant). Dental implants increase the stress values in the cortical bone and were compared with tooth abutments. An increase in the number of missing teeth in an FDP may also lead to higher stress values in the cortical bone regardless of the abutment type (dental implant or tooth). Reduced number of dental implants can be compensated by increasing the number of dental implants. (19). The diameter and length of dental implants were constant in the present study for the standardization of ISMs.

In vivo and *in vitro* methods for stress analyses of living tissues, such as bones, teeth, and periodontium, are typically challenging (and sometimes even impossible) (11, 17, 18). Each method has advantages and limitations (17). FEA is a suitable method for stress analysis of structures with complex geometry (11, 17). We evaluated the stress in all models with FEA in the present study as stipulated by literature.

Ismail et al. (20) compared two-dimensional (2D) and 3D FEA and reported that 2D analysis was sufficient to assess principal stress distribution. However, the 2D method did not reflect the normal stress distribution in detail. In another study, minor differences were observed between 2D and 3D analyses. The authors opined that the 3D model may provide a better geometrical representation (21). Meijer et al. (22) reported that a 3D model of the region to be examined is sufficient and less time-consuming compared with creating a model of the entire mandible. In this study, we preferred the 3D FEA and we used a 3D image of the working region rather than modeling the entire mandible to obtain realistic models and results.

The maximum occlusal force during mastication varies with natural dentition and dental implants due to muscle size, shape of bones/temporomandibular joint tissues, and the extent of jaw separation (23, 24). Furthermore, factors such as the bite direction and sex of the patient are known to affect the maximum bite force (24, 25). Paphangkorakit and Osborn (24) reported that the maximum occlusal force in the anterior region is in the range of 90–307 N, whereas Waltimo and Könönen (25) reported that the maximum physiologic occlusal force in the mandibular right molar region is approximately 300 N. In a study by Haraldson et al. (26), the median value of the maximal force in dental implants was 143.5 N. In the present study, we applied a static 100 N load for each tooth with a food-shaped model, which is within the reported physiological limits. This kind of loading may present a more realistic load distribution, thanks to the replication of food-shaped model.

We used principal stress (compressive and tensile stress) values to evaluate brittle materials such as bones. Failure occurs if the compression stress in bone is equal to or exceeds the highest compression stress. Thus, principal stress allows evaluation by determining the difference between the tensile and compressive stress (27). Hence, we used principal stress in this study for the analysis of stress values in bone.

A comparison of the natural tooth with the dental implant revealed that an intrusion in natural dentition occurs during mastication, and stress accumulates around the dental implant. Overload may impose high stress on the supporting bone, which leads to bone resorption. The direct opposite of this phenomenon may result in disuse atrophy of bone (28). Most FEA studies evaluate stress levels, implying that lower stress represents a more favorable result. However, in the present study, we evaluated the magnitude and distribution of stress only.

The highest tensile strength of the cortical bone as 121 MPa and the maximum compression strength was reported as 167 MPa (29). In this study, the highest tensile stress value was 29 MPa in the cortical bone of ISM3. This value is lower than the highest tensile strength of bone. The highest compression stress value was 27 MPa in the cortical bone of ISM0. This value is lower than the maximum compression strength of bone.

In a systematic review, Heydecke et al. (7) evaluated the survival rates with regard to the required number of dental implants. They reported that a dental implant-to-replaced-units-ratio of 2/3 can be considered adequate. However, for full-arch dental implant-supported FDPs, the corresponding ratio is between 1/3 and 1/2, which is lower than the first calculated ratio. In present study, we compared the ISMs with identical tooth-supported planning by means of stress transmission to the peripheral bone, and dental implants transmitted higher

stress values to bone. The maximum-stress-ratio (ISM/identical TSM) was between 1.32 and 1.80 for maximum principal stress value and between 2.81 and 4.42 for minimum principal stress values in the cortical bone. This ratio is not a dental implant-to-replaced-units ratio; however, it seems plausible that dental implants present higher stress on the bone than tooth abutments, and the importance of avoiding overload is a key consideration during planning of dental implant treatment. The trends in the change of stress values differed according to types of abutments in identical situations. These findings reveal that the behavior of dental implants is different from that of tooth abutments in supporting an FDP. Furthermore, these findings also revealed that it is not suitable to use Ante's law in the planning of dental implants. We therefore recommend further studies to determine the biomechanical conditions of dental implant treatment.

To the authors' knowledge, this was the first study comparing the stress distribution in natural teeth and dental implants in identical conditions by using Ante's law. Undoubtedly, the current study has some limitations. In dentistry, 3D FEA models have been widely used to study the biomechanics of loaded stress. However, in the current study, use of the FEA program was limited by unrealistic assumptions such as homogeneous, linear elastic, and isotropic conditions for the bone, tooth, and periodontal ligament. The design and material of the dental implant and prosthesis were constant to simplify the models. It should be kept in mind that the variations in type of material, diameter, length, angulation, and surface treatment of dental implants and the design and material of the prosthesis can affect the stress in peripheral bone (9, 23, 30). Furthermore, we assumed that the bonding of the bone and dental implant was perfect and that the masticatory forces were static and loaded axially using a suitable model (fitting for the foodstuff in the occlusal surface of the crowns) as compared to the dynamic masticatory forces, (oblique to the occlusal surface). Consequently, the reconstruction did not replicate all the natural details. Mathematical models can be used only to explain experimental results, and in science, their predictive power is used for comparisons (18). In the present study, we evaluated the distribution and magnitude of stress in identical edentulous treatment plans with different types of abutments. However, the numbers and distribution of abutments were not changed. Although we could not replicate the natural stress values because of these limitations, we observed differences with respect to the magnitude and distribution of stress between differently planned edentulism models. We recommend further studies to understand more about the biomechanical needs for bone stimulation and the effects of other variables on stress distribution of tooth and dental implant supports.

Within the limitations of this finite element study, dental ISMs showed higher stress values than TSMs. The increase in the number of missing tooth enhanced the stress in peripheral bone for both abutment types (tooth or dental implant). We observed a similar behavior with respect to the distribution of stress with dental implant and natural tooth abutments supporting partial FDP. However, we recorded different trends with respect to the change in the magnitude of stress with increase in the number of missing teeth in identical treatment plans. We considered the importance of avoiding overload in dental implant planning because of the higher stress values occurring in the peripheral bone of ISMs. Our results reveal that it may not be suitable to use Ante's law to plan dental implants because of different trends of change in the magnitude of stress in identical treatment plans, even if the distribution of stress was similar. We recommend further studies to understand more about the biomechanical effects of the number and distribution of dental implants and to determine the biomechanical differences between dental implants and tooth abutments.

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Original Article

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Close to Half of the Granulomatous Mastitis may be Tuberculosis Mastitis

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BACKGROUND/AIMS
Granulomatous mastitis (GM) is a chronic inflammatory benign disease that presents differential diagnostic difficulties as well as delays in diagnosis and treatment. The purpose of this study was to analyze the demographic and clinical findings of GM patients and describe the treatment outcomes after empirical antituberculosis treatment.

MATERIAL and METHODS
Forty-eight women with breast symptoms and a verified diagnosis of GM from the year 2014–2016 were evaluated. Of these patients, 20 of them who were nonresponders to the standard nonspecific treatment were included in the study. The study group consisted of these patients who were placed on antituberculosis treatment and followed-up to evaluate the treatment response.

RESULTS
The median age at time of diagnosis was 34 years (range, 21–52). Of the total, 19 (95%) women had unilateral and 1 (5%) had bilateral breast involvement. Median time from the initiation of symptoms to the hospital admission was 7 days (range, 1–364), and median time from admission to diagnosis was 4.5 months (range, 1–120). Among the patients, 75% of them were admitted to the hospital in the first 60 days and 75% were admitted to three different health care centers until the definitive diagnosis. In addition, 41.7% (20/48) of patients could not be treated with nonspecific antiobitics and steroids but were treated empirically with anti-TB drugs. These patients had a complete response to the empirical antituberculosis treatment regimen.

CONCLUSION
Our results showed that 41.7% of GM may actually be TB mastitis according to our empirical treatment success results. Suspicion of breast tuberculosis is essential among pathologically verified GM patients who are especially clinically nonresponders to other treatment, with prolonged symptoms and recurrence. Empirical antituberculosis treatment can be recommended in pathologically proven GM patients especially in high-incidence regions for tuberculosis.

Keywords: Granulomatous mastitis, extrapulmonary tuberculosis, antituberculosis drugs, empirical treatment

INTRODUCTION

Granulomatous mastitis (GM) is a rare benign inflammatory disease of breast with an unknown etiology. However, tuberculosis (TB), sarcoidosis, mycotic and parasitic infections, and foreign body reactions have been accused as the etiology. It usually affects women of childbearing age. The condition presents with a hard palpable mass with skin erythema and lymph node enlargement. Nipple retraction, sinus formation, and breast atrophy may accompany to the findings (1). The clinical and radiological presentation of granulomatous mastitis usually mimics malignancy or infections (2). GM is usually unilateral; however, it may localize in all breast quadrants (3). Added to the difficulty in differential diagnosis of the condition, there has also been no consensus on the optimal treatment strategy for GM, leading to a delay in the diagnosis

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and treatment of the disease. The aim of this retrospective study was to present the clinical and histopathological data and also to show the clinical outcomes of GM patients who received empirical antituberculosis treatment.

MATERIAL and METHODS

Patient Selection

Forty-eight women admitted to our outpatient clinics with breast pain complaints, palpable mass, skin erythema, and sinus formation meeting the histopathological criteria for GM were evaluated from the year 2014–2016. The patients underwent physical examination and ultrasonographic evaluation. Of the 48 patients who were histopathologically diagnosed as "granulomatous disease of the breast," 28 patients were treated successfully with antibiotics and/or steroids without recurrence and the remaining 20 women who had highly suspicious clinical and laboratory data for TB were included in the study. The TB contact, active disease history, treatment compliance, and treatment results of the patients were obtained from the dispensary reports. Also, details about the patient's symptoms and type of breast involvement were provided from the hospital records.

Study Design

This study was designed as a retrospective, single center, and non- interventional study.

Ethical Situation

Study was conducted in accordacne with the Declaration of Helsinki Guidelines. All the participants were provided written informed consent. The study was approved by the local medical expertise and education board of Ankara Oncology and Training Hospital (number: 17 date: 09.12.2017).

Diagnostic Procedures and Data Collection

The histopathological diagnosis was performed by ultrasound (US) guided tru-cut breast biopsy and the specimens were obtained from the ultrasonographically suspicious lesions.

Main Points:

- Granulomatous mastitis (GM) is a chronic inflammatory benign disease that presents differential diagnostic difficulties as well as delays in diagnosis and treatment.
- An important portion of GM may actually be TB mastitis according to our empirical treatment success results.
- Suspicion of breast tuberculosis is essential among pathologically verified GM patients who are especially clinically nonresponders to other treatments, with prolonged symptoms and recurrence.
- Clinical features with histopathologically proven GM can be a factor for the antituberculosis treatment choice especially in developing countries with especially high-incidence regions for tuberculosis.
- Although antituberculosis treatment is a safe and an effective choice in these group of patients, future molecular test approaches for the accurate diagnosis of GM is needed.

Demographic features, history of TB and close contact with TB patients, climacteric status, systemic and local symptoms, chest X-ray findings, duration of symptoms, duration of diagnosis, mammographic/ultrasonographic findings, diagnostic procedures, treatment strategies and outcomes, and side effects were recorded.

Surgical or Biopsy Specimen Evaluation

Histopathological examination of surgical or biopsy materials revealed "granulomatous disease of the breast" with noncaseating granuloma formation, destruction of the ductal structure, infiltration of the inflammatory cells, and micro-abscess formation. Tissue samples were examined using hematoxylin-eosin and Ehrlich Ziehl-Neelsen (EZN) for acid -fast bacilli.

Treatment Strategy and Inclusion-Exclusion Criteria

After nonspecific antibiotic therapy and steroid treatment was applied, anti-TB treatment was started for the non- responders. All the patients were treated with isoniazid (300 mgr/day), rifampicin (600 mgr/day), pyrazinamide (2000 mgr/day), and ethambutol (1500 mgr/day) according to the "National TB programme" recommended doses (4). The standard anti-TB treatment with four drugs was continued for 2 months initially, and the maintenance therapy was continued with isoniazid and rifampicin for a minimum of 4 months. All the cases were followed-up at the TB dispensary and treated with directly observed treatment. The treatment response was evaluated according to clinical and US findings. Follow-up period was 2 years.

Main inclusion criterion was histopathologically proven "granulomatous disease of the breast" with noncaseating granuloma formation. The other inclusion criteria were i) women treated with nonspecific antibiotherapy (amoxicillin +clavulanic acid 1 gr 2x1 combined with ciprofloxacin 500 2x1/per day for two weeks) and steroids (30 mgr/day prednisolone for two weeks) with no treatment response, ii) prolonged symptoms and clinical-radiological findings, iii) recurrent symptoms and findings, iv) patient rejection to the major surgical approach.

Women with a diagnosis of TB mastitis (n=3) (accurate diagnosis confirmed by histopathological and/or microbiological methods) were excluded.

Statistical Analysis

Descriptive statistical analysis was performed. All the statistical analysis were performed by using SPSS software version 24.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

All the patients were fertile and gave birth to at least one child. Most of the patients had an uneventful period during and after pregnancy; however, breast induration and the nipple irritation history was declared during the lactational period in 4 (20%) of patients.

None of the patients had a history of TB. Only two patients had a TB contact with their first-degree relatives, indicating household contact. Clinical characteristics of the patients are shown in Table1. The median age at time of diagnosis was 34 years (range, 21–52). The major complaints were breast mass, pain, and nipple discharge.

TABLE I. Clinical characteristics of patients with granulomatous mastitis who received empirical anti-tuberculosis treatment

Patients with GM who received empirical anti- tuberculosis treatment n = 20	Number of Patients n	Percentage %
History of TB	0	0
Contact with TB	2	10
Symptoms		
Isolated symptoms (mass/pain/ nipple discharge)	6	30
More than one symptom	14	70
Suspicion of breast cancer	9	45
Treatment response		
Complete response	20	100
Relapse	1	5
Involvement of breast		
Unilateral	19	95
Bilateral	1	5
Multifocal	14	70

TB: Tuberculosis ; GM: Granulomatous mastitis

Breast US revealed skin thickening and edema, mastitis, abscess formation, and suspicious lesions mimicking malignancy. Of the total, 19 (95%) women had unilateral and 1 (5%) had bilateral breast involvement. Fourteen (70%) cases had unilateral multifocal involvement with no specific quadrant localization. In 9 (45%) patients, breast carcinoma was highly suspected both clinically and radiologically. Wide local excision was the mainstay of both accurate diagnosis and surgical treatment, and it was performed in all the cases. Baseline clinical characteristics of patients are given in Table I.

Median time from the initiation of symptoms to the hospital admission was 7 days (range, 1–364), and median time from admission to diagnosis was 4.5 months (range, 1–120), indicating both a delay in admission and in initiating an appropriate treatment. Median number of health care centers admitted during diagnosis and treatment was 2.5 (range, 1–4). Of the total, 75% were admitted to hospital in the first 60 days and 75% of patients were admitted to three different health care centers until the definitive diagnosis.

The median tuberculosis skin test results of the patients were 12 mm (range, 1–20). None of the patients had active pulmonary or sequela radiological TB findings on the chest X-ray. All the histopathological examination of the surgical materials revealed "granulomatous disease of the breast" with noncaseating granuloma formation, destruction of the ductal structure, infiltration of the inflammatory cells, and micro-abscess formation. None of the specimens had a positive stain for acid-fast bacilli during the examination of the tissue samples. All the patients had complete response to standard treatment regimen. One patient had recurrence and re-treatment was started.

DISCUSSION

Among the 48 patients with GM, 28 were responders to the standard antibotic and steroid treatment, while the remaining 20 patients were treated with anti-TB succesfully and safely.

According to Guideline of Tuberculosis Treatment and Diagnosis published by the Turkish Ministry of Health in 2019, extrapulmonary TB is detected in 35% of patients with the diagnosis of TB in Turkish population (5). Since 2003, active surveillance study of TB has been proceeded among hospitals in Ankara, and extrapulmonary involvement of TB cases is detected according to the data reports and close follow-up. According to our clinical experience and previous literature, difficulty in diagnosis is a common problem in these cases (6). Breast involvement of TB is a rare condition with an uncertain incidence. There were only 120 cases reported until 1999 (7). The incidence of the disease has been stated as less than 0.1% of all breast lesions in Western countries and 3–4% in TB endemic regions, such as India and Africa (8, 9). EZN stain, tuberculin skin test, and routine histopathological studies are sometimes not sufficient neither for ruling out nor for confirming the diagnosis of TB. A differential diagnosis including malignancy, nonspecific suppurative infections, fungal infections, or TB is required when mastitis with abscess formation, recurrence, and long duration of symptoms are present.

Clinically, patients present with a hard lump that mimics carcinoma, which may lead to nipple retraction and sinus formation (10, 11). Radiologically and clinically, GM may be mistaken for breast cancer. Even mammographic and fine needle aspiration cytology findings may be misinterpreted as malignancy (12).

It has been shown that GM is usually unilateral and may be located in all breast quadrants, except for the subareolar area (13). In our study, most of the cases had unilateral involvement. Bilateral involvement was present in only one case. In previous studies, bilateral involvement has been reported in only a maximum of two patients (14). In their series, Velidedeoğlu et al. reported 10 cases with bilateral involvement and stated that bilateral GMs have a higher rate of relapse and resistance to medical treatment compared to unilateral GMs (15).

According to the literature, most patients with GM are relatively young and fertile women ranging between 11 and 83 years; however, the disease usually is common in the third or fourth decade (16, 17). In our study, most of the cases were also young fertile females with a median age of 34 years at time of diagnosis. This finding is concordant with literature.

Some authors have suggested that GM is sometimes a self-limiting condition with duration of 2 to 24 months; however, a chronic presentation could last for several years (18). Furthermore, GM may have a progressive clinical course with multiple recurrences. Since it is a rare condition, it may lead to a delay in appropriate diagnosis and subsequent initiation of treatment. In our study, diagnostic period as well as initiation of treatment was prolonged due to factors caused by both patients and physicians. Apart from the nature of the disease, we think that there are mainly three factors leading to this situation: 1) During the follow-up period, a high number of patients changed their health care centers 2) In most of the cases, fine needle aspiration biopsy (FNAB) was performed for histopathological diagnosis instead of wide local excision, which was the mainstay for both accurate diagnosis and surgical treatment. Since FNABs were not always diagnostic, multiple biopsies were performed, especially for the patients with a suspicion of malignancy. 3) Different therapeutic regimens including antibiotics, steroids, and abscess drainage were applied and physicians had

to wait for the treatment response. We think that the delay in diagnosis and treatment of the disease caused either by physicians or patients is an important issue concerning granulomatous lesions of the breast. Delayed approach may lead to the destruction of the breast tissue, resulting ultimately with unnecessary mastectomies.

Up to date, there has been no clear consensus regarding the optimal treatment strategy in GM cases. As GM is a benign and non life-threatening disease, it is crucial to apply accurate and optimum regimen that will not lead to permanant deforming and serious side effects. Antibiotics, steroids, methotrexate (MTX), azathioprine, wound drainage, wide surgical excision, mastectomy, or close follow-up have been proposed (19-21).

In patients without a definitive diagnosis of TB both microbiologically and histopathologically, GM may be considered as an extrapulmonary involvement of TB in the breast. We think that in patients treated with nonspecific antibiotherapy/steroids with no response, and who had prolonged and recurrent symptoms with clinical-radiological findings, and finally in patients who rejected major surgical approaches, empirical antituberculosis treatment may be a choice. In our study, all the patients had a complete response to standard antituberculosis treatment with no side effects. Only one patient had a recurrence one year after completing the treatment due to low compliance to therapy. To our knowledge, there has been no previous report regarding antituberculosis treatment for GM.

Extrapulmonary TB can sometimes be presented as breast tuberculosis. However, difficulties in the differential diagnosis are frequently seen in GM/ breast TB patient groups. Suspicion of breast tuberculosis is essential among pathologically verified GM patients who are especially clinically nonresponders to GM treatment, with prolonged symptoms and recurrent findings.

We conclude that, clinical features with histopathologically proven GM can be a factor for the antituberculosis treatment choice, which is a safe and an effective approach. In addition to the surgical approaches, empirical antituberculosis treatment can be started in these groups of patients, particularly in developing countries with especially high-incidence regions for tuberculosis. In these groups of patients with diagnostic difficulty, new molecular tests may be recommended.

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Informed Consent: All participants were provided written informed consent.

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Author contributions: Concept - Ç.Ö., F.D.A.; Design - T.Ö.; Supervision - T.Ö., M.H.T.; Resource - S.Ç.I., F.D.A.; Materials - Ç.Ö., F.D.A.; Data Collection and/or Processing - Ç.Ö., T.Ö., M.H.T.; Analysis and/or Interpretation - F.D.A., Ç.Ö.; Literature Search - Ç.Ö.; Writing - Ç.Ö.; Critical Reviews - M.H.T., T.Ö.

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Original Article

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Evaluation of the Electrocardiographic Parameters of Anemic Children Before and After Anemia Correction

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BACKGROUND/AIMS
Iron deficiency is the most common and widespread nutritional disorder, which leads to iron deficiency anemia (IDA) if left untreated. IDA can present in various forms with the involvement of multiple systems, varying from arrhythmia to left ventricular dysfunction and even heart failure in cardiological terms. Nowadays, electrocardiography (ECG) is the most accessible and valuable method of diagnosing rhythm and conduction disorders. In this study, we aimed to evaluate the ECG parameters, such as QT, QTc, QT dispersion, Tp-e interval, and Tp-e/QTc ratio used in the diagnosing malignant ventricular arrhythmias, of children before and after IDA treatment.

MATERIAL and METHODS
This study included 30 children with no cardiac or chronic disease and was conducted between December 2017 and June 2018. All the children were diagnosed with IDA and treated in the Pediatrics Outpatient Clinics of Gaziantep University Medical Faculty. Pre- and post-treatment QT, QTc, Tp-e interval, Tp-e/QTc ratio, and QT dispersion values of the patients were compared.

RESULTS
Post-treatment values of hemoglobin, mean corpuscular volume, Ferritin, and Fe were significantly lower than the pretreatment values, while total iron-binding capacity was found to be significantly higher. The QTc, Tp-e interval, and Tp-e/QTc ratio were significantly lower after the treatment.

CONCLUSION
Our study revealed that QTc, Tp-e interval, and Tp-e/QTc ratios on the ECG decreased after treatment of the IDA. Children diagnosed with IDA should be carefully monitored for ventricular arrhythmias throughout the treatment.

Keywords: Iron deficiency anemia, electrocardiography, childhood

INTRODUCTION

Iron deficiency is the most common and widespread nutritional disorder, which leads to iron deficiency anemia (IDA) if left untreated (1). IDA can either be asymptomatic or present with the involvement of multiple systems. In terms of cardiovascular manifestation, patients who are diagnosed with IDA can have a clinical picture varying from arrhythmia to left ventricular dysfunction, and even heart failure (2).

Electrocardiography (ECG) is still the most valuable method because it is an inexpensive, accessible, and non-invasive technique used in the diagnosis of rhythm and conduction disorders. Studies commonly investigate new ECG parameters like Tp-e interval, Tp-e/QTc ratio as well as QT and QT, showing ventricular repolarization abnormalities in the diagnosis of malignant ventricular arrhythmias, which is a leading cause of sudden cardiac death (3, 4). It is known that sudden cardiac death can occur without an underlying heart disease. On this basis, the relationship between anemia and ventricular arrhythmias is frequently studied in both pediatric and adult patients. The relationship between IDA and electrocardiographic measurements in children has also been a subject of various studies, and previous studies have shown that anemia prolongs the values of Tp-e interval, Tp-e/QTc ratio, as well as QT and QTc (5, 6, 7). However, to the best of our knowledge, no study has compared the pre- and post-treatment ECG values of patients with IDA. In our study, we aimed to compare pre- and post-treatment QT, QTc, Tp-e interval, Tp-e/QTc ratio, and QT dispersion in children

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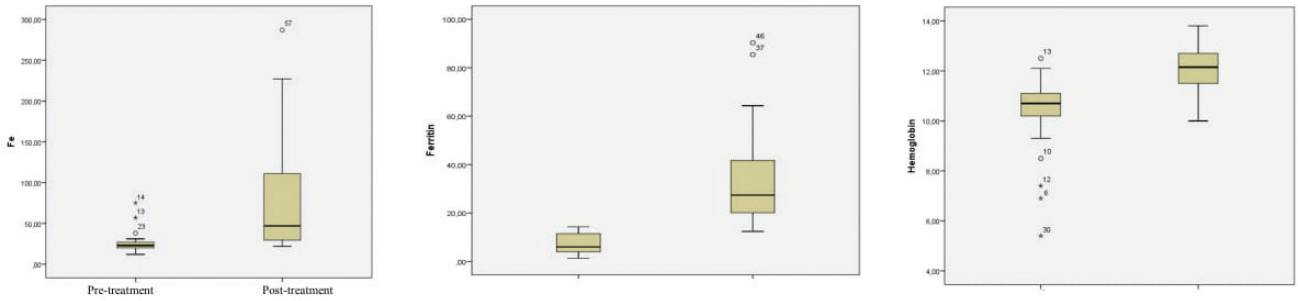

FIGURE I. Comparison of the hematologic parameters of the groups

diagnosed with IDA for the early diagnosis of life-threatening arrhythmias during treatment.

MATERIAL and METHODS

This prospective study involving 30 children diagnosed with IDA was conducted at the Pediatrics outpatient clinic of Gaziantep University Faculty of Medicine between December 2017 and June 2018. The patients consisted of children who consulted to our hospital because of their incidental anemias. Patients with an underlying congenital or rheumatologic heart disease and chronic disease, as well as those with ventricular dysfunction, arrhythmia, hypo-hyperthyroidism, electrolyte imbalance, or acute inflammatory disease, or patients receiving drug therapy were excluded from the study because it may affect the ECG parameters. Detailed physical examinations and 12-derivation ECG as well as the full blood count, serum electrolytes, urea, creatinine, iron, ferritin, and total iron-binding capacity (TIBC) values of these patients, were examined. Hemoglobin electrophoresis from each patient was also examined for the differential diagnosis of IDA. A 6 mg/kg/day ferrous sulfate treatment was administered to the IDA patients for 12 weeks. ECG measurements were repeated after the treatment in the patients whose anemia was corrected, and the results were compared to pretreatment results. Voluntary informed consent was obtained from the patients/parents and presented to the Ethics Committee. This study was conducted in line with the approval obtained by the decision of Gaziantep University Clinical Trials Ethics Committee dated 06.06.2018 and numbered 2018/92.

Electrocardiography

Standard 12-derivation ECGs of the patients were recorded at rest in the supine position with an amplitude of 1 mV/cm and speed of 25 mm/sec (Mortara ELI 280; Nihon Kohden, Tokyo, Japan). The electrocardiographic records were transferred to a computer via scanners and computerized to obtain more meticulous measurements. QT interval was defined as the time from the onset of the QRS complex to the point of the T wave's return to the isoelectric line. The deepest point between the T and U waves was measured in the presence of the U wave. Electrocardiographic records were considered analyzable when a T wave was available in eight or more electrodes. QT interval was not measured in the absence of the T wave. Since QT interval varies with the heart rate, QTc was calculated using Bazett's formula (8). QT interval was measured in all the available leads, including lead I, II, and V5 in particular. The mean value of three measurements of the QT interval was used for further analysis. The difference between the longest and the shortest QT interval was calculated as the QT dispersion (QTd). Tp-e interval was measured from T_{peak} (the highest point of T wave) to T_{end}. T_{end} was defined as the intersection point between the tangent point of the downward slope of the T wave and the isoelectric line. U wave was ignored. Tp-e/QTc ratio was calculated from these measurements. All the Tp-e measurements were performed in the precordial leads.

Main Points:

- Iron deficiency is the most common and widespread nutritional disorder, which leads to iron deficiency anemia in children
- Iron deficiency anemia can present in various forms with the involvement of multiple systems, varying from arrhythmia to left ventricular dysfunction and even heart failure in cardiological terms.
- Patients with iron deficiency anemia should be followed-up for life-threatening arrhythmias during treatment

Iron Deficiency Anemia

Iron (Fe), ferritin, TIBC, hemoglobin (Hb), hematocrit (Hct), and mean corpuscular volume (MCV) values of all the patients were studied for the assessment of the diagnosis and treatment of IDA. Hb values -2SD below the age-appropriate levels and ferritin values below 15 ng/mL were taken into account for the diagnosis of IDA (9).

Statistical Analysis

The data obtained were analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 statistical package software (IBM SPSS Corp.; Armonk, NY, USA). The Mann–Whitney U test, independent groups Student's t-test, dependent groups t-test, Wilcoxon test, and Pearson correlation analyses were used together with descriptive statistics. Mean, standard deviation, lowest, and highest values were used and expressed in tables and graphics for the descriptive statistics. The level of significance was accepted as 0.05.

RESULTS

This study included 30 patients who were diagnosed with and treated for IDA. The mean age of the patients was 4.8±4.4. Nineteen patients were males, and 11 were females. Comparison of the pre- and post-treatment hematological parameters of the

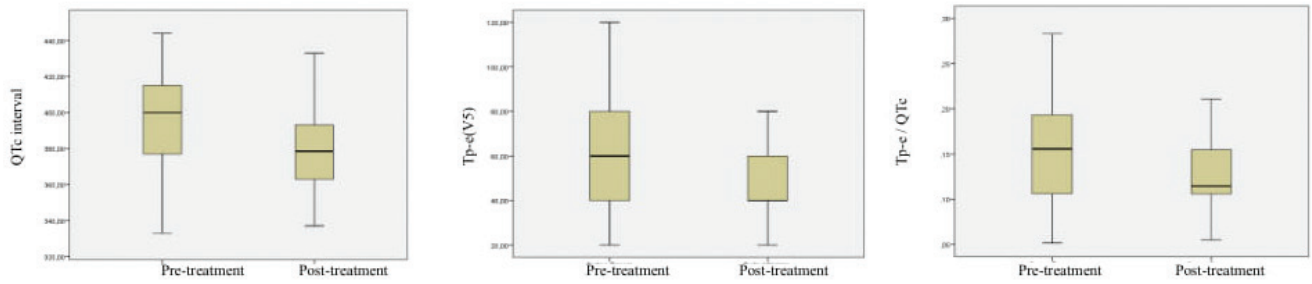

FIGURE 2. Comparison of the electrocardiographic parameters of the groups

TABLE I. Comparison of the hematologic parameters of the groups. RBC red blood cells, MCV mean cell volume, Fe iron, TIBC total iron-binding capacity

	Pre-treatment		Post-treatment		
Hematologic Parameters	**Mean±SD**	**Minimum - Maximum**	**Mean±SD**	**Minimum - Maximum**	**P value**
Hemoglobin (g/dl)	10.3±1.6	5.4-12.5	12.1±0.9	10.0-13.8	0.000
RBC (x/)	4.8±0.5	3.5-5.4	4.9±0.5	4.0-5.7	0.213
MCV (fL)	69.1±6.0	52.0-79.6	75.0±4.7	68.1-87.7	0.000
Ferritin (ug/L)	7.5±4.1	1.3-14.3	33.8±20.0	12.4-90.3	0.000
Fe (µg/dl)	26.5±13.3	12.0-75.0	85.0±73.7	22.0-287.0	0.000
TIBC (µg/dl)	412.1±55.9	331.0-572.0	348.7±54.6	256.0-509.0	0.000

TABLE 2. Comparison of the electrocardiographic parameters of the groups. bpm beat per minute, ms milliseconds, QTc corrected QT interval

	Pre-treatment		Post-treatment		
Electrocardiographic Parameters	**Mean±SD**	**Minimum - Maximum**	**Mean±SD**	**Minimum - Maximum**	**P value**
Heart rate (bpm)	118.0±29.8	72.0-171.0	109.3±25.5	73.0-153.0	0.054
QT (ms)	294.3±44.5	200.0-400.0	286.7±37.3	220.0-380.0	0.240
QTc (ms)	396.6±29.4	333.0-444.0	381.6±24.4	337.0-433.0	0.010
Tp-e (V5) (ms)	61.3±22.2	20.0-120.0	50.0±14.6	20.0-80.0	0.001
QT Dispersion (ms)	35.3±13.6	20.0-80.0	33.3±10.9	20.0-60.0	0.573
Tp-e (V5) / QTc	0.2±0.1	0.1-0.3	0.1±0.0	0.1-0.2	0.002

30 patients is shown in Table I and Figure I. Compared to the post-treatment values, Hb, MCV, Ferritin, and Fe values were significantly lower while TIBC was significantly higher. Comparison of the pre- and post-treatment electrocardiographic parameters of the patients is shown in Table 2 and Figure 2. When compared to the pretreatment values, it was found that QTc interval, Tp-e interval, and Tp-e/QTc ratio were significantly decreased after the treatment.

DISCUSSION

This study showed that QTc, Tp-e interval, and Tp-e/QTc ratio values were significantly decreased after treatment in patients whose IDA was corrected. Our study also found a negative correlation between QTc and both Hb and Ferritin (Hb: r=-0,24 p=0,193; Ferrritin: r=-0,133 p=0,484). Studies, particularly in the adult literature have shown that IDA is correlated with cardiomyopathy, left ventricular dysfunction, and premature ventricular contractions (7, 10). However, similar studies are limited among pediatric patients.

QT interval defines ventricular depolarization and repolarization, and a prolonged QT interval increases the risk of fatal ventricular arrhythmia and sudden cardiac death (11). Studies have shown prolonged QTc intervals in patients with renal failure and thalassemia, resulting in high Fe stores (12, 13). Similarly, several studies on pediatric and adult patients with sickle cell anemia in the USA showed QT interval prolongations (14-16). However, another study on anemia patients with different etiological causes found normal QT intervals in anemia patients (17). A study by Karadeniz et al. (18) on pediatric patients with anemia demonstrated a negative correlation between ferritin levels and QTc. In our study, we showed that the QTc values of patients whose IDA was corrected with treatment were significantly decreased compared to the pretreatment values. There was a negative correlation between ferritin and Hb values and QTc. Different results in the literature might be attributed to the different etiologies of anemia and the different measuring techniques. Similar results in diseases that present with both anemia and high Fe stores might be due to the fact that iron is a significant element in the enzymatic system of cardiomyocytes.

QT dispersion is defined as the difference between the longest and shortest QT distance in a 12-derivation ECG. This difference between QT distances indicates a non-uniform ventricular repolarization, and as it prolongs, it may lead to the development of severe ventricular arrhythmia, which can result in sudden cardiac death, like in long QT interval (19, 20). Since there is no consensus on the pathological upper limit of the reference intervals and values, the relationship of QTd with cardiac mortality is controversial, but various studies argue otherwise. In a study by Kulanet al. on patients with MVP, QTc dispersion was found to be higher than in the control group (21). In a study by Karadeniz et al. (18) on pediatric patients, QTc dispersion was found to be significantly higher in patients with low iron stores, while it had a significantly negative correlation with ferritin. In our study, we did not find a significant difference between pre- and post-treatment values. The differences in studies might be due to the different measuring techniques and the difficulty in determining the endpoint of the T wave.

The distance between the peak point and endpoint of the T wave is defined as the Tp-e interval, and it is a measure of the transmyocardial distribution of ventricular repolarization. Prolongation of Tp-e interval might be associated with dangerous rhythm disorders and ventricular arrhythmias (3). However, various studies showed that the Tp-e/QTc ratio could reveal ventricular repolarization abnormalities more precisely because it is not affected by the heart rate and body mass index (22). Tp-e/QTc ratio was found to be higher in patients with the risks of an arrhythmogenic condition, such as long QT syndrome, Brugada syndrome, acute myocardial infarction, and short QT syndrome (3, 23, 24). In our study, we showed that both the Tp-e interval and Tp-e/QTc ratio were significantly higher in children before the treatment. We also found a negative correlation between post-treatment Hb and both Tp-e interval and Tp-e/QTc ratio (Hb and Tp-e interval: r=0,179 p=0,343 Hb and Tp-e/QTc ratio: r=0,266 p=0,155).

The impact of anemia and iron deficiency on cardiovascular hemodynamics has been demonstrated in several studies (25, 26). Iron is stored in cells as an important element of the enzymatic system of cardiomyocytes. Many studies reported that cardiovascular hemodynamics were affected in both iron deficiency and iron overload secondary to chronic blood transfusions (2, 27, 28).

These studies compared patient groups with and without anemia and revealed that anemia caused myocardial diseases by affecting the increased cardiac output, increased sympathetic activation, and ventricular functions (28, 29). To the best of our knowledge, our study is the first one that was conducted with dependent variables, differently from other studies. In our study, we compared the cardiac functions of patients with corrected anemia to the pretreatment values. The study showed that QTc, Tp-e interval, and Tp-e/QTc ratio values were significantly decreased after treatment in patients whose IDA was corrected. Low Hb levels were considered to reduce the systemic vascular resistance by decreasing the blood viscosity (30). In this context, decreased myocardial tissue oxygenation in iron deficiency anemia and the accompanying autonomic imbalance might be a potential reason for the higher QTc, Tp-e interval, and Tp-e/QTc ratio measures before the treatment.

Our study had some limitations. The primary limitation was the small sample size, restricts the strength of detecting small differences. Secondly, our patients were anemic children with low iron stores. It would be beneficial to conduct a comparison study with patients who have low iron stores but have not yet developed anemia.

In conclusion, our study showed that the QTc, Tp-e interval, and Tp-e/QTc ratios decreased on the ECG after the iron deficiency anemia was treated. Therefore, these parameters, which have been used as new markers for predicting atrial and ventricular arrhythmias in many studies, should also be carefully evaluated in children with iron deficiency, and patients should be followed-up for life-threatening arrhythmias during treatment. However, additional studies, including more extensive series and different multicenter units, are needed in this regard.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (06.06.2018/92).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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Author contributions: Concept - M.T.T.; Design - M.T.T.; Supervision - M.T.T.; Resource - M.T.T. M.U.; Materials - M.U.; Data Collection and/or Processing - M.U.; Analysis and/or Interpretation - M.U.; Literature Search - M.T.T.; Writing - M.T.T.; Critical Reviews - M.T.T.

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Examination of the Relationship Between Exercise Barriers and Physical Activity, Sleep, and Fatigue in Older Individuals

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BACKGROUND/AIMS
This study aimed to determine exercise barriers in older individuals and to examine their relationship with physical activity, sleep, and fatigue.

MATERIAL and METHODS
A total of 100 older individuals aged more than 65 years who were staying in a private nursing home and elderly care center were involved in this study. The sociodemographic information of the individuals and the used scales were recorded through face-to-face interviews held by a physiotherapist. Their exercise barriers, physical activity levels, sleep conditions, and fatigue were evaluated by the Exercise Benefits/Barriers Scale, Physical Activity Scale for the Elderly (PASE), Pittsburgh Sleep Quality Index (PSQI), and Fatigue Severity Scale.

RESULTS
The mean age of older individuals was 71.32±6.33 years. There were significant positive and low relationships between exercise barriers in older individuals and the PSQI's sleep quality and day dysfunction owing to sleepiness (DAYDYS) subparameters, the PSQI total score and fatigue. Furthermore, significant negative and low relationships were found between the $PASE_{(Leisure\ activity)}$ and sleep duration, sleep quality, $PSQI_{(MEDS)}$, $PSQI_{(Total)}$, and fatigue severity, between the $PASE_{(Home\ activity)}$ and $PSQI_{(Total)}$ score, and between the $PASE_{(Work\ activity)}$ and sleep duration, sleep latency, and fatigue.

CONCLUSION
The study results suggest that conditions such as sleep quality and fatigue can be considered an exercise barrier. Regular exercise training planned for older individuals individually or as a group will improve sleep quality and provide improvement in their fatigue level. It is crucial to plan and implement in particular personal exercise and physical activity programs and lifestyle modifications, physiotherapy rehabilitation, and energy conservation techniques for sleep quality to maintain and improve the health of older individuals.

Keywords: Older, exercise barriers, physical activity, sleep, fatigue

INTRODUCTION

In the general population, persons older than 65 years experience fatigue significantly more than their younger counterparts (1). Fatigue, specifically in the elderly population, has been associated with many chronic diseases (2). Fatigue is a common symptom associated with these chronic diseases. Several factors, such as pain, sleep deprivation, and the stress of illness or surgery, could contribute to fatigue experienced by elderly persons. Pain may contribute to fatigue by increasing heart rate, blood pressure, respiratory rate, muscle tone, and oxygen consumption. Sleep deprivation results in limited non-rapid eye movement phase during sleep, decline in protein synthesis, and a slower rate of healing (3). In all age groups, insufficient oxygen transport to the muscles mainly caused by anemia, insufficient pumping of blood to

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the muscles caused especially by antineoplastic and cardiotoxic drugs (4), and severe muscle mass atrophy from the catabolic effects of sedentary habits and long-term bed rest (5) **c**an contribute to fatigue.

Nowadays, living by increasing the quality of life has become an issue that is as important as living long. Physical activity is one of the main factors to get older healthily and to minimize age-related health risks using various methods (6). The health benefits of physical activity are well known. Physical activity is effective individually in preventing chronic diseases and socially in improving public health, and it provides physical, social, mental, and spiritual benefits to women and men of all ages (7). Regular physical activity prevents the development of cardiovascular diseases, heart diseases, certain types of cancer, and all causes of mortality. Furthermore, regular physical activity has positive effects on blood pressure, lipid and lipid-protein profile, weight control, mental health, and psychological well-being (8). Regular physical activity supports the quality of life by strengthening the psychological well-being and physical functionality (9). Even moderate physical activity performed 3–4 times a week for 30-60 minutes is usually sufficient to reveal its positive effects on our health (10, 11).

Although the benefits of regular participation in physical activity are known, recent studies have revealed that participation in a physical activity is generally less than the recommended level (12). Moreover, poor physical fitness results from muscle weakness, decreased muscle mass, gait problems, fatigue, and impaired balance. It is necessary to develop the ability to perform daily life activities to improve the quality of life in geriatric cases. Likewise, performing daily physical activities requires a certain level of physical fitness (13). Physical fitness becomes increasingly important for older individuals because the decrease in physical activity is also a risk factor for falls (14). In particular, physical activity and physical fitness levels decrease with aging (15, 16). The physical activity levels of older adults are too low worldwide, with most studies reporting that between 40% and 80% of older people do not meet the physical activity guidelines (17, 18). In Turkey, physical inactivity rate in older adults is 33% (19). The results of scientific studies conducted to evaluate the physical activity habits in different segments of society indicate that physical activity has not yet become a lifestyle among older individuals in Turkey. This is thought to be caused by numerous perceived or actual exercise barriers (20)**.** General barriers for all older individuals include physical exertion, expense, embarrassment, and lack of time, motivation, and facilities. In addition, cohort effects may be seen in older individuals who were raised to avoid vigorous exercise and choose exercises considered 'proper for girls or boys' (21)**.** Barriers are significantly more important in influencing exercise patterns than perceived benefits (22). Therefore, the society should be inspirer and encouraging for older individuals to be more dynamic and active and to acquire regular exercise habits (23). Because it is never too late to start exercising and benefit from the many advantages that it provides (24), further research into the management and improvement of perceived barriers to exercise is needed. Therefore, this study aimed to determine exercise barriers in older individuals and to examine their relationship with physical activity, sleep, and fatigue.

Main Points:

- Poor quality sleep is an exercise barrier in older individuals.
- Fatigue is an exercise barrier in older individuals.
- Personalized exercise and physical activity programs should be planned for the maintenance and improvement of health in older individuals.
- Lifestyle modifications and physiotherapy rehabilitation programs are very important to improve sleep quality.
- It is very important to plan and apply energy conservation techniques to prevent fatigue.

MATERIAL and METHODS

Individuals aged more than 65 years who were staying in a private nursing home and elderly care center and volunteered to participate in the study were included. Based on the formula that is used for calculating the sample size of the unknown population, the minimum sample number was determined to be 90 older individuals by accepting a 95% confidence level and taking the margin of error as 0.1. Older individuals in the institution who met the inclusion criteria were included in the study. Healthy older individuals aged 65 years or older and who agreed to participate in the study, did not use a walking aid, were independent in mobilization, and did not have cooperation and communication problems (individuals with the mini-mental test score of >24) were included in the study. Patients who had cardiac diseases (angina pectoris, acute myocarditis, a history of myocardial infarction in the last 3 months, aortic aneurysm), pulmonary embolism and deep vein thrombosis in the last 3 months, a history of cerebral aneurysm or intracranial hemorrhage, acute retinal hemorrhage or past ophthalmic surgery, active infection, malignancy, multiple organ failure, terminal disease status, a history of fractures in the lower and upper extremities in the last 3 months, severe hearing and visual loss, Alzheimer's disease, Parkinson's disease, dementia diagnosis, and benign paroxysmal positional vertigo diagnosis were excluded from the study.

Ethics committee approval was received for this study from the ethics committee of Kırıkkale University, Non-interventional Research Ethics Committee, was found to be appropriate in terms of medical ethics (Meeting date: 16.01.2019; decision no: 2018.12.10).

A total of 100 older individuals were evaluated using the face-to-face interview method. First, parameters such as age, gender, marital status, nutritional characteristics, habits, smoking and alcohol use, used assistive devices, personal background information, family history information, educational status, social security, previous or current occupation, vision problems, sleep problem, frequency of falls, causes of falls, and the presence of chronic diseases were obtained. Their exercise barriers, physical activity levels, sleep conditions, and fatigue were evaluated by the Exercise Benefits/Barriers Scale, Physical Activity Scale for the Elderly (PASE), Pittsburgh Sleep Quality Index (PSQI), and Fatigue Severity Scale, respectively.

The Exercise Benefits/Barriers Scale: Ortabağ et al. performed the validity and reliability study of the scale in Turkish (25). The Exercise Benefits/Barriers Scale was developed by Sechrist, Walker, and Pender to determine the perceptions of individu-

als who would participate in the exercise of the exercise benefits and barriers (Cronbach's alpha coefficient, 0.87). The scale consists of 43 items. The scale has 4 answers ranging from 4 (strongly agree) to 1 (strongly disagree) in a conditional choice Likert scale format. The scale items 4, 6, 9, 12, 14, 16, 19, 21, 24, 28, 33, 37, 40, and 42 are scored inversely. The total score of the scale ranges from 43 to 172. The scale has 2 subgroups: the Exercise Barrier Scale and the Exercise Benefit Scale. Each subgroup can be used alone independently. The score range of the benefit scale is between 29 and 116, and the score range of the barrier scale is between 14 and 56. The sum of the scores of all items in the scale gives the total score of the Exercise Benefits/Barriers Scale. The higher the total scale score is, the more the individual has understood the benefits of the exercise (26).

The Physical Activity Scale for the Elderly: Ayvat et al. performed the validity and reliability study of the scale in Turkish (27) The PASE is short and easy to use. Validity and reliability studies have been performed for this scale, and in the literature, it is frequently used in the older population. The questionnaire assesses the physical activity of older individuals over the past week and includes the components of leisure, housework, and work-related physical activity. Participation in leisure time activities, such as walking activity outside the house, mild, moderate, and severe sports and recreational activities, and muscle strengthening exercises, is recorded as never, rarely (1–2 days/week), sometimes (3–4 days/week), and often (5–7 days/week), and the duration of activities is classified as <1 hour, 1–2 hours, 2–4 hours, and >4 hours. Cronbach's alpha coefficient was 0.714 for the initial evaluation (27).

The Pittsburgh Sleep Quality Index: Buysse et al. (28) developed the PSQI, which is used to assess sleep disturbances in individuals, and Ağargün et al. (29) conducted the validity and reliability study of the scale in Turkish. The PSQI is a 19-item self-report scale that assesses sleep quality and disturbances over the past month. Each item of the test is scored equally between 0 and 3. The scale consists of 7 subscales that assess subjective sleep quality, sleep latency, sleep duration, habitual sleep activity, sleep disorders, sleep medication use, and loss of daytime functionality. The scores of the subscales are summed up to obtain the total PSQI score, which ranges between 0 and 21. A total PSQI score of >5 indicates an insufficient sleep quality of an individual, with a sensitivity of 89.6% and specificity of 86.5%, and a severe disorder in at least 2 of the areas mentioned earlier or a moderate disorder in at least 3 of them (Cronbach's alpha coefficient, 0.80).

The Fatigue Severity Scale: The FSS was used to measure the individuals' fatigue. The validity and reliability of this scale have been proven (30). It is indicated as the best example of one-dimensional scales. The person specifies how much he or she agrees with each item by choosing among the numbers from 1 to 7; 1 indicates that he or she strongly disagrees, and 7 indicates that he or she strongly agrees. The score of the scale, which consists of 9 questions, ranges between 9 and 63. A score of 36 or higher indicates severe fatigue (intraclass correlation coefficient, 0.90; Cronbach's alpha coefficient, 0.91) (31).

Statistical Analysis

SPSS version 15 software was used for statistical analyses (SPSS Inc.; Chicago, IL, USA). Descriptive statistics was used to analyze the sociodemographic characteristics of the individuals. The data distribution normality was evaluated using the Shapiro-Wilk test. The variables obtained from the measurements were expressed as percentage (%) and arithmetic mean±standard deviation (X±SD). Correlations were examined by Pearson's correlation analysis (<0.3 (poor), 0.3–0.5 (fair), 0.6–0.8 (moderately strong), and ≥0.8 (very strong). P<0.05 was considered statistically significant.

RESULTS

The mean age of the study participants was 71.32±6.33 years. Their demographic information, marital status, educational level, the information on chronic diseases, vision and sleep problems are presented in Table 1. Notably, 79% of the individuals had a chronic disease. While 58% of the individuals had vision problems, 42% did not have any. While 37% of the participants stated that they had sleep problems, 63% stated that they did not have any (Table 1). The individuals' chronic pain distribution and Standardized Mini-Mental Test, PASE, PSQI, and FSS test scores are presented in Table 2.

There was a weak positive correlation between the age of the individuals and the PSQI's Need Meds To Sleep (MEDS) sub-

TABLE 1. Sociodemographic characteristics of individuals

	X±SD, n (%)
Age, year	71.32±6.33
Height, cm	160.65±26.59
Body weight, kg	72.26±11.68
BMI, kg/cm^2	26.53±4.46
Gender (n [%])	
Female	51 (51.0)
Male	49 (49.0)
Marital status (n [%])	
Married	73 (73.0)
Widowed	27 (27.0)
Educational status (n [%])	
Primary school	54 (54.0)
Secondary school	9 (9.0)
High school	14 (14.0)
University	6 (6.0)
Uneducated	17 (17.0)
The presence of chronic disease (n [%])	
There is	79 (79.0)
There is not	21 (21.0)
Visual problem (n [%])	
There is	58 (58.0)
There is not	42 (42.0)
Sleep problem (n [%])	
There is	37 (37.0)
There is not	63 (63.0)

BMI, body mass index

TABLE 2. The individuals' pain percentages according to regions and the SMMT, Exercise Barriers/Benefits Scale, PASE, PSQI, and FSS test mean scores

	X±SD	Med (min–max)
SMMT	26.26±2.03	26.26 (24–30)
Exercise Barrier Scale	34.22±6.10	34.22 (19–47)
Exercise Benefit Scale	65.95±12.49	65.95 (33–107)
Exercise Barriers/Benefits Scale total score	100.57±13.96	100.57 (70–136)
PASE leisure activity score	33.38±37.39	33.38 (0–228.55)
PASE housework activity score	69.47±43.23	69.47 (0–146.00)
PASE work activity score	3.15±7.53	3.15 (0–21)
PASE total score	118.46±165.08	118.46 (0–163.64)
Duration of Sleep (DURAT)	0.20±0.56	0.20 (0–3)
Sleep Disturbance (DISTB)	1.63±0.63	1.63 (1–3)
Sleep Latency (LATEN)	1.34±0.84	1.34 (0–3)
Day Dysfunction Due To Sleepiness (DAYDYS)	0.93±0.92	0.93 (0–3)
Sleep Efficiency (HSE)	0.53±0.96	0.53 (0–3)
Overall Sleep Quality (SLPQUAL)	1.12±0.67	1.12 (0–3)
Need Meds To Sleep (MEDS)	0.48±1.04	0.48 (0–7)
PSQI Total (PSQITOT)	6.12±2.84	6.12 (2–13)
FSS	39.90±12.75	39.90(9–63)

SMMT, Standardized Mini-Mental Test; PASE, Physical Activity Scale for the Elderly; FSS, Fatigue Severity Scale; PSQI, Pittsburgh Sleep Quality Index

scale and a very weak positive correlation between the PSQI total score and FSS. There was a weak positive correlation between the Exercise Barrier Scale and the PSQI's Day Dysfunction Due To Sleepiness (DAYDYS) and Overall Sleep Quality (SLPQUAL) subscale scores and a very weak positive correlation between the PSQI total score and FSS score. A very weak negative correlation was found between the Exercise Benefit Scale and the PASE total score. It was determined that the Exercise Barrier and Benefit Scale had a weak positive correlation with the DAYDYS subscale of the PSQI and a very weak positive correlation with the PSQI total score (Table 3).

A weak negative correlation was found between the $PASE_{(Leisure\ activity)}$ score and the scores of the Duration of Sleep (DURAT) and SLPQUAL subscales of the PSQI, and a very weak negative correlation was found between the $PASE_{(Leisure\ activity)}$ score and the scores of the MEDS subscale, total PSQI, and FSS. A very weak negative correlation was detected between the $PASE_{(Housework\ activity)}$ and the PSQI total scores. A very weak positive correlation was determined between the $PASE_{(Work\ activity)}$ and the DURAT scores, and a weak negative correlation was detected between sleep latency (LATEN) and FSS scores (Table 4).

DISCUSSION

Our study examined the relationship between exercise barriers/benefits and physical activity, sleep, and fatigue in older individuals. As a result, significant correlations were found between exercise barriers in older individuals and the PSQI's sleep quality and DAYDYS subparameters, the PSQI total score, and fatigue. Furthermore, significant correlations were detected between the $PASE_{(Leisure\ activity)}$ and sleep duration, sleep quality, $PSQI_{(MEDS)}$, $PSQI_{(Total)}$, and fatigue severity, between the $PASE_{(Home\ activity)}$ and $PSQI_{(Total)}$ score, and between $PASE_{(Work\ activity)}$ and sleep duration, sleep latency, and fatigue.

Exercise and physical activity have very significant benefits in older individuals and in all individuals (32). The importance of exercise for older individuals has been stated in many studies. Exercise positively affects bone structure, coordination, and mobility and thus decreases the risk of falls and fractures (33). Moreover, an important goal of exercise and physical activity in older individuals is to reduce the risk of falling. Falls in older individuals often cause injury, loss of functional independence, diseases associated with falls, and premature death (34). Alternatively, falling and the fear of falling are associated with increased psychological discomfort, limitation of activity and independence, and social isolation (35). Although significant evidence on the benefits of exercise for older individuals has been indicated, studies have reported that older individuals lead an increasingly passive life (36). In terms of physical activity, there are studies on motivational factors and exercise barriers in older individuals (37). In a study in which exercise barriers were explained, an individual's assessment of his or her health status as poor, pain, the lack of motivation, finding exercise boring, low belief in the individual's ability to exercise, exercise-associated pain, dizziness, shortness of breath, social concerns, and weather were indicated as the lack of information about the benefits of exercise (38). Burton et al. (39) reported that the barriers to older adults participating strength exercise training were poor health, risk of injury, pain, fatigue, lack of willpower, lack of positive attitude, low self-efficacy, lack of enjoyment, being too old, risk of heart attack, stroke or death, problems that interfere with daily living (work, social, etc.), nervousness or depression, lack of time, lack of knowledge, inconvenience, cost, low priority, lack of social support, lack of exercise facilities, geographic location, and lack of age-appropriate programs. Another study reported that the lack of time was a selected barrier by 27.4% of individuals aged 60–64 years, 16.1% of those aged 65–69 years, and 7.1% of those aged ≥70 years. The lack of company (e.g. friends) and cognitive problems emerged as the most important barrier to physical activity among older adults (40). Sleep problems in older adults can cause fatigue, daytime sleepiness, and napping. Sleep problems also affect general functioning and activities of daily living and are associated with an increase in functional impairments, poorer quality of life, and cognitive and mental issues (41). Therefore, we believe that sleep problems can also be an exercise barrier in older individuals. It is crucial to identify and overcome exercise barriers to enable the transition of older individuals from a sedentary lifestyle to a more active lifestyle (42).

By preventing chronic diseases often through reducing the associated effects of age-related biological changes on health and well-being, regular physical activity and exercise increase the average life expectancy (43). Maintaining an active life physically and mentally, an adequate and balanced diet, avoiding smoking and alcohol use, regular sleep, and stress control are key to healthy aging. Maintaining a physically active life leads to developing and maintaining physical fitness and supporting mental activities and reduces the risk of chronic diseases in

TABLE 3. Correlation between years, exercise barriers/benefits scale with sleep, physical activity, and fatigue

		Years	Exercise Barrier Scale	Exercise Benefit Scale	Exercise Barriers/ Benefits Scale Total
PSQI					
Duration of Sleep (DURAT)	r	0.007	-0.042	0.053	0.018
	p	0.943	0.679	0.603	0.856
Sleep Disturbance (DISTB)	r	0.172	-0.013	-0.025	-0.006
	p	0.088	0.900	0.801	0.949
Latency	r	0.134	-0.001	0.051	0.047
	p	0.182	0.993	0.618	0.641
Day Dysfunction Due To Sleepiness (DAYDYS)	r	0.130	0.279**	0.154	0.297**
	p	0.198	0.005	0.127	0.003
Sleep Efficiency (HSE)	r	0.018	-0.071	0.147	0.099
	p	0.858	0.482	0.146	0.328
Overall Sleep Quality (SLPQUAL)	r	0.012	0.299**	-0.037	0.094
	p	0.904	0.002	0.717	0.353
Need Meds To Sleep (MEDS)	r	0.293*	0.026	0.129	0.103
	p	0.003	0.798	0.201	0.308
PSQI total (PSQITOT)	r	0.198*	0.207*	0.127	0.211*
	p	0.049	0.039	0.207	0.035
PASE					
PASE leisure activity score	r	-0.038	0.089	-0.183	-0.102
	p	0.704	0.381	0.068	0.314
PASE housework activity score	r	-0.190	-0.131	-0.017	-0.047
	p	0.058	0.193	0.864	0.642
PASE work activity score	r	-0.132	0.054	0.022	0.085
	p	0.189	0.594	0.828	0.402
PASE total	r	0.081	0.066	-0.215*	-0.152
	p	0.423	0.516	0.031	0.131
Fatigue					
FSS	r	0.239*	0.260**	-0.138	0.042
	p	0.020	0.009	0.172	0.679

*p<0.05; **p<0.001. US, unaffected side; AS, affected side; PASE, Physical Activity Scale for the Elderly; FSS, Fatigue Severity Scale; PSQI, Pittsburgh Sleep Quality Index

older individuals (44). Sleep is one of the essential components of health-related quality of life (45). Increasing physical, social, psychological, and environmental changes with aging can lead to frequent sleep problems (46). Sleep quality is critical to maintain the homeostasis of the human body, which has been reported to be effective in the regulation of body temperature, metabolism, and immunity and the development, maturation, and plasticity of the brain, memory formation, and integration (47). It is believed that the need for sleep does not change with age, but sleep ability, as required, decreases mainly because of other factors such as physical or psychiatric diseases, excessive medication use, progression in the endogenous circadian rhythm, and age (48). Inadequate sleep quality in older individuals may result in decreased physical functionality, memory problems, increased risk of falls, and increased early mortality rates (48). Although there are very few studies, the relationship between sleep and physical function has been examined. Results indicate that sleep complaints and sleep disturbances are associated with functional independence (49). Furthermore, sleep quality is emphasized to be low in sedentary older individuals who have functional limitations (50). In the literature, physical activity in older individuals for at least 20–30 minutes per week was stated to positively affect sleep quality and general health (51). In the study conducted on 2825 older individuals to evaluate sleep problems, Stenholm et al. (52) demonstrated that they were closely related to fatigue and physical functionality and that the evaluation of these factors in older individuals was important to identify individuals who had the risk of mobility dependence.

When the literature is examined, no studies that indicate that sleep quality may be one of the exercise barriers in older individuals are found. In the literature, studies have shown that sleep quality in older individuals is associated with functional independence. Therefore, because we believe that sleep quality may also be an exercise barrier, we evaluated sleep quality in older individuals in our study. The study results showed that a significant correlation was found between exercise barriers and sleep quality, DAYDYS, and the PSQI total score. Based on these results, we believe that sleep and sleep quality are exercise barriers in older individuals. We believe that regular and high-quality sleep ensures that older individuals keep fit and encourages them to exercise. Furthermore, in this study, in accordance with the literature, a significant correlation was detected between the $PASE_{(leisure\ activity)}$ and sleep duration, sleep quality, $PSQI_{(MEDS)}$, and $PSQI_{(Total)}$, and a significant correlation was also

TABLE 4. Correlation of physical activity with sleep and fatigue

		PASE			
		Leisure activity	**Housework activity**	**Work activity**	**PASE total**
PSQI					
Duration of Sleep (DURAT)	r	-0.290**	-0.051	0.198*	0.028
	p	0.003	0.616	0.048	0.781
Sleep disturbance (DISTB)	r	-0.137	-0.119	-0.020	0.005
	p	0.173	0.240	0.843	0.958
Latency	r	-0.085	-0.038	-0.270**	-0.099
	p	0.402	0.708	0.007	0.327
Day Dysfunction Due To Sleepiness (DAYDYS)	r	-0.172	-0.053	0.093	-0.136
	p	0.086	0.602	0.358	0.178
Sleep Efficiency (HSE)	r	-0.160	-0.087	0.001	-0.126
	p	0.111	0.390	0.989	0.210
Overall Sleep Quality (SLPQUAL)	r	-0.296**	0.002	-0.076	0.053
	p	0.003	0.985	0.455	0.600
Need Meds To Sleep (MEDS)	r	-0.208*	-0.137	0.075	-0.122
	p	0.038	0.174	0.458	0.226
PSQI Total (PSQITOT)	r	-0.227*	-0.205*	0.012	-0.148
	p	0.023	0.041	0.907	0.141
Fatigue					
FSS	r	-0.212*	-0.140	-0.394**	-0.141
	p	0.034	0.164	0.000	0.163

*p<0.05; **p<0.001. US, unaffected side; AS, affected side; PASE, Physical Activity Scale for the Elderly; FSS, Fatigue Severity Scale

detected between the $PASE_{(home\ activity)}$ and $PSQI_{(Total)}$ score and between the $PASE_{(work\ activity)}$ and sleep duration and sleep latency. Physical activity in older individuals has been proven to be critical in terms of physical, mental, and psychological aspects (32). With this study, we believe that older individuals should be encouraged to do physical activity to improve their sleep duration and sleep quality and that their physical activity should be increased.

Fatigue is a condition that is felt at moderate and severe degrees during the aging process and is more common compared with adult individuals (53). In a study by Larsen et al. (54) who monitored fatigue in daily living activities, they evaluated older individuals in the 5th, 10th, and 15th years and noted that fatigue levels increased 9-fold in the 5th year and 2-fold in the 10th and 15th years compared with the 5th year. This situation was associated with increased functional disability in older individuals. Yu et al. (53) stated that fatigue occurring with daily living activities in older individuals who were followed up for 1.5 years caused mobility deficiency by 3-fold in older women and 2-fold in older individuals. They also found that the rate of chronic fatigue in older individuals was 47.9%. They also emphasized that the most common cause of fatigue in older individuals was sleep disturbance and the lack of exercise.

In the literature, it has been reported that the prevalence of fatigue increases with age and it is higher in older female individuals than in male individuals, and this is the most common cause of activity limitation in older individuals (55). In our study, a positive correlation was also found between age and fatigue severity. Similar to the literature, this study found that fatigue severity increases with increasing age. The reason for observing fatigue at a rate of 27% to 50% in older individuals may be chronic diseases, pain, malnutrition, and psychosocial factors (56). Fatigue in older individuals affects pain and mobility, leading to an inability to perform daily living activities (57). However, the interrelationship of other factors in the aging process, such as inflammation, depression, sleep complaints, self-efficacy, fatigue, and physical function, is complex and has not been fully explained (58). In our study, a significant relationship was found between the fatigue levels of older individuals and exercise barriers, the $PASE_{(Leisure\ activity)}$ and $PASE_{(Work\ activity)}$. In accordance with these results, we believe that fatigue is an exercise barrier in older individuals and that fatigue level is a factor affecting their physical activities.

According to the results of our study, a significant correlation was found between exercise barriers and sleep quality, DAYDYS, PSQI total score, and fatigue. A significant correlation was detected between the $PASE_{(Leisure\ activity)}$ and sleep duration, sleep quality, $PSQI_{(MEDS)}$, and $PSQI_{(Total)}$, and there was also a significant correlation between the $PASE_{(Home\ activity)}$ and $PSQI_{(Total)}$ score and between the $PASE_{(Work\ activity)}$ and sleep duration and sleep latency. Moreover, a significant correlation was found between fatigue levels and exercise barriers, the $PASE_{(leisure\ activity)}$ and $PASE_{(work\ activity)}$. Considering these results, the evaluation of exercise barriers of older individuals in detail and the suggestion of appropriate physiotherapy and rehabilitation approaches will increase the functional independence of older individuals and improve their quality of life. According to the results of our study,

conditions such as sleep quality and fatigue can be considered an exercise barrier. Regular exercise training planned for older individuals individually or as a group will improve sleep quality and provide improvement in the fatigue level. It is crucial to plan and implement in particular personal exercise and physical activity programs and lifestyle modifications, physiotherapy rehabilitation, and energy conservation techniques for sleep quality to maintain and improve the health of older individuals.

Limitations of the Study

Our work was done in a single nursing home. We believe the number of elderly individuals is insufficient. This study can be done by increasing the number of elderly individuals. In addition, the physical activities of older individuals can be evaluated with more objective tools.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kırıkkale University, Non-interventional Research Ethics Committee, was found to be appropriate in terms of medical ethics (Meeting date: 16.01.2019; decision no: 2018.12.10).

Informed Consent: All individuals included in the study were informed in detail about the purpose and methodology of the study, and their consent for participation in the study was obtained.

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The Prevalence of Overweight and Obesity among Students between the Ages of 6 and 15 years in Konya

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BACKGROUND/AIMS
This study was conducted to determine the prevalence of overweight and obesity among primary school students.

MATERIAL and METHODS
A total of 10781 students (5622 boys, 5159 girls) aged 6–15 years participated in the study. Descriptive statistics of the data were expressed as mean, standard deviation, maximum, minimum, and range values. The Kolmogorov–Smirnov test was applied and Q-Q plot analysis was performed visually to determine if the data was normally distributed. Since the data were not normally distributed, the LMS (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation) method was used to calculate the percentiles.

RESULTS
The prevalence of overweight was 7.4% in both sexes, while the prevalence of obesity was 5.8% for boys and 5.3% for girls. The age group with the highest prevalence of overweight was 13 years (9.6%) in boys and 15 years (13.5%) in girls, while that with the highest prevalence of obesity was found to be 8 and 10 years (6.6%) in boys and 8 years (6.5%) in girls.

CONCLUSION
It is remarkable that obesity is high in both sexes, especially in young children. Preventive interventions to stop this trend are recommended to focus on the early stages of childhood.

Keywords: Childhood obesity, students, overweight, prevalence

INTRODUCTION

Obesity is characterized by an increase in adipose tissue that leads to many chronic diseases and premature deaths and is a worldwide global epidemic (1). Obesity, which is an important cause of morbidity due to hypertension, dyslipidemia, insulin resistance, and severe psychological stress, is increasingly being observed in childhood (2). Childhood obesity is one of the most serious public health problems of the 21st century. The problem is global and affects many low and middle-income countries regularly, especially in urban settings. Overweight and obese children are more likely to become obese in adulthood and may develop noncommunicable diseases such as diabetes and cardiovascular diseases at a younger age (3). It also contributes to an increase in health expenditures. For all these reasons, it is important to prevent childhood and to identify overweight and obese children at an early stage, so that they can start treatment to gain and maintain a healthy weight (4).

One of the most reliable indicators for assessing a child's health is the weight and height measurements by age. Anthropometric measurements are the most commonly used methods for evaluating the nutritional status of not only individuals, but also the society. Although the standards proposed by the World Health Organization are suggested to be valid for almost every country in the first years of life, differences can be detected between societies at this early age (5).

This study was conducted to determine the prevalence of overweight and obesity among primary school students.

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TABLE I. Descriptive statistics of subjects

			Height (cm)		Body Weight (kg)		Body Mass Index (kg/m²)	
Gender	Age group	n	Mean±SD	Min-Max (Range)	Mean±SD	Min-Max (Range)	Mean±SD	Min-Max (Range)
Boys	6	77	119,59±5,44	110,0-134,0 (24,0)	23,73±4,22	16,5-42,7 (26,2)	16,51±2,05	11,9-23,8 (11,9)
	7	447	122,10±5,55	108,5-144,0 (35,5)	24,52±4,88	16,8-64,3 (47,5)	16,35±2,20	11,4-31,0 (19,6)
	8	441	127,30±5,60	111,0-148,5 (37,5)	26,95±4,96	17,2-54,4 (37,2)	16,53±2,08	12,3-27,4 (15,1)
	9	544	132,90±6,18	115,0-159,0 (44,0)	30,80±6,40	18,3-56,6 (38,3)	17,31±2,59	13,4-28,3 (14,9)
	10	1126	136,20±6,23	104,0-155,5 (51,5)	32,82±6,64	19,6-62,3 (42,7)	17,60±2,79	13,0-32,0 (19,0)
	11	1121	141,39±6,55	122,0-165,0 (43,0)	36,96±8,30	20,7-89,3 (68,6)	18,36±3,20	12,1-37,2 (25,1)
	12	873	147,39±7,54	123,0-173,0 (50,0)	41,90±10,26	24,1-91,1 (67,0)	19,11±3,50	12,9-34,8 (21,9)
	13	501	155,38±8,36	134,0-181,0 (47,0)	48,14±11,90	26,4-117,5 (91,1)	19,76±3,74	13,7-38,8 (25,1)
	14	440	162,77±8,49	142,0-192,5 (50,5)	55,57±12,43	32,7-105,8 (73,1)	20,85±3,88	14,9-36,7 (21,8)
	15	52	166,61±7,62	150,5-182,0 (31,5)	55,81±12,32	37,1-91,4 (54,3)	19,99±3,59	14,8-31,6 (16,8)
Girls	6	79	117,07±4,28	109,0-128,0 (19,0)	21,94±3,12	16,4-30,2 (13,8)	15,98±1,86	12,2-23,0 (10,8)
	7	465	120,98±5,36	101,0-141,0 (40,0)	23,83±4,46	14,5-45,9 (31,4)	16,20±2,26	12,2-29,6 (17,4)
	8	444	125,85±5,55	106,5-147,0 (40,5)	26,26±5,17	17,1-49,1 (32,0)	16,48±2,43	12,5-27,7 (15,2)
	9	461	131,69±5,87	117,0-155,0 (38,0)	30,05±6,75	18,5-63,0 (44,5)	17,21±2,99	12,5-30,2 (17,7)
	10	1089	135,48±6,71	113,0-162,0 (49,0)	32,38±7,19	17,0-72,0 (55,0)	17,51±2,89	11,0-34,7 (23,7)
	11	1007	141,56±7,24	119,0-169,5 (50,5)	36,55±8,29	21,2-85,9 (64,7)	18,10±3,03	12,1-32,5 (20,4)
	12	778	148,46±7,75	120,0-170,0 (50,0)	42,28±9,54	20,0-79,1 (59,1)	19,04±3,28	12,6-33,6 (21,0)
	13	387	156,04±6,41	129,0-177,0 (48,0)	49,16±10,50	27,9-100,0 (72,1)	20,09±3,55	12,0-33,7 (21,7)
	14	397	159,33±5,62	143,0-181,0 (38,0)	53,94±10,67	31,9-97,8 (65,9)	21,20±3,78	14,4-38,7 (24,3)
	15	52	159,01±5,40	149,0-179,0 (30,0)	53,89±11,2	34,5-94,8 (60,3)	21,25±3,82	15,1-30,3 (15,2)

MATERIAL and METHODS

The study was conducted on a total of 10781 (5622 boys, 5159 girls) students in the 6-15 years age group studying in 16 primary schools in Konya city center. The necessary permission for the study was obtained from the Provincial Directorate of National Education and the schools were informed before the study. Body weight measurements of children were obtained with light weight clothes and without shoes and jackets by electronic weighing with a sensitivity of ±100 gr. Height measurements were taken with the shoes removed, heels combined, hip, and shoulders based on the wall with 1-mm spacing.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Selçuk University Faculty of Sports Science Non-interventional Clinical Research. Prior to the study, the subjects were informed about the study, and their written consent stating that they agreed to participate in the study were received.

Main Points:

- Obesity is characterized by an increase in adipose tissue and is a worldwide global epidemic.
- In this study, the prevalence of overweight and obesity among primary school students were determined.
- The prevalence of overweight was 7.4% in both sexes, while the prevalence of obesity was 5.8% for boys and 5.3% for girls.
- As a result, it is striking that obesity is high in both genders, especially in young children.

Statistical Analysis

Considering the obtained data, mean and standard deviation values were used to calculate the percentile values (5, 10, 25, 50, 75, 90, and 95) for each sex and age group. For each category, based on statistical Z-scores, the expected BMI was calculated according to how many Z-points are away from the average. However, because the 85th percentile for BMI was the recommended threshold value for "overweight" classification for children and adolescents (6, 7), 85% was also included in the calculations and for the "overweight" category as the cut-off point. Descriptive statistics of the data are given as mean, standard deviation, maximum, minimum, and interval. The Kolmogorov-Smirnov test and Q-Q plot analysis were used to test the normal distribution of the data. The following formula (8) is used to calculate the values:

$$Z_{LMS} = \frac{1}{\sigma_L \lambda}\left[\left(\frac{y}{\mu}\right)^{\lambda} - 1\right]$$

Reference values were calculated for each age group using the calculated Z values for the obtained critical percentile values.

RESULTS

In Table I, average, minimum, maximum, and standard deviation values of height, body weight, and body mass index variables are given according to the age groups for girls and boys.

It was found that BMI values did not meet the normal distribution assumption according to the Kolmogorov-Smirnov test results (p<0.01) (Table 2).

Table 3 shows the percentile values of the body mass index according to the age groups of the boys.

The distribution by the BMI categories for boys is shown in Table 4. Accordingly, the "overweight" prevalence of boys aged 6-15 years ranged from 2.6% to 9.6% (overall prevalence 7.4%), and the highest prevalence was found to be in the 13-year category (9.6%). When the obesity prevalence was examined, it was found that the children in the 8 and 10 years age groups had the highest obesity prevalence (6.6%) and the overall obesity prevalence was 5.8% (Table 4).

Table 5 shows the percentile values of body mass index according to the age groups of girls.

The distribution by BMI categories for girls is shown in Table 6. Accordingly, the "overweight" prevalence of girls between the ages of 6-15 years ranged from 4.9% to 13.5% (overall prevalence 7.4%), and the highest prevalence was found to be in the 15-year category (13.5%). When the prevalence of obesity was examined, it was found that children in the 8-year age group had the highest obesity prevalence (6.5%) and the overall obesity prevalence was 5.3% (Table 6).

TABLE 2. Testing the appropriateness of BMI values to normal distribution

	Kolmogorov-Smirnov		
	Statistical Value	**df**	**p**
Boy	0.124	5622	0.00*
Girl	0.101	5159	0.00*

*p<0.01

DISCUSSION

To determine the prevalence of overweight and obesity among primary school students, the prevalence of overweight was 7.4% in both sexes; the prevalence of obesity was 5.8% for boys and 5.3% for girls. The age group with the highest prevalence of overweight was 13 years (9.6%) in males and 15 years (13.5%) in females; The highest prevalence of obesity was found in the age range of 8 and 10 years (6.6%) in boys and 8 years (6.5%) in girls (Table 4, 6).

TABLE 3. BMI percentile values for boys

	Percentiles							
Age	**5%**	**10%**	**25%**	**50%**	**75%**	**85%**	**90%**	**95%**
6	13.44	14.06	15.19	16.51	17.94	18.78	19.37	20.25
7	13.09	13.74	14.94	16.35	17.89	18.80	19.44	20.40
8	13.42	14.05	15.19	16.53	17.98	18.84	19.44	20.33
9	13.51	14.26	15.66	17.31	19.13	20.22	20.98	22.14
10	13.54	14.34	15.82	17.60	19.57	20.75	21.58	22.84
11	13.75	14.65	16.33	18.36	20.63	22.00	22.97	24.45
12	14.11	15.08	16.90	19.11	21.60	23.11	24.18	25.82
13	14.44	15.47	17.40	19.76	22.43	24.04	25.20	26.96
14	15.32	16.39	18.40	20.85	23.61	25.29	26.48	28.30
15	14.84	15.84	17.72	19.99	22.54	24.08	25.18	26.85

TABLE 4. Distribution by BMI categories for boys

	Weak		Normal		Overweight		Obese	
Age	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
6	1	1.3	69	89.6	2	2.6	5	6.5
7	2	0.4	400	89.5	22	4.9	23	5.1
8	8	1.8	377	85.5	27	6.1	29	6.6
9	5	0.9	464	85.3	40	7.4	35	6.4
10	12	1.1	971	86.2	69	6.1	74	6.6
11	13	1.2	953	85.0	96	8.6	59	5.3
12	10	1.1	743	85.1	72	8.2	48	5.5
13	7	1.4	424	84.6	48	9.6	22	4.4
14	9	2.0	369	83.9	35	8.0	27	6.1
15	1	1.9	44	84.6	4	7.7	3	5.8
General	68	1.2	4814	85.6	415	7.4	325	5.8

TABLE 5. BMI percentile values for girls

	Percentiles							
Age	**5%**	**10%**	**25%**	**50%**	**75%**	**85%**	**90%**	**95%**
6	13.18	13.75	14.78	15.98	17.27	18.03	18.56	19.35
7	12.86	13.53	14.75	16.20	17.78	18.72	19.38	20.38
8	12.91	13.62	14.93	16.48	18.19	19.20	19.92	21.00
9	12.90	13.74	15.32	17.21	19.33	20.61	21.52	22.90
10	13.32	14.14	15.67	17.51	19.55	20.78	21.65	22.97
11	13.72	14.57	16.18	18.10	20.24	21.53	22.45	23.83
12	14.31	15.23	16.96	19.04	21.37	22.76	23.76	25.27
13	14.99	15.98	17.84	20.09	22.61	24.13	25.21	26.86
14	15.78	16.83	18.81	21.20	23.88	25.51	26.66	28.41
15	15.77	16.84	18.83	21.25	23.96	25.61	26.77	28.55

TABLE 6. Distribution by BMI categories for girls

	Weak		Normal		Overweight		Obese	
Age	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
6	1	1.3	66	83.5	7	8.9	5	6.3
7	5	1.1	410	88.2	23	4.9	27	5.8
8	1	0.2	390	87.8	24	5.4	29	6.5
9	3	0.7	403	87.4	34	7.4	21	4.6
10	24	2.2	922	84.7	85	7.8	58	5.3
11	23	2.3	846	84.0	86	8.5	52	5.2
12	17	2.2	662	85.1	56	7.2	43	5.5
13	10	2.6	327	84.5	33	8.5	17	4.4
14	16	4.0	332	83.6	29	7.3	20	5.0
15	2	3.8	41	78.8	7	13.5	2	3.8
General	102	2.0	4399	85.3	384	7.4	274	5.3

According to the 2015-2016 data, the prevalence of obesity in the United States was higher among youths aged 6-11 years (18.4%) and adolescents aged 12-19 years (20.6%) compared with children aged 2-5 years (13.9%) (9). In Nigeria, with an average age of 14.6 years, 2.1% of children were overweight and 1.7% were obese (10). In a study that investigated a systematic review of childhood obesity in the Middle East and North Africa, the prevalence of overweight and obesity in Kuwait was 25.6% and 34.8% among young boys, and 20.8% and 20.5% among girls (11). In studies conducted in different regions of our country, 5%-13.8% of the children were found to be overweight and 4.9%-20.7% were obese (12-16). In a study conducted in semi-rural children aged 6-14, it was determined that approximately one out of every three children were overweight or obese, while boys were overweight and obese (17.7% and 15.2%) and girls (13.3% and 9.2%) (17). Our data support the fact that overweight and obesity are an increasing public health problem.

In these studies, the frequency of obesity among the students; sex, child's birth weight, parent's body mass index, high socio-economic level, high maternal education, number of obese relatives, feeding habits, parents' dissatisfaction with the child's weight, sport activity, time spent in front of a computer and television, and nutrition preferences were reported (13, 18-22). In a study, it was found that the prevalence of obesity increased significantly in rural areas and that the awareness of the families about their children's weight was low and it was concluded that the family-based approach to combating childhood obesity should be strengthened and the number of parental education should be increased (15). To detect the excess weight and obesity problems early and take the necessary precautions, it is necessary to monitor the body weight, height, and body mass index of the students from an early age. In addition, national health policies and social responsibility projects should focus more on combating child and adolescent obesity and developing solution-oriented policies (23). Öztürk and Aktürk (24) found that the prevalence of overweight and obesity was significantly higher in the 5-8 years age group and in students in schools classified as socioeconomically good. Therefore, they stressed the need to raise awareness of families and students about this problem, which is likely to increase in the coming years, by using other channels, such as health personnel and the media. In this study, physical activity levels and nutrition habits of 7-14 year-old students were examined to increase the level of physical activity and activities to be combined with healthy eating habits that

could prevent future health problems and healthy aging awareness in early ages, with the right interaction with other family members who are more active (25).

In conclusion, as a result, further research is needed to fully investigate the role of a sedentary life style, nutrition, and other specific risk factors, to manage this common and growing health problem, and to evaluate various interventions. There is an increasing tendency to obesity in our country, especially at young ages. We recommend that health policy makers prioritize early childhood to stabilize this rising trend and implement intervention strategies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University Faculty of Sports Science Non-interventional Clinical Research.

Informed Consent: Written informed consent was obtained from the students who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Ş.A., S.R.; Design - Ş.A., S.R.; Supervision - Ş.A.; Fundings - Y.U.K.; Materials - Y.U.K.; Data Collection and/or Processing - S.R.; Analysis and/or Interpretation - Y.U.K.; Literature Search - ŞA., S.R.; Writing - Ş.A., S.R.; Critical Reviews - Ş.A., S.R.

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Original Article

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Evaluation of the Effect of Gabapentin on Tendon Healing in an Experimental Rat Model

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BACKGROUND/AIMS
To investigate the effect of gabapentin used in postoperative pain prophylaxis on tendon healing.

MATERIAL and METHODS
A total of 32 Wistar albino rats were randomly divided into 4 groups. Groups A and C were administered gabapentin by oral gavage, while Groups B and D were defined as the control groups. In all the rats, a transverse cut was made on the left Achilles tendon, approximately 0.5 cm proximal to the attachment point of the bone, then it was sutured using the Kessler method. Rats in Groups A and B were sacrificed on day 15 and those in Groups C and D on day 45. Differences between the groups were evaluated biomechanically using the tensile test, and immunohistochemically by examinations of collagen type I (COLIA), Proliferating Cell Nuclear Antigen (PCNA), and Transforming Growth Factor β1 (TGF-β1).

RESULTS
In the biomechanical evaluations, no significant difference was found between the study and control groups on days 15 and 45 in terms of the tensile test results (day 15, p=0.908; day 45, p=0.798). In the semi-quantitative comparisons of positive cell involvement in the immunohistochemical data evaluations, no statistically significant difference was also found. [TGF-β1, p(15)=0.328, p(45)=0.195; PCNA p(15)=0.645]. PCNA-positive cells were seen at a high rate in the first 15 days in both groups and the involvement of these cells was found to be similar on day 45.

CONCLUSION
In the immunohistochemical and biomechanical evaluations, gabapentin was not found to have any negative effect on tendon healing. It can be concluded that gabapentin can be used in cases with appropriate indications after tendon surgery. Nevertheless, there is a need for further studies in this area to investigate the mechanism of gabapentin's effect on the tendon.

Keywords: Gabapentin, tendon healing, experimental study

INTRODUCTION

Tendon health and function is very important for orthopedic surgeons. Tendon injuries can occur in some trauma patients, and for trauma surgeons, not only the tendon repair surgery is important, but also the functional treatment outcomes. Good functional treatment outcomes are obtained with early physical therapy (1). Early movement after the repair depends on the method used and the tendon healing (2). Postoperatively or during the physical therapy, several medications are administered to the patient as pain prophylaxis. The effects of conventional analgesics on tendon healing have been frequently discussed in the literature (3, 4). The use of gabapentin for pain prophylaxis after orthopedic surgeries is increasing. In the literature, it has been shown that gabapentin leads to a reduction in postoperative pain severity and total opioid consumption (5). It is often recommended for pain prophylaxis after surgeries such as rotator cuff repair, total knee arthroplasty, and total hip arthroplasty (5-9).

It has also been found to be effective in treating patients with chronic pain syndrome and diseases such as fibromyalgia, neuropathic pain, complex regional pain syndrome, trigeminal neuralgia, post-herpetic neuralgia, and neuropathic arthropathies (10).

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The reported positive effects of gabapentin in postoperative pain prophylaxis have led to the increased use of this drug. There are studies in literature regarding the effects of gabapentin on fracture and wound healing (11, 12). Gabapentin [1-(aminomethyl)cyclohexane acetic acid] is an anti-epileptic agent (13). Despite the analog structure of gabapentin γ-aminobutyric acid, its function is mediated through pre-synaptic P/Q type voltage-gated calcium channels (14).

Although gabapentin use against musculoskeletal pain is gradually increasing, its effect on tendon healing is unknown. To the best of our knowledge, there is no study in the literature that has evalauted the effect of gabapentin on tendons. Thus, this study is the first in the literature to evaluate the effects of gabapentin on tendon healing. The main purpose of this study was to assess the histological and mechanical effects of gabapentin on tendon healing in a rat model of Achilles tendon transection.

MATERIAL and METHODS

This study was approved by the Animal Research Local Ethics Committee (decision no:56, dated:15.08.2017). It was conducted according to the Guide for the Care and Use of Laboratory Animals. A total of 32 female Wistar albino rats, aged 10±1.2 weeks, each weighing 200–220 gr, were used in the study. The animals were obtained from the Animal Research laboratory and all through the experiment, all the care of the animals was undertaken in the same center. To ensure the adaptation to the new environment, all the animals were kept and fed in new cages in the laboratory, one week before starting the experiment. A total of 8 rats were housed in each cage in a manner that did not prevent movement. Fresh food and water were given daily.

Preparation of the Groups

The rats were randomly divided into 4 groups of 8. Groups A and C were administered gabapentin while Groups B and D as the control groups were not administered no drugs. The drugs were administered by the oral gavage route starting from 4 hours postoperatively. The daily gabapentin dose for Groups A and C was calculated based on the body surface area and was determined to be equal to the human dose of 1200 mg/day. To standardize the stress factors for the control group rats, 1% methylcellulose was administered by oral gavage at the same time as the treatment to the study group rats. The Groups A and B rats were administered ketamine anesthesia and sacrificed by cervical dislocation on postoperative day 15, and the same procedure was applied to the Groups C and D rats on postoperative day 45.

Main Points:

- To the best of our knowledge, no study in the literature has examined the effect of gabapentin on tendons.
- The fact that no difference was observed between the groups biomechanically demonstrates that gabapentin could be used in pain prophylaxis after tendon surgery, when there are suitable indications
- The immunohistochemical and biomechanical evaluations of this study showed that gabapentin does not have a negative effect on tendon healing.

Surgical Technique

Anesthesia consisting of a xylazine and ketamine HCl mixture was injected intramuscularly to all the rats by the same surgeon. A single dose of antibiotic (cefazolin sodium 5mg) prophylaxis was given. The left lower extremity was prepared with povidone-iodine solution and a sterile drape. A longitudinal 3-cm skin and subcutaneous incision was made from the midline along the course of the Achilles tendon. The Achilles and plantaris tendons were stripped from the surrounding fascia. A full-layer transverse cut was made, approximately 0.5 cm proximal from the attachment site of the Achilles tendon to the calcaneus. The plantaris tendon was also included in the cut. Primary repair of the sectioned tendons was performed with the modified Kessler method using 6-0 Ethilon monofilament nylon sutures (Ethicon, USA) (Figure 1). The skin and subcutaneous layers were sutured with 3-0 Ethilon monofilament nylon sutures. No fixation was used postoperatively. All through the experiment, standard care was applied to all the animals, and they were permitted to move freely within their cages.

Biomechanical Evaluation

The biomechanical differences between the study groups in terms of the breaking strengths of the tendons were investigated in the Biomechanics Laboratory of the Dentistry Faculty of our university. From each group, 8 calcaneus-Achilles complex samples were placed on a Lloyd LF Plus model device (Ametek Inc, Lloyd Instruments, Leicester, UK) using a specially designed holder (Figure 2). The normal tendons were evaluated using the non-operated right-side Achilles tendon complex. Tensile force was applied at 5N/sec. Before starting the test, calibration was performed for the loading and extension amounts of all the Achilles tendon com-

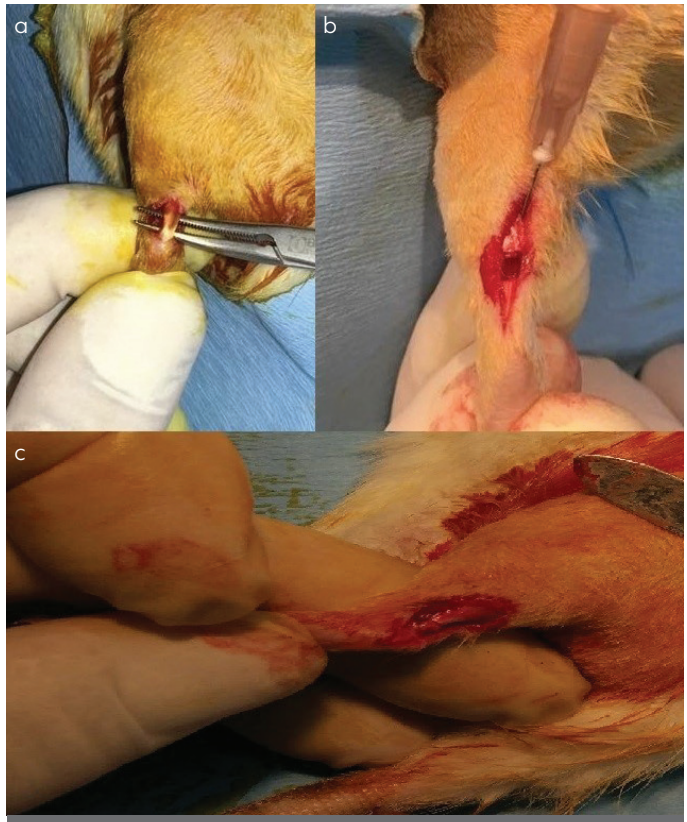

FIGURE 1. a-c. Photograph of the Achilles tendon a) before transection, b) after transection, and c) after surgical repair

FIGURE 2. Specimen during the mechanical test

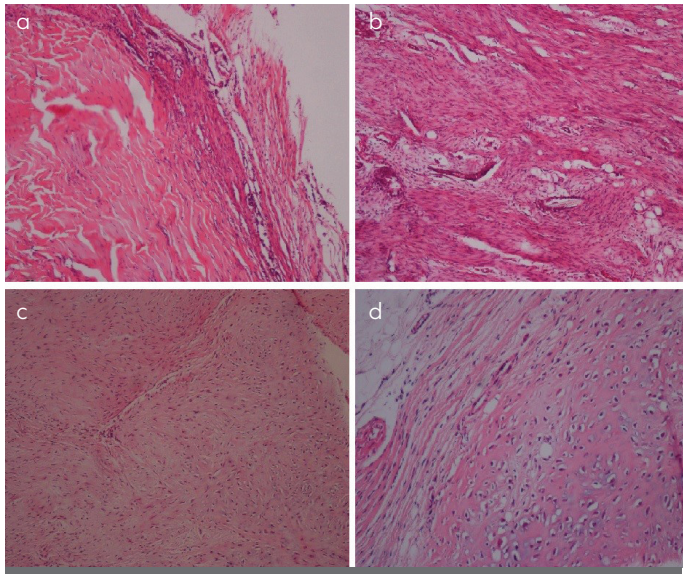

FIGURE 3. a-d. a) Group A collagenized areas, b) Group B, c) Group C, d) Group D chondrocytes-like cell (H & E, ×20)

plexes. The extension amount of the tendons was measured via a computer attached to the device. All the loading and deformation tests were applied and recorded using the Lloyd Instruments Data Analysis Package system. For pre-tensile equalization, a 2N pre-loading was applied to all the tendons.

Histological Evaluation

The samples obtained from the experimental animals were examined in the Pathology Department laboratory. Tissue samples were fixed in 10% formaldehyde for 24 hours and then subjected to routine tissue processing.

As per routine histological procedures, the tissues were embedded in paraffin blocks. Slices of 2.5 micron thickness were obtained with a Leica microtome. The slices to undergo immunohistochemical staining were placed on positive loaded slides and those to undergo hematoxylin-eosin (HE) staining on normal slides.

As per the routine processes, the HE and immunohistochemical staining processes were completed [COLIA (Santa Cruz Biotechnology, Concentrate,1/100 dilution, monoclonal, CLone COL-I,LOT NO :E0918), TGFβI (Biogenex, Santa Cruz Biotechnology, Concentrate 1/100 dilution, monoclonal, CLone 3CII,LOT NO: E0918), and PCNA (Scytek, Concentrate 1/100 dilution, monoclonal, Clone PCI0,LOT NO: 47438)]. The stained preparates were examined microscopically. These processes were performed in the same manner on day 15 and 45 of the study and control groups.

Statistical Analysis

Statistical analysis of the data obtained in the study were performed using SPSS vs 22.0 software (IBM SPSS Corp.; Armonk, NY, USA). Since the number of data in the groups was <30, non-parametric tests were applied. Differences between the study and control groups were evaluated using the Mann Whitney U-test. The Wilcoxon Rank test was applied to determine differences within the same group at different time points. Results were examined at a 95% confidence interval. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Histological Results

Subjective microscopic evaluations of the groups were performed with HE staining. A similarity was found in terms of neovascularization, fibroblasts, and the amount of connective tissue in the endotendineum (Figure 3). Type IA collagen (COLIA), proliferative cell nuclear antigen (PCNA), and transforming growth factor βI (TGFβI) were evaluated semi-quantitatively with immune histochemical staining. The samples were numbered and percentage slices were scored for PCNA, TGFβI, and COL-IA, according to the immunohistochemical involvement of the cells under a microscope at ×10 magnification by a pathologist blinded to the groups (Table I). Positive cell involvement was recorded. In the statistical evaluations of the positive cells, similar results were obtained in the study and control groups at 15 and 45 days (TGFβI, p(15)=0.328, p(45)=0.195. PCNA, p(15)=0.645).

In terms of PCNA, the absence of cell involvement in the samples obtained on day 45 was similar to the samples obtained from the healthy tissues, and this was interpreted as the completion of the healing process. COL-IA in all the groups showed similar properties, and no significant differences were determined (Figure 4).

Biomechanical Results

During the biomechanical examination, the greatest loading forces (Newton) were found on the calcaneus-Achilles complex. While breakage in Groups A and B was close to the area of the tendon injury, it occurred with stripping away in the form of avulsion from the calcaneus attachment point in Groups C and D.

TABLE I. Immunohistochemical results and statistics

		Minimum	Maximum	Mean	Standard Deviation	P value*	P value**
TGF-βI	Group A	25,00	75,00	40,63	22,90	0,261	0,328
	Group B	25,00	100,00	56,25	32,04		
	Group C	25,00	100,00	65,63	26,52		0,195
	Group D	25,00	75,00	46,88	20,86		
PNCA	Group A	75,00	100,00	84,38	12,94	<0,001	0,645
	Group B	50,00	100,00	78,13	20,86		
	Group C	0,00	0,00	0,00	0,00		
	Group D	0,00	0,00	0,00	0,00		
COL-IA	Group A	80,00	100,00	92,50	8,90	0,731	
	Group B	90,00	100,00	95,00	5,30		
	Group C	80,00	100,00	95,00	7,66		
	Group D	80,00	100,00	91,30	8,30		

*Significance level p≤0.05
**Comparison between the groups on days 15 and 45

TABLE 2. Biomechanical test data and statistical results (N)

		Minimum	Maximum	Mean	Standard Deviation	P value
Day 15	Group A	34,68	51,07	41,69	6,05	0,908
	Group B	23,37	53,18	41,19	10,64	
Day 45	Group C	23,54	53,28	35,83	9,60	0,798
	Group D	20,42	57,32	36,98	11,49	

Significance level p≤0.05

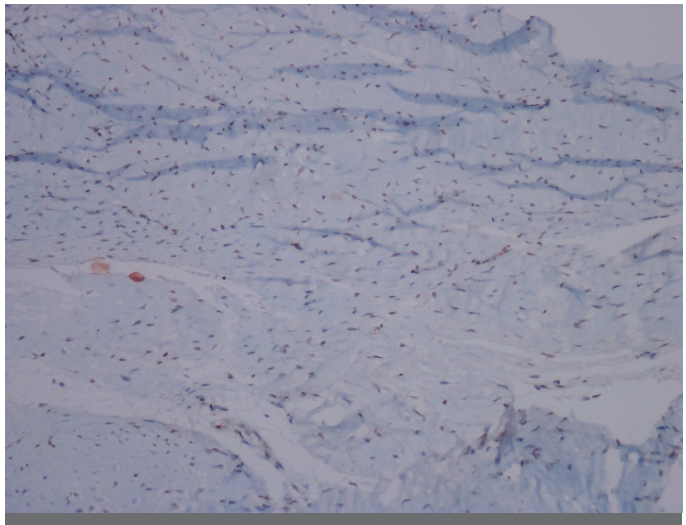

FIGURE 4. 80% staining of the tendon nuclei (COLIA, ×20)

The mean tensile resistance values were determined as 41.69±6.05 N for Group A, 41.19±10.64 N for Group B, 35.83±9.60 N for Group C, and 36.98±11.49 N for Group D. The statistical analyses of the biomechanical tests applied on days 15 and 45 showed no statistically significant difference between the study and control groups in terms of tensile resistance (Table 2). [p(15)=0,908 and p(45)=0,798].

DISCUSSION

This results of this study showed that gabapentin does not have a negative effect on tendon healing. To the best of our knowledge, our study is the first study in the literature to examine the effect of gabapentin on tendon healing. Tendon health and function is very important for orthopedic surgeons. Several local and systemic factors affect the tendon healing process (1). Therefore, the orthopedic surgeons must know whether the drugs used for treatment affect the tendon healing process.

This study aimed to determine the effect of gabapentin, which is used in postoperative pain prophylaxis after orthopedic surgeries, on tendon biomechanics and the tendon healing process. Tendon healing during acute injuries is a lengthy process because of the properties specific to its connective tissue. Weakness of the vascular structure and the presence of cells at a low metabolic rate provide limited contributions to tendon healing and the regeneration potential. The healing process occurs with the simultaneous appropriate development of regenerative and scar tissues (15). The fibrous scar tissue formed causes mechanical and functional weakening of the tendon structure. Acceleration of the healing process with the actual tendon regeneration tissue is one of the desired aims (2). A soft tissue healing process is observed following all orthopedic surgical approaches, not only in acute tendon injuries. For example, total knee and hip arthroplasty surgeries aim to provide very good tendon, ligament, and soft tissue balance. The use of gabapentin is recommended after these surgeries (8). In this context, the current study ex-

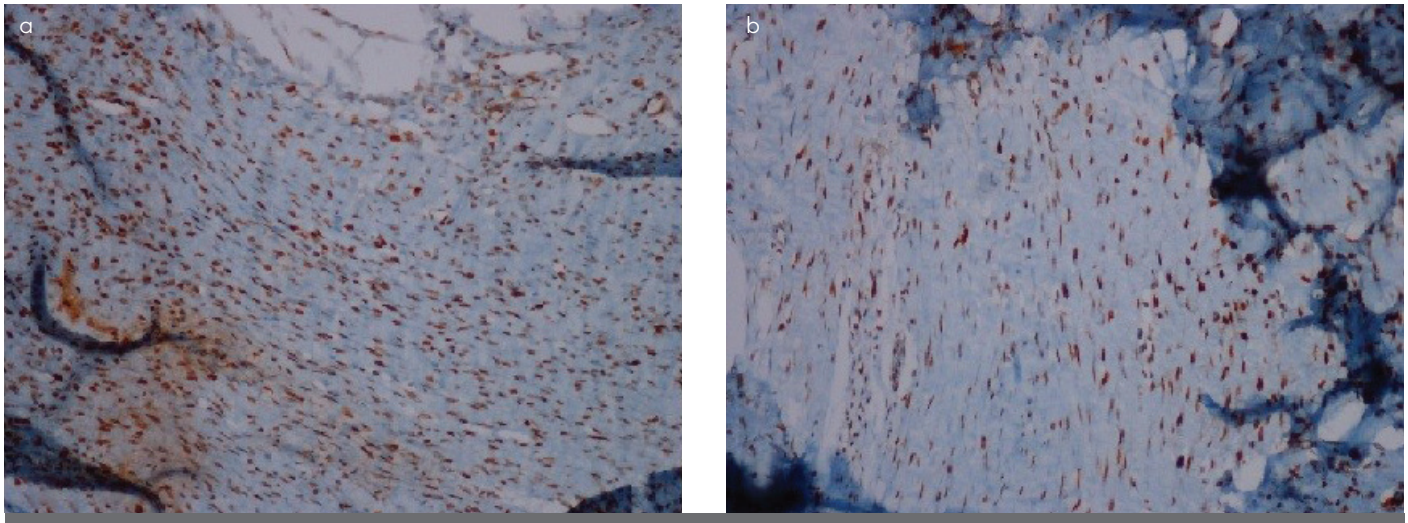

FIGURE 5. a, b. a) Group A nuclear 100% positive, b) Group B nuclear 80% positive (PCNA, X20)

amining the effect of gabapentin on tendon healing provides a contribution to the scarce literature in this field.

The mechanism of the effect of gabapentin has not yet been fully understood. However, reducing glutamate release by preventing calcium flow in the nociceptive pathways reduces pain transmission and sensitivity (14). Part of the effect is seen in voltage-gated calcium channels (16), which are located in tendons (17). There is a need for further studies in this area to examine the mechanism of the effect of gabapentin on tendons. In this respect, the current study can be considered as being of value in providing a viewpoint on this.

Although gabapentin is used in several clinical indications, it is used especially for postoperative and chronic pain control and to effectively reduce opioid consumption (18). There are studies in the literature related to gabapentin and pain prophylaxis, wound healing, and fracture healing, but its contribution to tendon healing has not yet been evaluated previously. The results of the current study showed that there was no significant difference biomechanically between the groups administered with gabapentin and the control groups (Table 2). The fact that no difference was observed between the groups biomechanically demonstrates that gabapentin could be used in pain prophylaxis with suitable indications after tendon surgery. Similar to the current study, there are studies in the literature that have recommended gabapentin in pain prophylaxis following tendon repair such as the rotator cuff repair surgery (7).

In the samples obtained on day 15 in the current study, PCNA-positive cells were observed to be dense around the epitenon; in other words, to have been intensified in the tendon periphery (Figure 5). The absence of PCNA-positive cells in all the groups on day 45 was interpreted as that the cellular regeneration had been completed (Figure 6). This was proven by the similar effect seen in the control samples obtained from the intact extremity. PCNA plays an important role in nucleic acid metabolism during the replication and repair process. PCNA interacts with the proteins necessary for the controlled cell cycle (19). In the early stages of the tendon repair process, it has been shown that the number of PCNA-positive cells increases. It is thought that these cells are undifferentiated mesenchymal stem cells that migrate from the paratenon toward the tendon healing area approximately 1 week after injury (20).

TGF-β1 plays a part in the tendon healing process associated with many different cytokines. It is known that TGF-β1 plays a role in collagen production and angiogenesis (21, 22). TGF-β1 expression has been shown to vary greatly at different times in tendon healing (20). This status in contrast to PCNA was seen in the immunohistochemical evaluations on day 45 of the current study. Similar results were obtained in terms of the rates of PCNA and TGF-β1-positive cells in the comparisons of the study and control groups on days 15 and 45. This was interpreted as gabapentin not having any negative effect on the tendon healing process.

This study has some limitations. Primarily, the histological evaluations were conducted semi-quantitatively. However, the microscopic examination was made by a pathologist blinded to the groups. Secondly, since the study was conducted on healthy animals, it was difficult to conclude that the same effects would be observed in humans.

In conclusion, the immunohistochemical and biomechanical evaluations of this study showed that gabapentin does not have a negative effect on tendon healing. Therefore, gabapentin can be used in cases with the appropriate indications after tendon surgery. Nevertheless, there is a need for further studies in this area to examine the mechanism of the effect of gabapentin on the tendon.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cumhuriyet University Animal Experiments (56/15.08.2017).

Informed Consent: The study was conducted according to the Guide for the Care and Use of Laboratory Animals.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - S.K.; Design - S.K., H.R.E.; Supervision - Ö.P., M.Y.A.; Resource - S.K., H.R.E.; Materials - S.K., Ö.P.; Data Collection and/or Processing - S.K., H.R.E., M.Y.A.; Analysis and/or Interpretation - Ö.P., M.Y.A.; Literature Search - S.K., H.R.E., Ö.P.; Writing - S.K., Ö.P.; Critical Reviews - H.R.E., M.Y.A.

Conflict of Interest: Authors have no conflicts of interest to declare.

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Original Article

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Association of Mean Platelet Volume with Bone Mineral Density in Fibromyalgia

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BACKGROUND/AIMS
We aimed to evaluate the mean platelet volume levels in patients with fibromyalgia and to determine whether there is a relationship between mean platelet volume and bone mineral density.

MATERIAL and METHODS
One hundred female patients with the diagnosis of fibromyalgia included in the study. The age, gender, weight, height, body mass index, mean platelet volume, fibromyalgia impact questionnaire score, bone mineral density (g/cm^2), and T- score of LI-4, femoral neck, and femur total were recorded.

RESULTS
The mean age of the patients was 48.29±10.53 years. The mean platelet volume level and fibromyalgia impact questionnaire score were 10, 45±1.87 fL and 61.71±17.16, respectively. The mean LI-L4 T-score was -1.52±1.26, mean femoral neck T-score was -0.89±0.99, BMD was 0.86±0.13 for LI-4, 0.89±0.13 for the total femur, and 0.75±0.09 for femoral neck. We found increases in the BMD, total, and femoral neck score when MPV decreased. MPV was found higher in osteoporotic fibromyalgia patients compared to normal BMD. No significant correlation was found between MPV and these parameters.

CONCLUSION
The mean platelet volume is meaningful for osteoporosis in fibromyalgia patients. Higher MPV may be related to the reason that osteoporosis is affected by inflammatory processes in fibromyalgia patients.

Keywords: Fibromyalgia, bone mineral density, mean platelet volume

INTRODUCTION

Fibromyalgia is a multi-symptom disorder, characterized mainly by chronic widespread musculoskeletal pain, chronic widespread pain, fatigue, sleep disturbances, and many other symptoms that impair the quality of life (QoL) (1). It is found in 2–4% of the population. Pain is the predominant symptom with allodynia and hyperalgesia being common signs (2). On physical examination of soft tissue tenderness, the presence of at least 11 of 18 defined tender points is observed (3). There are no specific laboratory abnormalities and they have a limited role in the evaluation of fibromyalgia (4). The multidisciplinary approach and patient self-management are important keys for the treatment of fibromyalgia. Successful management of fibromyalgia includes patient education, cognitive behavioral therapy, exercise, and drug therapy. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentin, pregabalin, pramipexole, tramadol, or other opioids are some of the pharmacological therapies effective in fibromyalgia (2). Somatic and psychological symptoms lead to poor health-QoL (5). Therefore, the approach to treating fibromyalgia should focus on maintaining or improving function, improving QoL, and managing symptoms (3).

With the aging population and longer life span, osteoporosis (OP) has become an epidemic, making this a major public health problem (6). Primary OP is most often related to either postmenopausal estrogen loss or age. Glucocorticoids, diabetes mellitus, rheumatoid arthritis, liver diseases, and hematological malignancies such as multiple myeloma are some of the etiological factors of secondary OP (7). OP is often called a "silent disease" or "silent thief" without warning signs or symptoms. Falls, fractures, and functional decline are important complications of OP, affecting QoL in patients (6, 8). OP in fibromyalgia has

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been investigated in various studies (9, 10). The related factors for OP in fibromyalgia patients are as follows: reduced daily activities, reduced sun exposure, and vitamin D deficiency (10). Erdal et al. (9) evaluated bone mineral density (BMD) in 38 fibromyalgia patients and 20 healthy controls. They found that BMD was lower in the fibromyalgia group compared to the control group (9). Moreover, Jensen et al. (10) analyzed BMD in 31 women with fibromyalgia and 41 healthy women. However, they found no differences in BMD in both the lumbar spine and the femoral neck.

Mean platelet volume (MPV) is one of the most widely used markers of platelet function and activation. It reflects the inflammatory burden in inflammatory disorders (11). It was found to increase with aging, a well-known risk factor for OP (12). Also, megakaryocytes can increase osteoblast proliferation in vivo and in vitro (13). The association between MPV and BMD is still the subject of research (14-16). Li et al. (14) found a significant negative correlation between MPV and femoral neck-lumbar BMD. According to Resorlu et al. (15), MPV was higher in osteopenic patients and a significant negative correlation was found between MPV and femoral neck T-score. In another study, a significant positive correlation was found between MPV and femoral neck BMD in a normal weight osteoporotic group (16).

To the best of our knowledge, the association between MPV and BMD has not been investigated in fibromyalgia. Our study aimed to assess the association between MPV and BMD in fibromyalgia patients. Also, we evaluated the fibromyalgia impact questionnaire (FIQ) score and body mass index (BMI) in fibromyalgia patients and their association with MPV.

MATERIAL and METHODS

In this retrospective study, a total of 100 patients with fibromyalgia who were admitted to Physical Medicine and Rehabilitation, Division of Rheumatology were enrolled in the study. Our study was conducted according to the criteria set by the declaration of Helsinki. All participants signed the informed consent form. All fibromyalgia patients were diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria (17). We recorded patients' age, body weight, height, BMI, MPV, FIQ scores, BMD (g/cm2) of the lumbar vertebrae LI-L4 and femoral neck, and total femur T-score.

OP is defined as a BMD with 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of <-2.5 SD) (18). The health status of fibromyalgia patients was determined by the FIQ score 1991 version. It consists of 10 items. The physical impairment items are rated on a 4-point Likert type scale. Responses range from 0 (always) to 3 (never). The "Feel Good" item response includes the number of days of the past week. The "Work Missed" item response includes the number of workdays in the past week. The other symptom-based items use a 100-mm anchored visual analog scale. The final score ranges from 0 to 80 (19).

Main Points:

- Osteoporosis is affected by inflammatory processes in fibromyalgia patients.
- Mean platelet volume is a simple and available blood parameter to evaluate activated platelets.
- Mean platelet volume elevation may be related to osteoporosis in fibromyalgia patients.

The inclusion criteria were age over 18 years and a diagnosis of fibromyalgia according to the ACR/EULAR 2010 criteria. Exclusion criteria were the presence ofa spinal implant, pregnancy, lactation, use of drugs which may cause OP and affect inflammation/MPV, and additional comorbidities (especially diseases affecting thrombocytes).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences version 19.0. Descriptive statistics were given as number (n), frequency (%), mean±standard deviation, and median [25-75p] according to the distribution analysis. The Kolmogorov-Smirnov test was used to determine whether the quantitative variables were normally distributed or not. One-Way ANOVA test was used to determine differences between independent groups. Pearson's and Spearman's correlation tests were used to determine the relationship between variables according to the normality distribution. A p-value of less than 0.05 was considered statistically significant.

RESULTS

One hundred fibromyalgia patients were enrolled in our study. Allpatients were female. The mean age of the patients was 48.29±10.53 years. The patients included in our study were divided into 3 groups based on DEXA as follows: normal, osteopenic, and OP. Among these patients, 49% were osteopenic and 16% were osteoporotic. There were no significant differences in age and gender between groups. The mean LI-4 T-score was -1.52±1.26 in all patients. The median T-score of total femur and femoral neck was -0.5 [-1.1–0.3] and -0.9 [-1.5–0.1], respectively. The mean BMD was 0.86±0.13 for LI-4, 0.89±0.13 for total femur, and 0.75±0.09 for femoral neck.

The mean MPV level was 10.45±1.87 fL in patients with fibromyalgia. It was 10.57±1.93 in osteopenic, 10.43±0.83 in osteoporotic, and 10.29±2.14 in normal patients with fibromyalgia. MPV was higher in osteopenic and osteoporotic patients compared with normal patients. However, no significant differences in MPV were found between groups. We found an increase in the BMD, total, and femoral neck score when MPV decreased. However, there was no significant correlation between MPV and these

TABLE I. The demographic features and laboratory findings of the patients with fibromyalgia

Age (years)	48.29±10.53
Gender (Female/Male)	100/0
Body Mass Index (kg/m^2)	31.47±7.12
Mean Platelet Volume (fL)	10.45±1.87
T-score/Lomber	
• LI-L4	-1.52±1.26
• T-Score/Femur*	
• Neck	-0.9 [-1.5-0.1]
• Total	-0.5 [-1.1-0.3]
Bone Mineral Density (g/cm^2)	
• LI-4	0.86±0.13
• Total Femur	0.89±0.13
• Femur Neck	0.75±0.09
Fibromyalgia Impact Questionnaire	61.71±17.16

*median [25-75p]

TABLE 2. The correlation analyses between mean platelet volume, fibromyalgia impact questionnaire and T-scores, bone mineral density in patients with fibromyalgia

Parameter (value)	Mean Platelet Volume (10.45±1.87)	FIQ (61.71±17.16)
T-score/Lomber		
• LI-L4 (-1.52±1.26)	p=0.997, r=0.000	p=0. 469, r=-0.073
T-Score/Femur*		
Neck (-0.9 [-1.5--0.1])	p=0.615, r=-0.051	p=0. 346, r=0.095
• Total (-0.5 [-1.1-0.3])	p=0.141, r=-0.162	p=0. 666, r=0.048
Bone Mineral Density (g/cm²)		
LI-4 (0.86±0.13)	p=0.151, r=-0.161	p=0. 431, r=-0.089
Total Femur (0.89±0.13)	p=0.196, r=-0.143	p=0. 959, r=0.006
Femoral Neck (0.75±0.09)	p=0.291, r=-0.117	p=0. 912, r=0.012

*median [25-75p], FIQ: Fibromyalgia Impact Questionnaire

parameters. The mean FIQ score was 61.71±17.16. The demographic features and laboratory findings of the patients with fibromyalgia are shown in Table I.

The correlation between T-scores of LI-4, femoral neck, total femur, and BMD of the same regions and MPV were calculated. There was no correlation between MPV and T-scores of femoral neck (p=0.615, r=–0.051), total femur (p=0.141, r=–0.162), and LI-4 (p=0.997, r=0.00). The distribution of correlation analyses between T-scores, BMD, MPV, and FIQ score is shown in Table 2.

When the BMI of patients was evaluated, 14%had a normal weight and 86% were above normal weight. There was no correlation between MPV and LI-4, total femur, and femoral neckT-score in patients with normal BMI. Moreover, no significant difference was found between BMI and these parameters. The results were similar in the group with BMI above normal limits. Patient age showed a negative correlation with LI-4 T-score and femoral neck T-score (r=0.231, p=0.02, r=0.253, p=0.01, respectively).

DISCUSSION

The pathogenesis of fibromyalgia includes central and autonomic nervous system dysfunctions, neurotransmitters, hormones, external stressors, and psychiatric aspects (20). Also, reports show that the immune system and inflammatory mechanisms play roles in this pathogenesis (21). Mast cells, dendritic cells, and T-lymphocytes have a role in the inflammatory processes of fibromyalgia (22). The upregulation of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6, are related to several disease-related comorbidities in fibromyalgia. All these processes are defined as "neuro-inflammation" (21).

In a study, higher neutrophil-lymphocyte ratio (NLR), MPV, and lower platelet distribution width (PDW) were reported in fibromyalgia patients compared to the control group (23). Akaltun et al. (24) evaluated MPV, NLR, and PDW values in 91 fibromyalgia patients and 33 healthy volunteers. They found higher MPV, CRP, and lower PDW in the fibromyalgia group. Also, they found a significant difference between the groups in terms of NLR (24). Haliloğlu et al. (25) reported higher MPV levels in fibromyalgia patients than in the control group (8.09±0.84 fl vs 7.73±0.65 fl). Also, higher NLR and MPV, and a lower PDW were reported in fibromyalgia patients in another study with 197 fibromyalgia patients and 53 healthy controls (23). The mean MPV of patients in our study was 10.45±1.87 fL. It was 10.57±1.93 in osteopenic, 10.43±0.83 in osteoporotic, and 10.29±2.14 in normal patients with fibromyalgia. The mean MPV was 10.29±2.14 in normal patients with fibromyalgia. The mean MPV was higher in osteopenic and osteoporotic patients compared to patients with normal BMD. However, there were no significant differences in MPV between groups. There are many factors such as adenosine diphosphate, thromboxane A2, platelet-activating factor, and pro-inflammatory cytokines that affect platelet activation (26). Serotonin has an important role in the pathogenesis of fibromyalgia and activates platelets (27). Significantly lower serum serotonin levels were reported in fibromyalgia patients compared to healthy individuals and a non-significant correlation was found between serum serotonin levels and platelet indices (27). However, we could not evaluate serotonin levels in patients with fibromyalgia.

The association between MPV and OP was reported in 175 Turkish postmenopausal women (16). In this study, 20 patients were normal, 37 patients were osteopenic, and 126 patients were osteoporotic. They found a positive correlation between MPV and femoral neck BMD in the normal weight osteoporotic group, and a significant negative correlation in the overweight-obese osteoporotic group. In our study, we evaluated 100 fibromyalgia patients. All the patients were female, with 49% of osteopenic and 16% of osteoporotic patients. With regards to BMI, there was no correlation between MPV and both femoral and LI-4 T-score in patients with normal BMI. The results were similar in the group with BMI above normal. Also, the association between MPV and BMD (30 normal vs 20 osteopenic) has been investigated in ankylosing spondylitis patients (15).

In a study, MPV was high in osteopenic patients than the normal group (16). The T-score of LI-4, femoral neck, total femur, and BMD(g/cm2) of the femur and lumbar vertebrae were evaluated in all patients included in our study. The mean BMD was 0.86±0, 13 for LI-4, 0.89±0.13 for total femur, and 0.75±0.09 for femoral neck. The mean total lumbar T-scorewas-1.52±1.26. The median T-score of total femur and femoral neck was -0.5 [-1.1–0.3] and -0.9 [-1.5–0.1], respectively in all patients.

The mean MPV was 10.57±1.93 in osteopenic and 10.43±0.83 in osteoporotic patients. We found an increase in the BMD ofLI-4 and femoral neck score when MPV decreased. However, there was no significant correlation between MPV and T-scores and BMD of these regions (Table 2).

OP in fibromyalgia has (9, 10). Aging is a well-known risk factor for OP. Also, MPV was found to been investigated in various studies increase with aging (1). Moreover, megakaryocytes in the bone marrow increase with age, leading to an imbalance between osteoblastic and osteoclastic functions (13). There was a statistically significant correlation between age and both LI-4 and femoral neck T-score. There were 5 geriatric patients in our study. Psychological factors, physical, and emotional distress have been frequently identified in fibromyalgia (28). Fibromyalgia has a greater impact on daily life; patients have more difficulties adjusting to the disease and generally use poor strategies to cope with pain (29). Erdal et al. (9) evaluated depression with the Beck scale and its correlation with BMD in fibromyalgia. They found a negative correlation between Beck's scale and BMD (9). In another study, pain and degree of physical activity in daily life were evaluated in premenopausal fibromyalgia (10). It

showed that self-reported pain and FIQ-activities of daily living among fibromyalgia patients were correlated with BMD. In our study, the mean FIQ score was 61.71±17.16. MPV increased with the FIQ score. No significant correlation was found between MPV and FIQ score (p>0.05). To the best of our knowledge, the association between FIQ score and BMD in fibromyalgia has not been previously investigated. In our study, the FIQ score was higher in osteopenic patients compared to patients with normal BMD (65.32±16.69 vs 59.18±17.98). However, there were no significant differences between groups and correlation for FIQ scores. This result shows that bone mass affects the health status of fibromyalgia patients. Also, no correlation was found between FIQ score and T-scores and BMD of the areas (Table 2). The limitations of our study were that we evaluated the association between MPV and BMD in a small number of fibromyalgia patients. Also, the study was designed as a cross-sectional-retrospective study. However, to the best of our knowledge, our study was the first to assess the association between MPV, FIQ score, and BMD in fibromyalgia.

Consequently, MPV is a simple and available blood parameter to evaluate activated platelets. According to our study, MPV was higher in osteoporotic fibromyalgia patients compared to normal BMD. This may be related to the fact that OP is affected by inflammatory processes in fibromyalgia patients. However, the difference was not significant. If there is no other condition to explain MPV elevation, it may be thought that this condition may be related to OP in the differential diagnosis for patients with fibromyalgia. More studies with more patients are warranted to elucidate the association between MPV and BMD in fibromyalgia.

Ethics Committee Approval: N/A

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - B.S.; Design - B.S.; Supervision - G.G.; Resource - B.S., G.G.; Materials - B.S.; Data Collection and/or Processing - B.S.; Analysis and/or Interpretation - B.S.; Literature Search - B.S.; Writing - B.S.; Critical Reviews - G.G.

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Bone Mineral Density and Lipid Metabolism After Alendronate and Strontium Ranelate Treatment

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BACKGROUND/AIMS
This study aimed to examine the alterations on metabolic changes in lipid levels and osteoporosis caused by alendronate (ALN) and strontium ranelate (SR) since shared biological linkages have great importance for new insights. Therefore, the treatments given for osteoporosis may also have a protective role against cardiovascular events.

MATERIAL and METHODS
In this retrospective study, 713 postmenopausal Turkish women were recruited. Biochemichal laboratory results and lipid parameters were recorded from the medical records of the patients. The lumbar spine (LI-L4), total femur (TF), and femoral neck (FN) were assessed for bone mineral density (BMD). Two hundred and sixty-three women were non-osteoporotic while 450 women were osteoporotic. Among the 450 osteoporotic women, 322 used ALN and 128 used SR. For each group, TF Dual energy X-ray absorptiometry (DEXA), FN DEXA and LI-L4 DEXA results and lipid changes were compared after 12-months treatment.

RESULTS
Patients who were given ALN showed significant improvement in the BMD measurement of LI-L4 and FN, but not in the results of TF DEXA. Significant changes similar to ALN were found in patients who were given SR. Patients using ALN had significantly higher levels of high-density lipoprotein (HDL). The SR group did not show marked lipid profile changes.

CONCLUSION
We demonstrated that osteoporosis in postmenopausal women may be related to atherosclerosis. ALN treatment has an enhancing effect on HDL levels; however, no effect was observed on serum lipid levels after SR treatment.

Keywords: Osteoporosis, lipid metabolism, alendronate, strontium ranelate

INTRODUCTION

Postmenopausal osteoporosis and atherosclerosis are two prominent conditions that are a major threat to women of increasing age. The postmenopausal decrease in estrogen levels causes a metabolic bone disorder referred to as osteoporosis (1). Due to the resulting lower bone mineral density (BMD) and microarchitectural worsening, the risks of fragility and fracture are higher (1, 2). Several studies have shown that patients with postmenopausal osteoporosis have a higher risk of developing cardiovascular diseases, and this is linked to the bone mass and lipid parameters (3-5). The inverse correlation between bone loss and cardiovascular events indicates that there is a parallel progression of common pathophysiological mechanisms of the two tissue damage processes. Cholesterol metabolism and lipid parameters are some of the risk factors considered in the progression of atherosclerosis and stimulation of osteoclastogenesis (6, 7). 3-hydroxy-3 methyl glutaryl coenzyme A (HMG-CoA) is responsible for the synthesis of mevalonate (MVA) through the enzyme HMG-CoA reductase. This metabolic pathway is an important route which plays a key role in different processes. MVA is further metabolized to farnesyl pyrophosphate, a precursor of cholesterol and sterols. These lipids are used in the modification of proteins that are involved in various aspects of cellular functions (8-10).

Various antiosteoporotic agents have been used to treat osteoporosis, including bisphosphonates (ex risedronate, ibandronate, zoledronate and alendronate (ALN)) strontium ranelate (SR), denosumab, raloxifene (selective estro-

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gen receptor modulator (SERM)), calcitonin and parathyroid hormone (4, 5).

Bisphosphonates are molecules that reduce the number and activity of osteoclasts resulting in a slowing down in bone metabolism and resorption (10, 11). ALN inhibits the enzyme farnesyl pyrophosphate synthase of the MVA pathway, thereby affecting the biosynthesis of sterol precursors, that are essential for prenylation of osteoclasts (11). Given that ALN influences the MVA pathway, it may play a role in the mechanism of lowering the circulatory lipid levels which may be protective against cardiovascular events.

The divalent strontium salt of ranelic acid called SR, is a molecule which stimulates bone formation and at the same time, it suppresses bone absorption (12). Recently, SR has been widely used to increase BMD and improve postmenopausal osteoporosis. The danger of fracture is less with increased BMD (13). Although SR is used effectively, its processing mechanisms have not been fully understood (13, 14). In in vitro studies, SR has been shown to stimulate bone differentiation and mineralization by increasing critical osteoblast transcription factors and osteocalcin (14). Moreover, SR reduces the adipogenic potential of bone marrow stromal cells, and at the same time, increases the osteogenic potential (15). Peroxisome proliferator-activated receptor gamma (PPARG) is the key factor that controls adiposides and osteoblastogenesis. PPARG regulates fatty acid storage and stimulates lipid uptake (16, 17). Therefore, SR may act on PPARG, which will result in the stimulation of bone formation and lower the lipid levels in the bone marrow and in the circulation.

High levels of serum lipids are related to higher risk of cardiac events. In particular, reduced concentrations of high-density lipoprotein cholesterol (HDL) are linked to the increased hazard of cardiovascular diseases (18-20). It has been considered that BMD and HDL levels might be correlated (20, 21). In the literature, there are studies examining the correlation between serum lipids such as HDL, triglycerides (TG) and low density lipoproteins (LDL); however, the results were contradictory. Some studies showed a negative correlation, whereas some others found a positive correlation (22-24).

Main Points:

- In the present study, osteoporotic patients had higher levels of high-density lipoprotein (HDL) and lower triglyceride (TG) compared to healthy postmenopausal women. It was hypothesized that in cardiovascular diseases and osteoporosis, steroid metabolites could be a link between as a common cause of the association between lipid levels and bone mineral density (BMD).
- In our study, patients using alendronate (ALN) had significantly higher levels of HDL at the end of one-year treatment. The effect of ALN on increasing HDL can be explained by its effect on the mevalonate pathway; ALN inhibits the enzyme farnesyl pyrophosphate synthase.
- In postmenopausal women, low BMD and cardiovascular diseases are increased which results in elevated morbimortality. In our study, in accordance with the literature, we found a positive association between HDL and ALN.

This investigation study aimed to search for a change in total cholesterol (TC), LDL, HDL, and TG levels after ALN and SR treatment.

MATERIAL and METHODS

This retrospective study was conducted in the Department of Obstetrics and Gynecology of the Faculty of Medicine of Dokuz Eylul University, İzmir, Turkey. Dokuz Eylul University ethics committee provided ethical approval in 26.12.2013 and the ethics approval form number is 1274-GOA. All patients in the study provided signed approval consent. The study population included 2 186 postmenopausal women who consulted the menopause outpatient clinic between November 2012 and July 2015 for dual energy x-ray absorptiometry (DEXA) for BMD scanning. After being amenorrhic for one-year, the patients were determined as menopausal. In the analysis, patients who were in menopause and aged between 45 and 80 years were recruited. Exclusion criterias were as follows: disorders in bone metabolism which were diagnosed by radiography or blood chemistry evaluations; the presence of systemic diseases including cardiovascular diseases, diabetes, medications or illnesses effecting bone metabolism; patients who had been under hormone replacement therapy; those with drug or alcohol abuse; and a history of consumption of ≥ 2 cups of caffeinated coffee days per week. Four hundred and fifty Turkish postmenopausal women with osteoporosis were assessed in the final analysis (Figure 1).

Patient medical records were examined and blood test results were recorded for the evaluation of serum levels of LDL, TC, HDL, TG and calcium (Ca) levels. Commercially available assay kits (Abott) with an auto-analyzer (Aeroset, Abott) were used to check for the levels of TG, TC, HDL, and LDL. Auto-analyzer (Abbott Architect CI6000, IL, USA) kits were used to assess Ca levels.

DEXA was used to measure the BMD of femoral neck (FN), lumbar spine (LI-L4) and total femur (TF). A structured questionnaire was documented for patients to evaluate the risk for low BMD. The results of DEXA for each patient were accessed from the department of radiology and from the medical records of the patients. The definition of osteoporosis was a T score ≤ –2.5 in LI–L4, FN, and TF. The tool for the calculation for DEXA results was Lunar

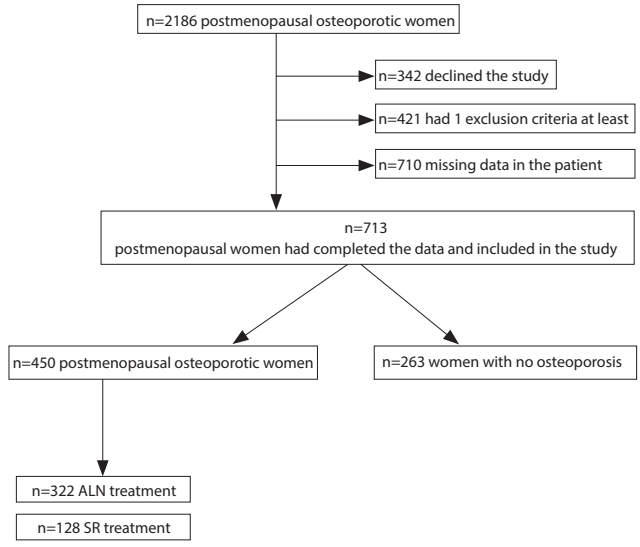

FIGURE 1. Flow chart of the study

TABLE I. Comparison of demographic characteristics and lipid parameters of osteoporotic and non-osteoporotic women

Descriptives	OP (n=450)	NOP (n=263)	*p
Age (years)	60.72±6.93	60.02±5.90	0.311
Gravida	3.70±2.10	3.59±2.08	0.562
Parity	2.32±1.34	2.22±1.30	0.064
TC (mg/dL)	212.75±38.16	216.55±37.22	0.615
TG (mg/dL)	121.90±56.54	123.29±45.89	0.004
HDL (mg/dL)	51.85±10.55	50.19±8.61	<0.001
LDL (mg/dL)	131.03±34.37	136.75±35.55	0.438
Ca (mg/dL)	9.45±0.61	9.12±0.58	0.141
BMI (kg/m^2)	26.97±3.65	26.95±3.69	0.458

Abbreviations: TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low Density lipoprotein, Ca: Calcium, BMI: Body mass index, OP: Osteoporotic women, NOP: Non-osteoporotic women
Independent t test is used
*p<0.05 is significant

TABLE 2. Comparison of demographic findings of osteoporotic women who were given alendronate and strontium ranelate

Descriptives	ALN (n=322)	STR (n=128)	P
Age	60.59±7.18	61.05±6.25	0.503
Duration of menopause	12.23±7.15	12.05±6.35	0.796
Menopausal age	48.24±3.68	48.91±3.03	0.050
BMI (kg/m^2)	27.07±3.69	26.70±3.56	0.324
Gravida	3.62±2.09	3.90±2.14	0.206
Parity	2.29±1.32	2.41±1.39	0.409
TC (mg/dL)	212.92±38.15	212.32±38.34	0.881
HDL (mg/dL)	51.37±10.09	52.37±10.26	0.726
LDL (mg/dL)	131.35±34.54	130.23±34.07	0.385
TG (mg/dL)	121.31±56.29	123.40±57.36	0.753
Calcium (mg/dL)	9.43±0.63	9.49±0.58	0.383
Lumbar I-Lumbar 4 DEXA	-2.82±0.54	-2.83±0.72	0.898
Total femur DEXA	-1.30±1.02	-1.26±1.02	0.670
Femur neck DEXA	-0.18±1.12	-0.15±1.23	0.823

Abbreviations: TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low Density lipoprotein, Ca: Calcium, BMI: Body mass index, DEXA: dual energy x-ray absorptiometry, ALN: Alendronic acid, SR: Strontium ranelate
Independent t test is used

DPX, GE Healthcare, USA; Software version:10.10.038. Calibration of the device was done daily. Patients in the osteoporosis group were further subdivided. Three hundred and twenty-two patients used ALN sodium and 128 patients used SR. For each group, after 12-months treatment, lipid parameters, serum Ca concentrations, and DEXA results were compared. The baseline characteristics of the groups are presented as the mean±standard deviation. A value of p<0.05 was considered as statistically significant.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences software (SPSS v15, SPSS Inc.; Chicago, IL, USA). P-values less than 0.05 were regarded as statistically significant.

TABLE 3. Comparison of lipid profile, serum calcium levels and DEXA results of the patients who were given ALN or SR at the end of one-year treatment

		ALN	*p	STR	*p
TC (mg/dL)	Before	212.92±38.15	0.508	212.32±38.34	0.248
	After	214.18±38.71		208.72±32.61	
LDL (mg/dL)	Before	131.35±34.54	0.469	130.23±34.07	0.793
	After	132.60±33.12		129.46±27.52	
HDL (mg/dL)	Before	51.37±10.09	0.001	52.37±10.26	0.084
	After	53.32±10.66		51.17±9.91	
TG (mg/dL)	Before	121.31±56.29	0.311	123.40±57.36	0.271
	After	129.77±63.62		118.78±50.86	
Ca (mg/dL)	Before	9.43±0.62	0.001	9.49±0.58	0.001
	After	9.23±0.55		9.16±0.53	
Lumbar I-Lumbar 4	Before	-2.82±0.54	0.001	-2.83±0.72	0.001
	After	-2.47±0.88		-2.57±0.81	
Total femur	Before	-1.30±1.02	0.356	-1.26±1.02	0.298
	After	-1.37±0.84		-1.37±0.70	
Femur neck	Before	-0.56±1.06	0.001	-0.56±1.02	0.001
	After	-0.17±1.12		-0.15±1.05	

Abbreviations: TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low Density lipoprotein, Ca: Calcium, DEXA: dual energy x-ray absorptiometry, ALN: alendronic acid, SR: Strontium ranelate
Paired samples are used
*p<0.05 is significant

RESULTS

The demographic characteristics and baseline findings of all 713 women are shown in Table I. Osteoporotic women were further subdivided and 322 were given ALN, and 128 were given SR. The initial characteristics of the osteoporotic women are compared in Table 2. In the intention-to-treat group, patients who were given ALN 70 mg/week showed significant improvement in BMD measurement of LI-L4 and the FN, but no change in TF DEXA results. In patients who were given SR 2 g/day, significant changes were found similar to those who received ALN after one-year follow-up (Table 3). Patients using ALN had significantly higher levels of HDL. There were no significant lipid parameter changes in the SR group. Serum Ca levels were significantly lower after one-year ALN and SR treatment (Table 3).

DISCUSSION

In clinical studies in the literature, SR and ALN have been shown to preserve bone loss and to decrease the risk of fracture. Several studies have shown that these drugs significantly improved bone mass and diminished the risk of fractures in the vertebra and hips (25-28). The current literature has shown that osteoporosis has a correlation with lipid metabolism and that ALN has effects on lipid parameters (21-24). In the current study, we examined the effects of ALN versus SR on BMD, lipid metabolism and serum Ca levels. Our results show that ALN and SR both increase the BMD of LI-L4 and the FN and reduce the risk of fracture. These results confirmed those of previous studies. Rizzoli et al. examined 88 osteoporotic postmenopausal women (26). For two years, the patients were randomized to ALN or SR treatment. Rizzoli et al found that an increase in cortical thickness and the cortical area were higher in the SR group compared to the ALN group (26). However, no dif-

ferences were observed in trabecular thickness between SR and ALN groups (21). The mechanism of action of SR remains unclear. SR may enhance osteoblast differentiation, bone matrix mineralization, preosteoblast replication, and collagen type I synthesis by means of a Ca receptor and lower bone resorption (25). On the other hand, ALN has a high affinity to bone minerals and reduces the number and activity of osteoclasts which results in inhibition of bone resorption (27). In the study of Reginster et al., SR was compared with bisphosphonates (29). They found that for women older than 75 years and for women with higher risk of vertebral fractures aged 80 years, SR proved to be more efficient and not as expensive as bisphosphonates (29). Unlike Reginster et al, in our study, there was no statistically significant difference in the efficacy of SR and ALN.

Previous clinical data found that reduced bone mass was associated with elevated levels of cholesterol. A diet with excessive cholesterol increases the risk of low BMD, probably by inhibiting the differentiation and generation of osteoclasts (30). In the present study, osteoporotic patients had higher levels of HDL and lower TG compared to healthy postmenopausal women. In 2018, Yang et al. showed an inverse correlation between HDL and LDL with BMD (31). It was hypothesized that steroid metabolites could have a link between cardiovascular diseases and osteoporosis as a common cause of the relation between lipid levels and BMD. The pathophysiological link between lipid levels and BMD has not yet been fully understood. Genetic factors may also play a role in the shared mechanism. Dennison et al. established that there is a significant association between fasting TG concentrations and LI-L4 BMD (32). Equally, patients with increased risk of vertebral fractures had reduced concentrations of TG (32). TG can alter the protein matrix and bone mineral, leading to better bone quality. TG metabolism in bone tissue may be correlated with higher osteoblastogenesis and lower osteoclastogenesis.

In the present study, patients using ALN had significantly higher levels of HDL at the end of one-year treatment. The effect of ALN on increasing HDL can be explained by its effect on the MVA pathway; ALN inhibits the enzyme farnesyl pyrophosphate synthase. Adami et al. found that ALN treatment caused a significant decrease in LDL and Apo B levels and raised Apo A and HDL levels (33). In addition, Celiloglu et al. observed that the use of bisphosphonates decreases Apo B/Apo AI ratios significantly and this was cardioprotective (34). High cholesterol levels are correlated with increased risk of cardiac pathologies. In particular, reduced concentrations of HDL are associated with elevated risks of negative cardiovascular cases (18). There were no significant lipid parameter changes in the SR treatment group. In our hypothesis, we expected to find a significant change in lipid levels with SR usage; however, the study results did not show this effect. In general, ALN is more widely used compared to SR, and in our study, patients using SR were fewer. This may be the major limitation of our study. Another limitation to the study is that it is done retrospectively.

Serum Ca levels were significantly lower after one-year ALN and SR treatment. This may be due to the transport of serum Ca to the bones. In addition, the Ca levels were between normal ranges before and after treatment. Although the difference was statistically significant, this is not clinically important.

In conclusion, in postmenopausal women, low BMD and cardiovascular diseases are increased, leading to elevated morbimortality. We have shown that there may be a link between atherosclerosis and osteoporosis.

There are conflicting results in the literature on the association between atherogenic lipid profiles and BMD. In literature, it is shown that alendronate (ALN) increases high-density lipoprotein (HDL), and it has cardioprotective effects. In our study, in accordance with the literature, we found a positive association between HDL and ALN. There is no study that has examined the effects of SR on lipid profile, but our study supports the fact that SR has no significant effect on lipid parameters.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylul University Faculty of Medicine (26.12.2013/1274-GOA).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - B.A.; Design - Ö.E.Ö.; Supervision - B.A.; Resource - A.C.Ö.; Materials - Ö.E.Ö., A.C.Ö.; Data Collection and/or Processing - A.C.Ö., Ö.E.Ö.; Analysis and/or Interpretation - A.C.Ö.; Literature Search - B.A.; Writing - Ö.E.Ö.; Critical Reviews - A.C.Ö., B.A.

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Review

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Lasers for Removing Obturation Materials and Medicaments from the Root Canal: A Review

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The complete removal of obturation materials from root canals is an important factor for successful endodontic retreatment. Many devices and techniques have been introduced for improving the removal of root fillings. A laser is one of the most effective devices. The application of different types of laser devices such as erbium: yttrium aluminium garnet (Er:YAG), erbium chromium: yttrium scandium gallium garnet (Er,Cr:YSGG), neodymium-doped: yttrium aluminum garnet (Nd:YAG), and neodymium-doped: yttrium aluminum perovskite (Nd:YAP) can effectively remove obturation materials and canal medicaments from the root canal system. However, regardless of the type of laser, these devices have some disadvantages when using them in the root canals. Thermal effects such as carbonization areas and partial dissolution in the gutta-percha and dentine have been observed after laser applications. Unfortunately, none of the retreatment protocols or laser types was able to remove the remnants of filling materials completely from the root canal system. This review was designed to evaluate the effectiveness of different laser devices in removing obturation materials and medicaments from the root canal system.

Keywords: Filling materials, laser, removal, retreatment, root canal

INTRODUCTION

The main purpose of root canal retreatment is to remove the obturation materials completely from the root canal and to reach the apical foramen. Because the residual obturation materials and smear layer are considered to harbor microorganisms, the success of root canal retreatment depends on the complete removal of the root canal obturation materials and smear layer (I). Many techniques and devices can be used to remove the obturation materials, including hand files, rotary systems, reciprocal systems, and solvents. However, a significant amount of residual obturation materials has been observed on the canal walls after using these techniques (2-4). Therefore, supplementary procedures should be applied after using hand or rotary files to improve the cleaning and complete removal of the obturation materials from root canals. Several devices have been introduced for this aim, including sonic, ultrasonic, and laser devices.

The first use of laser in endodontic treatment was in I97I by Weichman and Johnson (5). In the following years, many studies have been conducted to evaluate the application of laser in the root canal (6, 7). In addition to the use of laser devices in disinfection and preparation of the root canals, several studies have been conducted to evaluate the efficacy of different types of lasers to remove the gutta-percha and sealers from the root canal during the endodontic retreatment (8, 9). In the literature, the laser devices used in removing the obturation materials included erbium: yttrium aluminium garnet (Er:YAG), erbium chromium: yttrium scandium gallium garnet (Er,Cr:YSGG), neodymium-doped: yttrium aluminum garnet (Nd:YAG), and neodymium-doped: yttrium aluminum perovskite (Nd:YAP) lasers. These laser devices, which have different wavelengths, were evaluated in different output powers to remove not only the obturation materials but also the root canal medicaments.

During the root canal retreatment, several studies have been conducted to evaluate the efficacy of different types of laser devices in endodontic retreatment. Hence, this review aimed to identify studies that investigated the effectiveness of different laser devices on removing the obturation materials and medicaments from the root canal system. Table I summarizes these studies that evaluated the laser devices.

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Er:YAG Laser

The Er:YAG laser was introduced in 1975, and it was the first laser approved by the Food and Drug Administration for use in hard tissues in 1977. This laser beam has a wavelength of 2940 nm and can be used to remove both hard and soft tissues. The Er:YAG laser's high affinity to water and hydroxyapatite results in a cleaner root canal surface (10). Photon-induced photoacoustic streaming (PIPS) is one of the activation methods powered by the Er:YAG laser. This method uses a radial and stripped-shape design tip to transfer laser energy into the irrigant to enhance the removal of filling materials during a retreatment procedure (11).

Several studies in the literature have evaluated the use of the Er:YAG laser in removing the materials from the root canal system. Previous studies estimated the Er:YAG laser on removing the obturation materials from the root canal at a wavelength of 2940 nm with different output powers. The results were that the differences between several output powers were not significant in removing the filling materials (12, 13). At 3 energy levels (30, 40, and 50 mJ) of the Er:YAG laser (Dentlite; Hoya Photonics, Tokyo, Japan), the time required to remove the filling materials was significantly shorter when using the highest output power (12). On the other hand, Gorduysus et al. (13) concluded that the difference between the removal time at 40 and 50 mJ powers was not significant, but that carbonization areas were observed when using these output powers. In another previous study, the Er:YAG laser (Versawave; HOYA ConBio, Fremont, CA) at 2940 nm and 1.5 W output power was compared with irrigation solutions in removing calcium hydroxide from the root canal system. The Er:YAG laser was superior to the irrigation solutions in removing calcium hydroxide, but the difference was not statistically significant (14).

The PIPS method was used in previous studies to remove the remnants of filling materials after using rotary retreatment files. PIPS (Fidelis AT; Fotona, Ljubljana, Slovenia) using the parameters of 2940 nm, 1 W, 20 Hz, and 50 mJ was evaluated in oval-shaped root canals and showed significantly better performance in removing the filling remnants than sonic and ultrasonic devices (15). According to the results of Suk et al. (16), there was a significant reduction in the residual fillings when using PIPS (LightWalker; Fotona, Ljubljana, Slovenia) at 20 mJ, regardless of the canal sealer type. However, Dönmez Özkan et al. (17) concluded that using the PIPS (Fotona) technique after different rotary retreatment systems did not show a significant additional effect regarding the removal of filling material compared with conventional needle irrigation. In addition, many studies have evaluated the effect of using the PIPS method on removing different types of canal medicaments compared with other devices. All results showed that PIPS was significantly superior in removing the canal medicaments, regardless of the parameters used (18-21).

Main Points:

- The success of root canal retreatment depends on the complete removal of the root canal obturation materials and smear layer.
- The application of laser devices can effectively remove the obturation materials and canal medicaments from the root canal system.
- The time of laser irradiation and energy power used should be considered when applying the laser in the root canal to avoid the thermal effects.

Er,Cr:YSGG Laser

One of the erbium laser group, the Er,Cr:YSGG laser has a 2780 nm wavelength. The Er,Cr:YSGG laser requires higher energy than the Er:YAG laser for dental hard tissue ablation when used at the same parameters (22).

Some studies were found in the literature reporting on the use of the Er,Cr:YSGG laser in removing the canal medicaments and obturation materials. Using the Er,Cr:YSGG laser (Waterlase; Biolase Technology, Irvine, CA) at 25 mJ and 20 Hz left significantly less medicaments in the canal when compared with the irrigation needle (23, 24). Abduljalil and Kalender (25) evaluated the Er,Cr:YSGG laser (Waterlase MD; Biolase) for removing the filling materials at 2 different output powers after using rotary files. Regardless of the obturation technique, they reported that using the Er,Cr:YSGG laser at the parameters of 2780 nm, 20 Hz and 3.0 W was significantly more effective in removing the filling remnants than at the 1.5 W output power of this laser. However, using the Er,Cr:YSGG laser at 3.0 W power caused carbonization on the canal walls in some specimens.

Nd:YAG Laser

A fine flexible glass fiber made of quartz has been developed for the Nd:YAG laser to transmit the laser beam more effectively and to permit its concentration in a specific area. This has increased the potential usefulness of the Nd:YAG laser in root canal treatment and it is expected that the Nd:YAG laser will be increasingly used in the dental clinic, especially in the field of endodontics. This laser device is used at a 1064 nm wavelength (26).

The Nd:YAG laser has been investigated for removing the filling materials in many studies. According to the evaluation of Anjo et al. (26), using the Nd:YAG laser (STATLase EPY; ARA400, S.L.T. JAPAN, Tokyo, Japan) at 1064 nm and 900 mJ per pulse was superior to Gates-Glidden drills in removing 2 types of filling materials. Also, the time required for the removal of obturation materials was significantly shorter in the Nd:YAG laser groups. Yu et al. (27) reported that using the Nd:YAG laser (d-Lase 300; American Dental Laser, Birmingham, MI) at 1, 2 and, 3 W powers, respectively, and at 1064 nm removed the filling materials completely in 70% of the tested samples, but the temperature was increased up to 27°C. Viducic et al. (28) evaluated this laser (Twinlight Dental Laser; Fotona, Slovenia) with or without solvents and found that the area of remaining gutta-percha was smaller when using the laser at 20 Hz and 1.5 W without solvents, but that the difference was not statistically significant. In addition, the shortest time to achieve the working length of the canal was found in the group without solvents. In a study by Majori et al. (29), the effect of using the Nd:YAG laser (Pulse Master 600 IQ; American Dental Technologies, Corpus Christi, TX) was investigated in root canal retreatment. They reported that the higher output power (5.6 W) was better in the removal of obturation materials than the other output powers (1.5 and 2 W). When comparing the Nd:YAG laser with the K3 rotary sys-

TABLE I. Summary of studies evaluating lasers on removing the obturation materials and medicaments from the root canal.

Authors	Year	Type of Laser	Parameters	Results/Conclusion
Farge et al. (31)	1998	Nd:YAP	1340 nm wavelength - 5 Hz, 200 mJ - 10 Hz, 200 mJ	Nd:YAP at 10 Hz/200 mJ was an effective device for root canal preparation in root canal retreatment in combination with hand instruments.
Yu et al. (27)	2000	Nd:YAG (d-Lase 300; American Dental Laser, Birmingham, MI)	1064 nm wavelength 1.0 W, 2.0 W and 3.0 W, respectively	Nd:YAG removed the filling materials when using all these parameters respectively. The temperature was increased up to 27°C.
Viducic et al. (28)	2003	Nd:YAG (Twinlight Dental Laser; Fotona, Slovenia)	1064 nm wavelength 1.5 W, 20 Hz	The area of remaining gutta-percha was smaller when using the Nd:YAG laser without solvents, but there was no statistically significant difference between the groups.
Majori et al. (29)	2004	Nd:YAG (Pulse Master 600 IQ-American Dental Technologies; Corpus Christi, TX)	1064 nm wavelength - 100 mJ, 15 Hz, 1.5 W - 100 mJ, 20 Hz, 2.0 W - 160 mJ, 35 Hz, 5.6 W	Better removal of debris and gutta-percha from dentin surfaces in groups in which higher Nd:YAG laser power levels were used.
Anjo et al. (26)	2004	Nd:YAG (STATLase EPY; ARA400, S.L.T.JAPAN, Tokyo, Japan)	1064 nm wavelength 900 mJ/Pulse	Using the Nd:YAG laser was superior to Gates-Glidden drills in removing 2 types of filling materials.
Tachinami and Katsuumi (12)	2010	Er:YAG (Dentlite; Hoya Photonics, Tokyo, Japan)	2940 nm wavelength - 30 mJ/Pulse, 10 Hz - 40 mJ/Pulse, 10 Hz - 50 mJ/Pulse, 10 Hz	The differences between these output powers were not significant in removing the filling materials.
Kaptan et al. (14)	2012	Er:YAG (Versawave; HOYA ConBio, Fremont, CA)	2940 nm wavelength 1.5 W, 100 mJ, 15 Hz	The Er:YAG laser was superior to the irrigation solutions in removing calcium hydroxide, but the difference was statistically not significant.
Arslan et al. (18)	2014	Er:YAG-PIPS (Fidelis AT; Fotona, Ljubljana, Slovenia)	2940 nm wavelength 0.3 W, 20 mJ, 15 Hz	The results showed that PIPS removed significantly more antibiotic pastes than the EndoActivator and needle irrigation.
Arslan et al. (20)	2015	Er:YAG-PIPS (Fidelis AT; Fotona, Ljubljana, Slovenia)	2940 nm wavelength 0.9 W, 30 mJ, 30 Hz	PIPS was significantly superior to needle irrigation, sonic irrigation, and ultrasonic irrigation in removing calcium hydroxide from the root canal.
Keleş et al. (8)	2015	Er:YAG Er:YAG-PIPS Nd:YAG	2940 nm, 1 W, 50 mJ, 20 Hz 2940 nm, 1 W, 50 mJ, 20 Hz 1064 nm, 1 W, 50 mJ, 20 Hz	A comparison between the groups showed that Er:YAG laser application after the use of rotary instruments resulted in a significantly higher removal of filling remnants than PIPS and Nd:YAG.
Li et al. (19)	2015	Er:YAG-PIPS (Fidelis AT; Fotona, Ljubljana, Slovenia)	2940 nm wavelength 0.3 W, 20 mJ, 15 Hz	The PIPS and ultrasonic groups showed greater calcium hydroxide reduction in the apical third and greater cleanliness of the isthmus than the EndoActivator and needle irrigation groups. Calcium hydroxide residue scores in the PIPS and ultrasonic groups were significantly lower than those in the EndoActivator and needle groups in all regions of the root canals.
Samiei et al. (30)	2016	Nd:YAG	1064 nm wavelength	The Nd:YAG laser group was significantly cleaner than the K3 rotary system group in the coronal third.
Kuştarcı et al. (23)	2016	Er,Cr:YSGG (Biolase; San Clemente, CA)	2780 nm wavelength 0.50 W, 25 mJ, 20 Hz	Significantly less residual calcium hydroxide was obtained in the Er,Cr:YSGG laser-activated groups than in the needle-irrigated groups.
Keleş et al. (32)	2016	Er:YAG Er:YAG-PIPS Nd:YAG	2940 nm, 1 W, 50 mJ, 20 Hz 2940 nm, 0.9W, 45 mJ, 20Hz 1064 nm, 1 W, 50 mJ, 20 Hz	The least amount of residual smear layer and debris was detected in the Er:YAG laser group when compared with the PIPS method, Nd:YAG, self-adjusting file, and ultrasonic device.
Jiang et al. (15)	2016	Er:YAG-PIPS (Fidelis AT, Fotona, Ljubljana, Slovenia)	2940 nm wavelength 1 W, 50 mJ, 20 Hz	There was a significantly greater reduction in the amount of filling remnants in the PIPS group than in the sonic and ultrasonic groups.
Kamalak et al. (9)	2016	Er:YAG Er:YAG-PIPS Nd:YAG	2940 nm, 1 W, 50 mJ, 20 Hz 2940 nm, 0.9W, 45 mJ, 20Hz 1064 nm, 1 W, 50 mJ, 20 Hz	The lowest fracture resistance was detected in the PIPS technique group, but the differences were not significant when compared with the Er:YAG and Nd:YAG lasers groups. The groups that did not r ceive any retreatment procedure exhibited a signif cantly higher fracture resistance than the other experimental groups, which received the retreatment procedure.

TABLE I. Summary of studies evaluating lasers on removing the obturation materials and medicaments from the root canal. (Continued)

Authors	Year	Type of Laser	Parameters	Results/Conclusion
Eymirli et al. (24)	2017	Er,Cr:YSGG (Waterlase; Biolase Technology, Irvine, CA)	2780 nm wavelength 25 mJ, 20 Hz	For both EDTA and phytic acid, Er,Cr:YSGG laser-activated irrigation was more efficient than needle irrigation in removing both CH and TAP, but none of the tested techniques completely removed calcium hydroxide. Irrespective of the tested irrigation solutions and techniques, significantly less TAP remained in canals, with TAP being completely removed by laser-activated irrigation.
Gorduysus et al. (13)	2017	Er:YAG	2940 nm wavelength - 40 mJ/Pulse, 10 Hz - 50 mJ/Pulse, 10 Hz	There was no significant difference between 40 and 50 mJ laser output powers, but ultrasonic versus 40 or 50 mJ laser outputs were significantly different.
Suk et al. (16)	2017	Er:YAG-PIPS (LightWalker, Fotona, Ljubljana, Slovenia)	2940 nm wavelength 20 mJ, 2.06 J/cm2, 15 Hz	Regardless of the canal sealer type, there was significant reduction of the filling remnants after canal irradiation by PIPS in all groups.
Laky et al. (21)	2018	Er:YAG-PIPS (Lightwalker, Fotona, Ljubljana, Slovenia)	2940 nm wavelength - 0.15 W, 10 mJ, 15 Hz - 1.0 W, 25 mJ, 40 Hz	No significant differences were found for calcium hydroxide removal between the 2 PIPS technique groups. Sonic-assisted removal and needle irrigation resulted in significantly less calcium hydroxide removal than both laser groups.
Dönmez Özkan et al. (17)	2019	Er:YAG-PIPS (Fotona)	2940 nm Wavelength 0.3 W, 20 mJ, 15 Hz	Using the PIPS method after different rotary retreatment systems did not show a significant additional effect regarding the removal of filling material compared with conventional needle irrigation.
Abduljalil and Kalender (25)	2019	Er,Cr:YSGG (Waterlase MD; Biolase, Irvine, CA)	2780 nm Wavelength - 1.5 W, 75 mJ, 20 Hz - 3.0 W, 150 mJ, 20 Hz	Regardless of the obturation technique, using the Er,Cr:YSGG laser was significantly more effective in removing the filling remnants than 1.5 W output power of this laser.

CH, calcium hydroxide; EDTA, ethyenediaminetetraacetic acid; TAP, triple antibiotic paste.

tem for root canal retreatment, the laser group was significantly cleaner than the K3 rotary system group in the coronal third. Additionally, the mean time necessary for the debridement of root canals in the laser group was significantly shorter than that in the K3 group (30).

Nd:YAP Laser

Limited information was found in the literature regarding the use of the Nd:YAP laser in root canals. Farge et al. (31) evaluated the Nd:YAP laser in endodontic retreatment. This laser, which was used in that study at with the parameters of 1340 nm wavelength, 10 Hz, and 200 mJ, was an effective device for root canal preparation in root canal retreatment when used with hand instruments.

Combinations of Lasers

Several article in the literature have compared different types of laser devices. One of these studies that used microcomputed tomography has concluded that a comparison between laser groups showed that Er:YAG laser (Fidelis AT; Fotona, Ljubljana, Slovenia) irradiation after retreatment with rotary instruments demonstrated a significantly greater removal of filling remnants than Er:YAG laser-based PIPS and Nd:YAG laser (Fotona). An output power of 1 W was used for these laser devices and the wavelengths were set according to the manufacturer instructions (8). Furthermore, a study by Keleş et al. (32) reported that the least amount of residual smear layer and debris was detected with the Er:YAG laser (Fidelis AT, Fotona, Ljubljana, Slovenia) group when compared with the PIPS technique, the Nd:YAG laser (Fidelis AT; Fotona), a self-adjusting file, and an ultrasonic device. Kamalak et al. (9) reported that the fracture resistance of the tooth was evaluated after performing retreatment procedures with different lasers and other devices. The groups that did not receive any retreatment procedure exhibited a significantly higher fracture resistance than the other experimental groups that received the retreatment procedure. The lowest fracture resistance was detected when the PIPS method was used (2940 nm; Fotona), but the differences were not significant when compared with the Er:YAG (2940nm, Fidelis AT; Fotona, Ljubljana, Slovenia) and Nd:YAG (1064 nm; Fotona) laser groups.

According to this review, different types of laser devices have been evaluated for the removal of filling materials and medicaments from the root canal system in many studies. These lasers were used in several ways at different output powers and in combination with other tools and materials such as irrigation solutions or solvents.

In general, the laser device is an effective tool to clean filling materials from the root canal system. However, regardless of the retreatment procedure or laser type, the removal of the filling materials was reportedly more effective in the coronal and middle third than the apical third in several previous studies (25, 32). This could be because of the increased number of lateral and accessory canals in the apical third. In addition, moving the fiber tip of the laser in circular movements in the coronal and middle thirds and in parallel movements without touching the canal wall in the apical third could be another reason for this finding.

Regardless of the laser type used, thermal effects such as carbonization areas and partial dissolution in the gutta-percha and dentine were observed after laser applications (12, 16, 25). Thus,

the time of laser irradiation and energy power used should be considered when applying the laser in the root canal to avoid these thermal effects. However, none of the retreatment protocols or types of lasers were able to remove the remnants of filling materials completely from the root canal system (8, 25, 33, 34).

CONCLUSION

Different types of laser devices were evaluated for the removal of filling materials from root canal systems. Regardless of the disadvantages of lasers, including thermal effects, cracks, and carbonization, the laser devices were superior in removing and cleaning the root canal system in retreatment cases when compared with other devices. The time of laser irradiation and the output power should be considered to avoid the thermal effects of lasers. Because none of the retreatment techniques and devices were able to remove the filling materials completely from the root canal, further studies are required to evaluate the removal of root fillings by laser devices in combination with other materials and tools.

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Review

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White Spot Lesions: Recent Detection and Treatment Methods

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Nowadays, the importance of detecting and treating carious lesions before they turn into irreversible cavitations in dental tissue has been understood. The white spot lesion is the first visual finding of enamel caries. At this stage, it is possible to stop the caries formation and even heal the formed sub-surface lesion by various methods. Most dentists have difficulties while choosing preventive or interventional treatment methods for these situations. In line with the basics of minimally invasive dentistry, this review aims to provide an understanding of the histological character of white spot lesions and to inform clinicians about current methods of detection and treatment, and to approach these cases in their clinical routine with a minimally invasive perspective.

Keywords: White spot lesion, resin infiltration, remineralization, DiagnoCam, soprolife, fluorecam

INTRODUCTION

The stage before cavitation in the development of dental caries is called white spot lesion. It is characterized by subsurface demineralization areas formed under an intact enamel surface (1). The mineral content in the affected area is reduced, which in turn affects the translucent feature of the enamel, and the color of these areas appears more opaque white. Hence, initial enamel lesions or flat surface caries are also called white spot lesions (2). They are the first visible findings in caries formation and are considered as initial lesions by many clinicians. However, it should be remembered that demineralization must have a minimum depth of 300-500 μm to be visible (3). In actual practice, it is important to differentiate the etiology of these lesions because they can be due to caries or even hereditary. Lesions originating from caries progression become apparent opaque and chalky when the tooth surface is dried with air. This appearance is because the enamel tissue in this area loses its translucent feature due to subsurface demineralization. In contrast, developmental lesions are less or not affected by air-drying (4). The aim of the current review is to remain readers about the histological structure of white spot lesions and to provide information about current diagnosis and treatment methods.

Histological Characteristics of White Spot Lesions

In the carious lesions examined, it was determined that the mineral loss first occurred at the center of the enamel prisms. Although its cause cannot be fully explained, it is thought that the low crystal density at the center of the prism allows acid diffusion from the outside (5). The white spot lesion consists of four histological layers. These layers from the deepest part of the lesion to the surface are translucent layer, dark layer, lesion body, and superficial layer.

Translucent Layer

The translucent layer showing the direction of the enamel caries has the feature of being the deepest layer of the initial caries lesion. This layer got this name because of its appearance under polarized light after being painted with a quinoline solution that does not contain the structural elements seen in healthy enamel samples. Pores or cavities are formed between prisms with the penetration of hydrogen ions that occur during caries formation. Quinoline solution has the same light refraction coefficient value with the enamel. So, this layer with 1% pore volume becomes invisible in the polarized microscopy examination when stained with quinoline (6).

Dark Layer

The second layer that we encounter when coming up more on subsurface is called the dark layer. The reason for this black appearance formed under polarized light is the presence of too many pores in this area that are too small to ab-

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sorb a quinoline solution. Since these pores are filled with air, the affected area appears opaque white in the clinic. Total pore volume in the dark layer varies between 2% and 4% (4, 6). Some of the researchers working in this field say that this layer was not formed during demineralization, but through shrinking of the larger pores that existed as a result of ion accumulation. An increase in the volume of the lesion body was observed in this region during experimental remineralization. Caries is considered to occur very quickly in lesions where the dark layer is not observed (6). While it does not contain this layer in the first examination, monitoring of its formation in the examinations after the remineralization processes supports the view that the formation of the dark layer is related to the remineralization process (7).

Lesion Body

During the demineralization phase, the largest part of the initial caries lesion is the lesion body. It is the layer with the most pore volume among the enamel caries layers with its pore volume starting from 5% at the boundary of the lesion body, expanding to 25% in the center. Retzius lines are clearly observed within the lesion body, which shows that there is relatively more demineralization in this region compared to other areas and the porous structure is increased. The first penetration of caries into the enamel is in line with the Retzius lines (6).

If the pore volume is wide enough to allow penetration, it is possible to see bacteria in the lesion body. In some studies in which the lesion body was examined using a transmission electron microscope(TEM) and scanning electron microscope (SEM), bacterial invasion was found between the enamel prisms (8).

Superficial Layer

The migration of calcium and phosphate ions from the enamel prisms that has dissolved at the bottom and the fluoride movement from the mouth to the enamel surface have made the superficial layer more resistant to acid attacks (7). The more durable and intact structure of this layer is not due to the genetic or structural features of the enamel. These beneficial properties are the result of ion exchanges during demineralization/remineralization cycles. In this way, intact enamel surface acts as a barrier against bacterial invasion (6).

Classification of White Spot Lesions

There are various classifications for white spot lesions, but the most frequently used method is the International Caries Detection & Assessment System (ICDAS) classification, which is created by combining the most successful features of all detection and evaluation systems used in the detection of caries by Ekstrand et al. (9). Although we started to understand the formation of caries and the influencing factors, over the years, it was clear that ICDAS I was inadequate in evaluating the lesion activity. Therefore, ICDAS I was modified in 2004, and ICDAS II was launched (10).

In ICDAS II, radiographic images of enamel and dentin lesions are also included in the classification. It is divided into five classes as follows:

- EI: Lesion that reaches the outer half of the enamel
- E2: Lesion that has advanced to the inner half of the enamel
- DI: Lesion that is limited to the outer one-third of the dentin
- D2: Lesion that has advanced to the middle third of the dentin
- D3: Lesion that has advanced to the inner one-third of the dentin

Diagnosis Methods for White Spot Lesions

Nowadays, the importance of diagnosing carious lesions before they turn into irreversible cavitations has been understood. Most dentists have difficulty in deciding when to apply preventive methods and when to intervene. Evaluation of the patient's caries activity is also important in the diagnosis and treatment plan. White spot lesions in a caries-active mouth can quickly turn into cavitations. However, in people with low caries activity, the repair mechanisms will be more effective; therefore, the lesions may have the potential of healing. Hence, it is important to plan the treatment according to the caries activity in individuals after a correct diagnosis (II). The most commonly used diagnostic methods are listed next.

Visual Examination

The most used diagnostic method in the daily routine of dentists is visual examination (3). It can be determined if a lesion is active or inactive by a visual examination of white spot lesions. Chalky and rough surfaces indicate that the lesion is active, while smooth and shiny surfaces are indicative of an inactive lesion (I2).

To perform a visual examination correctly, the tooth surface must be dried with air for at least 5 seconds after cleaning with pumice and then examined with the help of light and mirror (4). Light is very important in the visual examination of white spots. As the existing pores are at the micro-level on the solid enamel with a refractive index of I.62, the enamel tissue appears translucent. However, the increase in micro-porosity due to continued demineralization causes a decrease in this refractive index. When the enamel surface gets wet, these pores are filled with water with a refractive index of I.33. Since the refractive index of water is very close to that of healthy enamel, the opacity of the lesion on the enamel surface will not be visible and the lesion cannot be distinguished. In contrast, after the air-drying process, the opaque enamel lesions become evident and distinct from the healthy enamel surface as the pores within the lesion will be filled with air which has a refractive index of I.0 (4). The advantages of this method are that it is simple to use, inexpensive, and clinically valid; whereas, its biggest disadvantage is that the method is difficult to be standardized.

Main Points:

- Detecting and treating carious lesions before they turn into irreversible cavitations in dental tissue is possible and can be done with a proper patient examination. Today's technology has made it easier for us to detect initial lesions at an early stage.
- Accurate diagnosis and individualized treatment methods according to lesion characteristics, should be used in the treatment of early stage lesions.
- Resin infiltration technique acts as a bridge between non-invasive and invasive methods. Depending on the lesion depth, dental practitioners can use this method alone or combining with other techniques such as bleaching and micro-abrasion.

Evaluation with Digital Photography

The conventional visual inspection does not provide a physical/numerical record of the teeth examined. Using a method for remote discussions, such as photography, could bring about a substantial improvement in dental education and case discussion. One would be able to discus clinical situations at a distance by sharing the examination results with professionals based at different locations. Health services are gradually adopting this concept in telemedicine and teledentistry initiatives, with encouraging results, especially in educational and diagnostic applications (13). Digital dental photography is a field that requires technical sensitivity and education, considering the dark, small, and moist mouth environment as well as the interaction of soft and hard tissues with light. Along with the training, it is recommended to use a light system, such as lateral twin flash or ring flash, and a camera that allows macro lens and lens replacement. The disadvantages of these equipments are that they are big and heavy and their cost is high. However, these disadvantages can be eliminated, thanks to the camera and photo shooting features of smart phones, which have become very popular today (14).

Fluorescence Techniques

The autofluorescence feature of the enamel decreases because of demineralization. These optical changes are directly related to the mineral content of the enamel (15). Therefore, autofluorescence principle is used in early caries diagnosis to show mineral loss. Clinically, the brands that use the fluorescence feature are DIAGNOdent (KaVo Dental Corporation, Biberach, Germany) and QLF (Inspektor Research Systems BV, Amsterdam, The Netherlands).

Quantitative light-induced fluorescence (QLF)

Generally, light spreads much faster in carious lesions than healthy dental tissues. Therefore, light absorption and fluorescence in the region of carious lesions is decreased. In this way, light emission measures can be used to evaluate the mineral loss. QLF technique works on this principle of fluorescence (16).

In recent years, FluoreCam (Therametric Technologies, Inc., Noblesville, IN, USA), a portable device that operates on the QLF principle, is available which is easier to use and carry. It stimulates the tooth surface with intense light and analyzes the resulting fluorescence image with its special software. As a result of the evaluation, three numerical data appear, indicating the size, density, and effect of the demineralized enamel lesion. There is no need for a darkroom as in case of QLF device while measuring, which makes it easier to use (17).

Laser Fluorescence

The DIAGNOdent pen has been developed for early diagnosis of carious lesions on occlusal and flat surfaces of teeth. This device emits a visible light of 638–655 nm wavelength using a diode laser, which is absorbed by organic and inorganic substances in the tooth structure, thereby the structures creating infrared fluorescence photons (18). The filtered fluorescence signals are collected with a different fiber bundle at the same tip that emits the light and are shown by a photodiode with scores from 0 to 99. The density of the recovered photons is directly related to the depth of the lesion. Scores greater than or equal to 20 and 25 indicate the presence of carious lesions. Higher values indicate greater caries penetration depth (18). Rodriguez et al. (19), reported that while the laser fluorescence method was effective in detecting the first demineralization in enamel, it was not effective in monitoring the progress of the lesion and was found insufficient to measure small changes in the mineral content. To improve this situation, the idea of examining the initial enamel lesion with laser fluorescence method after dying the lesion with a fluorescent dye was born and found successful (18).

The SoproLife camera is a modern caries detection method, based on laser induced fluorescence. This new method combines the advantages of visual examination, through a high magnification oral camera, and those of a laser fluorescence device (20, 21). Kockanat and Unal (22) reported that SoproLife camera and ICDAS II showed the highest sensitivity values against other tested detection methods.

Electronic Caries Monitor (ECM)

ECM is based on the measurement of the electrical resistance of the tooth structure during controlled drying. The electrical resistance value of a tooth depends on the porosity of the measured tooth region, amount of fluid in the porous area, temperature, mobility of the fluid in the porous area, and ion concentration. The ECM allows measurement in the range of 1 kW to >10 GW (23). It has been reported that ECM performs more successfully on flat surfaces and proximal surfaces compared to occlusal surfaces (24).

CarieScan PRO

The alternating current impedance spectroscopy technique, called the CarieScan PRO, uses multiple frequencies instead of a fixed frequency as used in ECM. The working mechanism is based on the fact that carious and healthy tooth tissues respond diversely to resistance tests at different frequencies (25). However, in a recent study, the CarieScan showed the lowest sensitivity values compared to SoproLife camera, DIAGNOdent pen, and visual examination (22).

Fiber optic transillumination–digital fiber optic transillumination (FOTI–DIFOTI)

The light transmission coefficient of caries differ from that of healthy teeth structures. During demineralization, which disrupts the dense hydroxyapatite content of the enamel, light photons scatter while trying to pass through the tooth and an optical distortion occurs. Since the light transmission coefficient of the intact enamel is higher than that of carious lesions, dark shadows are observed along the dentinal tubules when the carious tissues are examined with a fiber optic device (16). Initial caries lesions can be distinguished according to the intensity of the shadows formed by the light power of the device.

DIFOTI is a caries diagnosis method that uses the combination of FOTI and a digital camera to compensate for the deficiencies of FOTI. In this system, infrared radiation close to 780 nm wavelength is used instead of a white light source. This new diagnostic method gives hope in terms of diagnosis of initial caries and measurement of lesion severity because it is not invasive, does not use ionized radiation, and is more sensitive than radiographs in detecting early demineralization (16).

Near-infrared light transillumination (NILT)

An X-ray-free, photo-optical method, which is called near-infrared light transillumination (NILT), was released for caries detection in posterior teeth. High contrast between carious lesions and sound tissue can be obtained using this method. The NILT camera system (DIAGNOcam) that emits light at a wavelength of 780 nm was introduced to the market in 2012. The optical fiber arms of this device transmit light from the gingival and alveolar bones to the root of the tooth and from there to the crown. Then, an image is created from the occlusal surface with a charge-coupled device sensor (26, 27). A recent study stated that the DIAGNOcam method accurately detected hidden incipient enamel and dentin caries in primary and permanent teeth compared with other methods (27).

Prevention and Treatment Methods

Various options are available for the treatment of white spot lesions. Recent approaches are listed next.

Remineralization of White Spot Lesions

The physiological cycle can be turned into the direction of remineralization by preventing caries and increasing the duration of protective factors in the mouth. Generally, remineralization is a natural repair process, and many methods have been proposed to improve it.

Providing Oral Hygiene

Tooth caries is a major problem affecting not only the individual, but also the social institutions and health economy. Untreated caries affects more than 600 million children around the world. Such a big problem also creates a huge cost, and countries are looking for cost-effective solutions at the community level. Gaining awareness on individual oral hygiene and habits of daily brushing with fluoride toothpaste is one of the solutions for problems of tooth caries. Providing personal oral hygiene with tooth brushing and flossing is the most effective method that patients can individually perform to change the bacterial plaque composition and thereby change the process of white spot lesion formation (28).

Regulation of the Diet

Apart from the presence of bacterial plaque, another factor affecting caries formation is diet. Dietary foods not only act as inhibitors of the formation of cavities, but also are among the causes of the formation of caries. For example, some foods with hard and fibrous structure can help with mechanical cleaning, while others show an anti-caries effect by increasing the amount and flow rate of saliva with their taste and smell. Minerals, cocoa, tea, and proteins, such as cheese and milk, have a bacteriostatic effect by changing the metabolism of cariogenic bacteria. However, when fermented carbohydrates are frequently consumed, it may cause caries (29).

Use of Antimicrobial Agents

Chlorhexidine was released to public for the first time in the USA in the form of 0.12% mouthwash for periodontal treatments of patients who belonged to a high-risk group. It reduces Streptococcus mutans count and accelerates remineralization. It is recommended to use chlorhexidine mouthwash for 30 seconds just before bedtime because the reduced saliva flow rate at night helps in attaching chlorhexidine more easily to the structures inside the mouth. When chlorhexidine mouthwash is used in this way for 2 weeks, it reduces the number of Streptococcus mutans below the level potential for caries formation, and the effect of this decrease lasts between 12 and 26 weeks (6).

In recent years, the desire to return to the natural products has also affected the view of antimicrobial agents in dentistry. Antimicrobial properties of essential oils obtained from plants instead of artificial molecules are being investigated furthermore. Besra et al. (30) investigated the antimicrobial properties of various plant extracts on caries pathogens and concluded that the plants can be used individually or in combination in the treatment of dental caries.

Fluoride Applications

Fluoride shows its effect against caries in three different mechanisms. First, the presence of fluoride greatly increases the formation and accumulation of fluorapatite, which is formed by the combination of calcium and phosphate ions in saliva. Fluorapatite is resistant to dissolution; therefore, it replaces salts that contain manganese and carbonate, which are easily dissolved and lost due to demineralization, and makes the enamel more resistant to acids. The second mechanism is the remineralization of the initial cavity lesion with the fluorapatite crystals. The third and last mechanism is the antimicrobial activity of fluoride ions. Low concentrations of fluoride inhibit the production of the glycosyltransferase enzyme. The glycosyltransferase enzyme increases bacterial adhesion and provides glucose for extracellular polysaccharide formation. In high concentrations (12,000 ppm), topical fluoride applications have a direct toxic effect on oral microorganisms, including mutans streptococci (6). Fluoride applications can be classified as systemic and topical.

Systemic Applications

Systemic applications are effective methods, especially in individuals with high risk of caries formation and in communities where fluoride usage is low. Fluoridation of waters, which is one way of the systemic applications, shows not only systemic but also topical effect (6). World Health Organization (WHO) reported that consuming 1 mg of fluoride per day is beneficial for health. Systemic applications of fluoride are fluoridation of drinking water, salts, and milk and addition of fluorinated tablets or drops to the diet.

Topical Applications

Systemic fluoride intake was thought to be effective for a long time prior to the direct tooth application period. However, today, it is accepted that the use of topical fluoride is more beneficial during dental development and maturation. In high concentrations (12,000 ppm), which are generally applied professionally in dental clinics, topical fluoride has a direct toxic effect on oral microorganisms, including Streptococcus mutans (6). Fluoride varnishes were developed to make the contact time longer, to bond to the enamel for increased periods, and thereby prevent the quick loss of fluoride after application. Varnishes take the role of a reservoir for slow release and facilitate greater fluoride uptake (31). American Academy of Pediatric Dentistry guideline recommended that 5% (22,600 ppm) concentration of fluoride varnishes should be applied at least twice in a year for primary teeth and two or four times in a year for permanent teeth (32).

Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) applications

ACP is a tricalcium phosphate containing calcium and phosphate ions in an amorphous structure. When ACP enters a solution, it quickly turns into a stable structure, such as octacalcium phosphate or apatite. Casein is a phosphoprotein that makes up 80% of the proteins found in cow milk. Keeping calcium and phosphate ions in protein complexes is the most important feature of casein. These ions transform into smaller peptides, such as CPP, making them highly durable. Casein molecules act as a carrier that provides calcium and phosphate ions that can be used by the tissues, such as teeth or bones for remineralization (6). Mendes et al. (33) reported that the use of CPP–ACP was a good alternative for the remineralization of white spot lesions. The effect of remineralization can be improved when this product is applied in combination with fluoride. Although the applications, such as fluorides and CPP–ACP, have a positive effect on stopping caries progression, studies showed that these methods are not sufficient in terms of esthetic improvement according to the ICDAS (34).

Laser Applications

Laser alters the tooth surface and makes the tooth structure more resistant to dissolution during demineralization by providing recrystallization of hydroxyapatite crystals, changing the organic matrix composition, and differentiating the enamel surface structure and physical properties (35). Alqahtani et al. (36) showed that diode laser irradiation combined with topical fluoride application significantly increased the hardness and improved the esthetic appearance of WSLs compared to no treatment and fluoride treatment alone. In contrast, Molaasadollah et al. (37) reported that use of Er,Cr:YSGG laser irradiation plus 1.23% Acidulated Phosphate Fluoride gel was not significantly different from the application of fluoride gel alone in enhancing the remineralization of WSLs. The difference between these two studies may be due to the different types of laser used.

Ozone

It was reported that ozone application can reduce Streptococcus mutans and Streptococcus sobrinus counts on saliva-coated glass beads (38). However, this treatment method can only remove the microorganisms and stop the demineralization activity in the outer half of enamel lesions (39). A recently updated systematic review reported that there is a fundamental need for more evidence and appropriate researches before the use of ozone can be considered a viable alternative to current methods for the management and treatment of dental caries (40).

Microabrasion Applications

In the microabrasion technique, in addition to the porous enamel layer, stains adhering to these areas are eliminated by applying a mixture containing acid and abrasive particles to the tooth surface with a rubber cap under low pressure, similar to the mixture of pumice and water used during polishing. In this method, the erosive and abrasive particles of the acid are combined and the defective or discolored enamel tissue is eliminated (41). In this context, microabrasion is not a non-invasive, but minimally invasive treatment technique. Gu et al. (42) reported that microabrasion improved the esthetic appearance of WSLs and showed sufficient durability for 12 months. However, resin infiltration showed a better esthetic improvement effect when compared to microabrasion at 12 months.

Bleaching Applications

Kim et al. (43) claimed that bleaching of the tooth structure containing white spot lesions may provide a camouflage effect that makes the whiteness of the lesion less visible. It should be remembered that the bleaching process only improves the esthetic appearance with a camouflage effect on WSLs and does not treat the lesion. A recent systematic review showed that bleaching of WSL can diminish color disparities between carious and non-affected areas but researchers also reported that the certainty of the evidence was very low and further prospective *in vivo* studies are necessary (44).

Resin Infiltration

According to histological studies, it is a known fact that the microporosity increases in different layers of initial enamel lesions (6). These porous openings and enlarged intercrystalline areas function as points of propagation and passageways for acids and dissolved minerals. Based on this information, instead of completely removing the initial carious lesions as in conventional methods, the idea of filling the porous structure with low-viscosity resins would not only reduce the micropore structure, but also mechanically support the enamel tissue (45).

The resin infiltration method was first developed to stop proximal initial carious lesions (46). It is based on the principle that low-viscosity resins (infiltrants) penetrate the lesion by the effect of capillary forces after erosion of the non-cavitated surface layer, which is a characteristic feature of the white spot lesions. Infiltrant fills the porous lesions and thus, prevents acid and mineral diffusion (47). Resin infiltration shows high esthetic results due to the lesion's camouflage as a side effect during the treatment of white spot lesions (48). Torres et al. (49) showed that the resin infiltration technique gives better esthetic results than fluoride applications and remineralization methods. This success in masking lesions has been attributed to the refraction coefficient (1.52) of the resin used for infiltration that is close to the apatite crystals. In this way, the chalky, opaque appearance of WSL disappears and the color difference ceases to be visible. Perdigao (50) showed that in addition to masking the enamel WSLs, resin infiltration can envelop residual enamel crystallites forming an enamel hybrid layer. This hybridization makes resin-embedded enamel more resistant to acid attack than sound enamel.

CONCLUSION

It is important to detect and treat carious lesions before they turn into irreversible cavitations. White spot lesions are a stage where caries progression can be detected and arrested. As the histological structure of these lesions are explored and understood, it is emphasized that the application of minimally invasive techniques is the most appropriate approach for treatment. It is possible to stop and reverse caries progression in these lesions with the right application. Many methods have been proposed for the detection and treatment of these lesions. As mentioned above, less-invasive methods should be chosen for the treatment of white spot lesions. All these reasons led to the search for new techniques and materials. As a result of these searches, remineralization approaches with CPP–ACP and fluoride, microabrasion, and recently, resin infiltration methods were introduced. The treatment to be selected when treating these lesions should be based on the individual conditions. The depth,

formation time, and etiology of the lesion should be taken into consideration, and the right treatment or combination of treatments should be chosen.

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Review

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Anesthesia Management in Patients with Covid-19

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The coronavirus disease 2019 (COVID-19) pandemic that started in China in 2019 has led to millions of infection cases worldwide. As the number of people with COVID-19 has increased, the number of patients with health problems that require surgery during the pandemic also increased, and at the same time, anesthesia is needed for these patients. In patients infected with acute respiratory syndrome coronavirus 2, some features related to the clinical course of the disease should be known and considerations for the protection of healthcare workers and other patients due to increased contagiousness must be adopted. This review of the literature presents approaches in cases of patients diagnosed with COVID-19 and issues to be considered during anesthesia management.

Keywords: COVID-19, anesthesia management, 2019-nCoV virus infection

The 2019 novel coronavirus (2019-nCoV) infection (COVID-19) was first described as a new pneumonia syndrome in patients clustered around the Huanan Seafood Bazaar in Wuhan, China, in December 2019. The World Health Organization (WHO) declared this situation as a pandemic on March 11, 2020, and on the same day, the first case was reported in Turkey. According to the WHO data of June 09, 2020, 7,039,918 cases were detected worldwide, 404,396 of which resulted in death (1-7).

The agent of the disease, which is defined as COVID-19 in the current literature, also called 2019-nCoV or acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an enveloped RNA virus belonging to the Nidovirales subgroup of the Coronaviridae family, which includes Bat-SARS-like-(SL)-ZC45, Bat-SL ZXC21, SARS-CoV, and MERS-CoV.10 (1, 8, 9). 2019-nCoV with 9-12-nm long pointed protrusions varies in diameter from 60 to 140 nm. 2019-nCoV is inactivated by ultraviolet light, heat (56 min at 30°C), ethyl ether, 75% ethanol, chlorine used as a disinfectant, peracetic acid, and chloroform. It is not sensitive to chlorhexidine (1).

The virus is transmitted from infected individuals by respiratory droplets or by close/direct contact which is transmission vectors. Aerosol dispersion is also possible when exposed to high concentrations in a closed environment (1, 10). Although persons of all ages are sensitive to 2019-nCoV, the clinical course is usually symptom-free or mild in healthy individuals, and severe among elderly persons and in patients with comorbidities; It may even result in death (1-5, 11). In the literature, the incubation time of COVID-19 is reported to be between 1-14 days, most frequently 4 (2–7) days (1-5, 9, 12). In patients infected with COVID-19, fever, weakness, and dry cough are the most common symptoms. Tremors, muscle pain, headache, sore throat, loss of taste and smell senses (anosmia), and respiratory distress are also other common symptoms. Pneumonia is detected in approximately 15–20% of infected cases. In addition, respiratory failure, myalgia, diarrhea, widespread urticaria, erythematous rash, chickenpox-like vesicles, or embolism-related problems are reported. Rare symptoms such as sudden respiratory failure and circulatory disorders have also been reported. The severity of COVID-19 disease is classified as mild, moderate, severe, and serious based on clinical findings, laboratory tests, and imaging studies. In serious cases, dyspnea and/or hypoxemia may develop one week after the onset of the first symptom, and the patient may progress rapidly to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulopathy, and multiorgan failure (1-5, 12-17).

The standard method of COVID-19 testing is reverse transcriptase-polymerase chain reaction (rRT-PCR, polymerase chain reaction). The test is performed by taking throat or nasal secretions with swabs. Nucleic Acid Amplification Test

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(NAAT) is based on the determination of specific viral RNA sequences such as rRT-PCR and verification by nucleic acid sequence analysis method, which are used in the confirmation of COVID-19 cases. In cases in which the NAAT tests are negative and/or associated with COVID-19 infection, the study of serological tests such as ELISA or IgM/IgG rapid antibody tests in serum samples may be beneficial for the diagnosis (2, 6, 12, 16, 18).

Laboratory findings of COVID-19 are leucopenia, lymphopenia, thrombocytopenia, low albumin levels, and high C-reactive protein, erythrocyte sedimentation rate, neutrophil, and d-Dimer values. Levels of lactate dehydrogenase (LDH), creatinine, creatinine kinase, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), IL-6, Ferritin, and IgG and M may also increase. Procalcitonin was normal in most cases. (3, 5, 13, 16). Thorax computed tomography (CT) and posteroanterior chest X-ray show mostly bilateral multifocal ground-glass appearance and focal consolidations with peripheral and posterior distribution, especially in the lower lobes, and a large number of small band shadows and apparent multiple interstitial changes in the extranodal lungs in the early period of the disease, while multiple ground-glass opacities are observed in both lung bases and infiltration in both lung areas in the following period. Severe cases may also cause pathology in the lung parenchyma, but pleural effusion is rare in COVID-19 (1, 16).

Although there are no methods, vaccines, and medication whose effectiveness have been demonstrated in an evidence-based prospective randomized controlled trial in the prevention and treatment of infected patients, antivirals, hydroxychloroquine, serum from immune individuals, antibiotics, nucleoside analogists, protease inhibitors, recombinant soluble ACE2, Type I interferon, corticosteroids, intravenous immunoglobulins, drugs that block cytokines, and NSAIDs are used empirically (19-22).

Perioperative Management of Patients Infected with the Novel Coronavirus

With the declaration of a pandemic, the work patterns of both patients without COVID-19 and healthcare personnel have been changed by taking the protective measures, but due to the increase in the number of patients and the prolongation of the process, surgery and anesthesia applications have become inevitable for infected cases (23, 24).

The definitive diagnosis of COVID-19 is established at the right time by PCR from nasopharyngeal swabs and by IgM and IgG tests from the blood. However, reliable results will not be achieved if the test is not carried out according to the stage of the infection and the disease. Taking precautions against the possibility of COVID-19 in each patient will increase safety when contagiousness is common in the community.

When a surgical indication is needed for patients with COVID-19, the first thing to do is to arrive at an agreement with the surgical team regarding the importance, necessity, and urgency of the surgery. In COVID-19 cases, surgeries should be limited to life-threatening, rapidly progressing malignancies, and cases requiring urgent surgical intervention (25). It is an appropriate approach to postpone all non-urgent and non-emergent surgical and endoscopic procedures.

The patients diagnosed with COVID-19 should not walk around freely in the hospital, but should be moved along the specified route (1, 25). Stretchers and elevators should be disinfected with bleach, chlorine disinfectant tablets, or 70% alcohol after each patient.

For the anesthesiologists, balloon mask ventilation, non-invasive ventilation procedures (CPAP), endotracheal intubation, surgical airway access, bronchoscopy, extubation, disconnection of the anesthesia circuit, and cardiopulmonary resuscitation are the highest risk approaches because of the intense aerosol exposure (14). Therefore, anesthetists are likely to become infected (1). All the anesthetic approaches applied in the preoperative preparation, operating room, device preparation, and intraoperative-postoperative periods should be standardized in order to reduce this risk and increase the safety of patients.

Anesthesiologists and other healthcare professionals in the surgery room should wear personal protective equipment (PPE) such as protective gowns/clothes, N95/FFP2 masks, disposable surgical caps, goggles, face shields, gloves, and overshoes. In addition, some accessories such as ring, watch, key, wallet, and the phone should not be allowed to enter the surgery room (1, 26).

Preoperative Evaluation

In the preoperative evaluation, anesthesiologist should use PPE, and patients should wear a medical mask. The patients should be taken to the room alone to minimize close contact with infected cases, preoperatively. Before the evaluation of the case, body temperature should be measured with an electronic ear thermometer, and cases whose body temperature is higher than 37.3°C should be reported to the infection control team (1).

It should be questioned whether the cases have a close contact history with COVID-19 positive individuals, and detailed physical examination including fever measurement, lung examination, laboratory tests (Complete blood count, liver function tests, BUN, creatinine, CRP, Pro-calcitonin, Ferritin, CPK, LDH, D-Dimer, IL-6), Electrocardiography (ECG, especially QT distance), chest radiographs, and thorax CTs, if available (1, 10). Radiological findings are not expected to be seen in the first 48 hours of the infection; 98% of CT shows diagnostic features. Lung ultrasonography can be used in pregnant women whose CT evaluation cannot be done (27). Patients with comorbid diseases should be consulted with the relevant branches if necessary.

After the physical examination, hand hygiene should be provided by washing with a 2–3% hydrogen peroxide solution or with plenty of water and soap. Examination room equipment, floors, and surfaces should be disinfected with 2–3% hydrogen peroxide (1).

At the end of the preoperative evaluation, the patient or patient's relatives and the surgical team were informed about the possible risks and adverse side effects, and written consent was obtained from the patient/guardian and archived.

After evaluation, COVID-19 positive or strongly probable cases should was taken directly to the operating room. Surgery, if any, it should be performed in the COVID-19 operating room; otherwise, routine room cleaning and contact follow-up should be done when the surgery is finished (1).

The Preparation of the Operating Room and Devices

The operating room reserved for patients with COVID-19 should be away from other operating rooms and should be marked with routers so that employees can find it without searching. The operating room reserved for COVID-19 cases should be ventilated with <5Pa, 12 air. hour-1 negative pressure systems and negative pressure levels should be checked frequently. If there are no negative pressure systems, positive pressure systems and air conditioners should be closed. If it is determined that the negative pressure in the environment is not sufficient, additional portable high-impact particle air filters (≥25 cycles/hour) should be used (1, 14, 26, 28-30).

The surgery room should be organized into two areas; dirty and clean. Two anesthetists using PPE (above-mentioned), surgeons and their team, and nurses should be in the dirty area, while another anesthesia and surgical team should be in a clean area and everyone should protect their regions (14).

The door of the operating room should be kept closed during the surgery, the entrance and exit of the employees should be limited to essential situations, and only anesthesia personnel should remain in the room during the intubation and extubation stage (1, 30).

Medicines that are likely to be used in anesthesia should be brought into the room in a tray, syringes should be thrown away into medical waste after the procedure, the tray was sterilized (1, 28).

Anesthesia device of the operating room reserved for patients with COVID-19 should be fixed in the room. Devices used in the operating room such as anesthesia machines and defibrillators should be covered with full transparent nylon covers and discarded after each surgery. Breathing circuits should be disposable, and HME filters should be placed on the inspiratory and expiratory connections of the breathing circuits (1). The end-tidal carbon dioxide line should be placed close to the machine after the filters, and the end-tidal carbon dioxide and water trap should also be disposable (26). Waste management should be planned in advance (28, 31).

Cleaning staff should use masks, gowns, and gloves. The reusable equipment should be sterilized with glutaraldehyde and the operating room should be sterilized with UV. The suspended droplets in the air should be expected to precipitate in 30–60 minutes. Therefore, it is necessary to wait for 30–60 minutes between the two surgeries (32).

Management of Anesthesia

Patients with COVID-19 may be candidates for any surgery. Zhao et al. (33) retrospectively evaluated 37 cases who underwent an emergency surgery on 23–31 January 2020; Abdominal surgery (10), cardiovascular surgery (2), orthopedic surgery (6), obstetric and gynecological surgery (11), neurosurgery (2), and the others (6); 70% of the surgeries were performed with general anesthesia and 30% with spinal anesthesia. Zhong et al. (34) performed spinal anesthesia in 49 patients who were confirmed to be COVID-19 radiologically and underwent cesarean or lower extremity surgery. Rong et al. (35) also performed cesarean section by applying regional anesthesia with an epidural catheter to 14 of 17 cases with COVID-19 and general anesthesia with 3 endotracheal intubation.

General anesthesia and endotracheal intubation are recommended to reduce the risk of COVID-19 transmission in patients with COVID-19 diagnosed or suspected. Other methods can be selected depending on the patient's condition. For example, spinal anesthesia is preferred in cesarean procedures. If spontaneous breathing continues, patients should also wear an N95 or surgical mask during the surgery (1).

General Anesthesia

If it is not essential for general anesthesia, rapid serial induction should be applied without mask ventilation (1). During induction, neuromuscular blockers, intravenous general anesthetics, and opioids are recommended, respectively (10). There are also published articles suggesting that endotracheal intubation should be performed in a negative pressure room or ICU, from where the surgery is monitored preoperatively instead of the operating room (26).

The application of 5 min pre-oxygenation with 100% oxygen (26), covering the patient's nose and mouth with two layers of wet gauze or a nylon cover that covers the face and surrounding to avoid secretions of the patient during pre-oxygenation (1), reduction of ventilation by a mask during intubation, and no cricoid compression (1), [If the anesthetist is experienced, cricoid compression may be applied (26)] are recommended. For endotracheal intubation, oral intubation with a video laryngoscope or bronchoscope is recommended (1). Lyons (36) stated that using fiber optic laryngoscopy did not give extra speed and even high flow oxygen applied by nasal route during the procedure increased the risk of contamination. It is necessary to show the ultimate attention to prevent coughing in laryngoscopy (1). Aminnejad et al. (37) reported that administration of lidocaine at the beginning and the end of intubation and extubation in patients with COVID-19 reduced possible cough, and also reduced secondary aerosol spread. The adequate neuromuscular blockade should be provided to prevent cough (10), for this purpose, a high-dose rocuronium (1–1.2 $mg.kg^{-1}$) is recommended. Suxamethonium can be given at a dose of 1.5 $mg.kg^{-1}$, given the duration of the apnea and cough (38). Ketamine or etomidate may be used not to suppress the cardiac functions in hypotensive patients. However, etomidate can cause adrenal suppression (39).

If there is a suspicion of a difficult airway, difficult intubation guidelines should be taken into consideration. Spraying local anesthetics into the respiratory tract during awake fiberoptic intubation should not be applied unless indicated, as this may cause the virus to spread as aerosol (28). ETT placement following the supraglottic airway is another recommended method in cases that cannot be intubated (26, 38). Intubation should be done with a tube distally clamped without bending the patient's face. If difficult intubation is predicted, a guidewire should be inserted into the tube, the endotracheal tube should be reached to the ideal depth at one time (often the rim is 22 cm), the cuff should be inflated (to the extent that the leak is not allowed), then the clamp of the tube should be removed, and its location verified. The continuity of the breathing circuit should be checked during the surgery. If the line needs to be separated; the tube must be clamped first and the separation must be made from the farthest distance to the HME filter. If possible, it is recommended to use the closed airway aspirator systems to

reduce viral aerosol production. If not possible, suction applications should be minimized (1).

In the maintenance of anesthesia, to reduce lung damage due to the ventilator, a lung-protective ventilation strategy at low tidal volume should be applied. Tidal volume 4–8mL/kg, inspiratory plateau pressure <30 cmH_2O, PEEP <8 cmH_2O and recruitment maneuver every 30 minutes, blood gas analysis during surgery, and close monitoring of ventilation with $EtCO_2$ are recommended (10).

Inhalation anesthesia or total intravenous anesthesia depending on the clinical condition of the patient can be preferred for the maintenance of anesthesia. The primary aim of both methods is to provide fast recovery without a cough. It is emphasized that this can be achieved by avoiding the use of preoperative midazolam, with the lowest possible dose, and the shortest effective drugs (avoiding deep anesthesia and deep muscle relaxation and minimizing the opioid dose, etc.) (40).

The use of other drugs that will contribute to QT prolongation, metabolic, and electrolyte disorders should be avoided because hydroxychloroquine used in COVID-19 treatment causes QT prolongation on ECG (41).

Regional Anesthesia

Proper planning should be done so that the surgery can be performed entirely with regional anesthesia, without the need to return to intraoperative general anesthesia, which can be achieved with the harmony of the anesthesia and surgical team.

Although spinal anesthesia is recommended in patients with COVID-19 for lower extremity surgery or cesarean section, it should be proven that there is no thrombocytopenia (14, 34). In cases with COVID-19 encephalitis, the free drop of cerebrospinal fluid (CSF) should be prevented after lumbar puncture, since the virus is isolated from CSF (42). Although some articles are indicating that epidural and general anesthesia can also be applied in a cesarean procedure (35), febrile patients with COVID-19 may have a lumbar puncture during epidural catheter insertion, and neuraxial anesthesia can cause meningitis and encephalitis, even at a very low rate (43).

If it is decided to perform the peripheral nerve block, the block that will least affect the respiratory functions should be selected and carried out under the guidance of ultrasound to reduce the local anesthetic systemic toxicity (44).

N95 or surgical masks should be used for patients undergoing regional anesthesia during the surgery, if oxygen support is needed, the nasal cannula should be inserted, or oxygen should be given through the mask (1, 34).

Monitorization

All vital functions should be monitored as reported in the ASA standard (45). Since the medicines used in the treatment of COVID-19 can cause toxic myopathy and myocarditis, close ECG monitoring should be performed, and whether there is a QT prolongation on the ECG should be checked (41, 46). In patients with COVID-19, $EtCO_2$ should be measured as a standard, if sedation is also performed during regional anesthesia (40). $EtCO_2$ is also critical in confirming the endotracheal intubation. Aerosol spread may be reduced by monitoring the cuff pressure. Non-invasive monitoring of vital parameters is needed in patients with COVID-19. However, considering the clinical condition of the patient, intraoperative blood gas analysis, and close $EtCO_2$ monitoring can be performed depending on the severity of lung involvement. Acute kidney injury (47) may be seen in patients with COVID-19. The urinary catheter will also provide monitoring for fluid management. Echocardiography (ECO), USG (Vena Cava Inferior diameter measurement) can be used to evaluate tissue perfusion. Pulmonary pressure and blood lactate levels may be measured. Central venous pressure monitoring (CVP), and the effect of respiration on vena cava sizes can be evaluated by USG (Mmod) (48-50). Since the aim is a rapid recovery among patients with COVID-19, the use of high-dose neuromuscular blockers can be prevented by neuromuscular monitoring during the surgery.

Cerebral events, microvascular encephalopathy, septic encephalopathy, and cerebral autoregulation disorder may be seen in critical patients with COVID-19 (42). Therefore, the balance between cerebral oxygen delivery and consumption should be monitored by non-invasive methods, as well as blood pressure measurement in the evaluation of cerebral perfusion (51).

Fluid Replacement

It is recommended to apply fluid to meet the needs of patients provided that hypovolemia is avoided, since patients with COVID-19 may experience restrictive lung diseases, kidney failure, and thrombosis (52). The purpose of fluid treatment is to balance the amount of fluid that the patient takes and extracts and avoid excessive fluid overload. Therefore, close monitoring is recommended.

In fluid management, crystalloids should be preferred over colloids. Anaphylactoid reaction with crystalloids is not seen in volume replacement, but if there is endothelial damage, it may lead to extravasation and related problems. Colloids, although it is a good option for maintaining oncotic pressure, synthetic colloids also have negative effects on the coagulation and less frequent risks of allergic reactions (53).

In fluid management, passive leg raise test, mini-fluid loading test, and the ratio of pulsatile flow to non-pulsatile flow (PVI) in the capillary bed should be evaluated conservatively (54).

Extubation Period

If the patient meets the extubation criteria, the patient should be extubated in the operating room using the closed aspiration system. Soft extubation should be applied to prevent aerosol scattering by cough, and IV lidocaine should be applied if there are no contraindications (37). McGrath et al. (55) reported that coronaviruses caused laryngitis without causing sore throat, resulting in airway edema and that dysphagia and dysphonia might be observed after extubation. During extubation, two layers of wet gauze can be used to cover the patient's nose and mouth or the mask is placed under a transparent nylon cover to reduce aerosol exposure. Extubation can be performed under the transparent cover via a hole allowing only the connector portion under the transparent cover. While one of the HME filters is removed with ETT, the second is immediately attached to the face mask. When sufficient spontaneous ventilation is pro-

vided, the patient can be transferred from the operating room with a face mask and O_2 if necessary (I, 14).

Patients should not stay in the recovery room or postoperative care unit. However, they should be transferred to a room where they are monitored under negative pressure or to the intensive care unit (26). If the patient is to be transferred without extubation, a filter should be added to the endotracheal tube and ventilation should be continued with a disposable manual ventilator. If the patient is to be transferred with the transport ventilator, the filter should be attached to the endotracheal tube and connected to the breathing circuit; the breathing circuit should be discarded after the transfer (I).

Postoperative Period

When the patient with COVID-19 is transferred to the room monitored under negative pressure or to the ICU depending on its clinical condition, a consultation with the infectious diseases team should be made (I, 31).

In the postanesthetic care unit, patients should be periodically evaluated for respiratory, cardiovascular, neuromuscular functions, mental state, temperature, pain, nausea, vomiting, fluid therapy, urine output, drainage, and bleeding. An appropriate monitoring standard should be maintained until full recovery. If the patient will remain intubated or the airway will be provided with a supraglottic or similar tool, pulse-oximetry, non-invasive blood pressure monitoring, ECG, and airway continuity should be closely monitored. Difficult airway equipment, a nerve stimulator, a thermometer, and patient warming tools should be available to assess the neuromuscular blockade (56). Due to the fact that patients with COVID-19 may have renal failure, limited fluid treatment should be applied, and the amount of urine and possible bleeding should be closely monitored. In cases where thrombosis is expected, thromboprophylaxis can be applied with low molecular weight heparin.

Since pulmonary, myocardial, and renal damage may occur in critically ill patients with COVID-19 in postanesthetic care, lung compliance, airway pressure, oxygen index, arterial blood pressure, CVP, myocardial enzymes, and intracranial pressure can be monitored.

Postoperative nausea and vomiting should be treated aggressively using 2 to 3 antiemetics to prevent transmission. Although all known analgesics and methods can be used in the treatment of pain, liver, kidney, and bleeding coagulation system functions and side effects of selected analgesics should be considered. In pain management, the option should be individualized for the patient. High-dose opioids may cause undesirable effects such as respiratory depression and airway obstruction requiring airway manipulation. Local anesthetics should be preferred if appropriate (40).

As a result, the anesthetic management of patients with COVID-19 has distinctive features in terms of both protecting the healthcare workers and other patients and coping with the reasons resulting from the patient's clinic. Appropriate precautions and proper anesthesia management can prevent employees and anesthesiologists from injuries related to COVID-19.

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Author contributions: Concept – A.H.A.; Design – B.I.; Supervision – B.I.; Resource – A.H.A.; Materials – A.H.A.; Data Collection and/or Processing – A.H.A., B.I.; Analysis and/or Interpretation – B.I.; Literature Search – A.H.A.; Writing – A.H.A.; Critical Reviews – B.I.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

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Lymphoepihelioma-like Carcinoma of the Skin in the Mediterranean

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Lymphoepithelioma-like carcinoma of the skin (LELSC) is a rare cutaneous neoplasm with a low malignant potential. The neoplasm microscopically similar to undifferentiated nasopharyngeal carcinoma. LELSC is mostly found in the sun-exposed regions of the body. This case report presents an 88-year-old woman with a 7 × 6 mm nodule on the forehead. The Mediterranean region is one of the regions where the sunlight is dense and our patient is the first case which seen and reported in this region.

Keywords: Lymphoepithelioma, skin, sun, light

INTRODUCTION

Lymphoepithelioma-like skin carcinoma (LELSC) is a rare malignant tumor with limited metastatic potential. It is mostly found in sun-exposed regions of the body. Its histological features resemble undifferentiated nasopharyngeal carcinoma (1). To date, less than 70 cases have been reported in the English literature (2, 3). In this article, we present a case of LELSC from the Mediterranean, which has not been previously reported in this region.

CASE PRESENTATION

An 88-year-old woman presented with a 7×6-mm subcutaneous tumor on the left forehead for 12 months. The lesion was mobile and painless. The patient underwent surgery at the Department of Plastic Surgery, Near East University Faculty of Medicine Hospital. Consent form was obtained from the patient's daughter. The tumor was excised with 2-mm margins. Histopathologically, the tumor was non-encapsulated and subcutaneous. The tumor cells had large eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli, and surrounded by dense lymphoplasmacytic infiltrate (Figures 1, 2). These cells were positive for cytokeratin (CK) AE1/AE3 (anti-Pan keratin primary antibody, Roche, Mannhein, Germany), CK 5/6 (anti-CK 5/6 mouse monoclonal primary antibody, Roche, Mannhein, Germany) (Figure 3), and p63 (Ventana anti-p63 mouse monoclonal primary antibody, Ventana, Arizona, USA) (Figure 4) but were negative for Epstein–Barr Virus (EBV) (anti-EBV mouse monoclonal antibody, Cell Marque, California, USA). She did not have any complaints related to nasopharynx or cervical lymph nodes. She was diagnosed with LELSC. No recurrence or metastasis was observed a year after surgical excision.

DISCUSSION

LELSC was first reported in 1988 by Swanson et al. (4). Most cases present as a solitary erythematous firm nodule with telengiectasia or ulceration, similar to our case (1). The most common locations of LELSC are the face and scalp, but other locations, such as the arm and trunk, have also been reported (1, 3). The incidence of LELSC is equal for males and females, and they are more commonly seen in elderly patients (2, 4).

The etiopathogenesis of LELSC is unknown, unlike nasopharyngeal carcinoma. Few reports in Japan have shown the association between EBV and LELSC, although this relationship has not been proven (5, 6). LELSC is most commonly found in sun-exposed regions of the skin (2,7). To date, no case has been reported in the Mediterranean, although it is a region exposed to intense sunlight.

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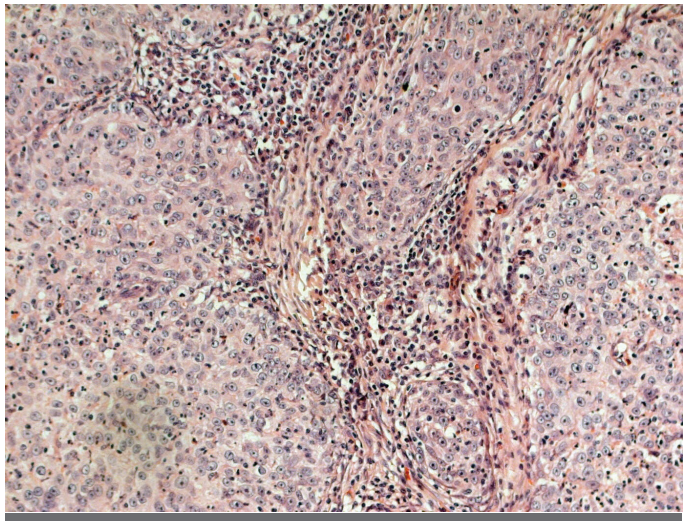

FIGURE I. Epithelioid tumoral cells and inflammatory infiltrate (HδE, ×100 objective)

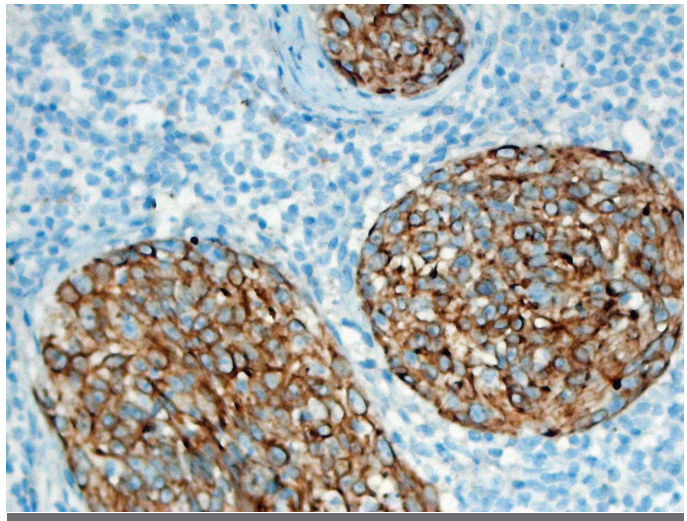

FIGURE 3. Tumoral cells show positive cytoplasmic immunexpression with CK5/6 (×100 objective)

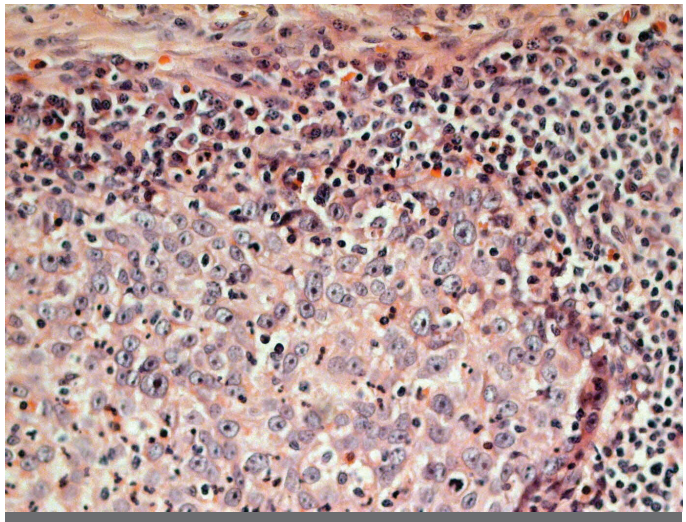

FIGURE 2. Epithelioid tumoral cells and inflammatory infiltrate (HδE, ×200 objective)

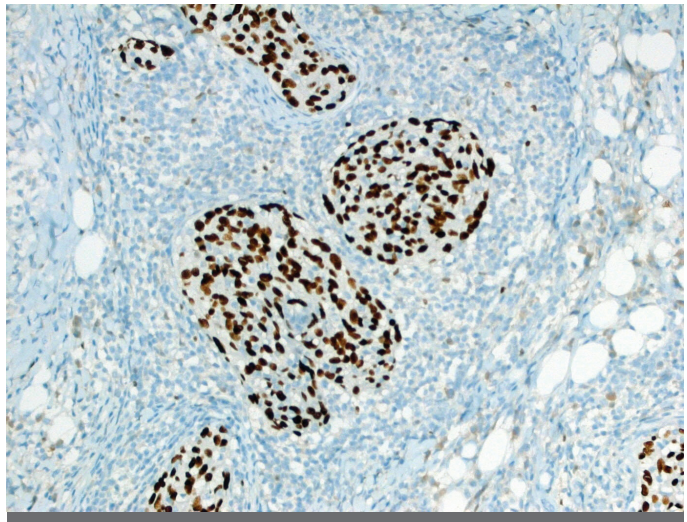

FIGURE 4. Tumoral cells show positive nuclear immunexpression with p63 (×100 objective)

Histopathologically, LELSC is an epithelial neoplasm in the deep dermis (4). It is a non-encapsulated lesion (3). The tumor consists of nests, cords, or sheets of polygonal epithelioid cells with amphophilic to eosinophilic cytoplasm, hyperchromatic nuclei, prominent nucleoli, and increased mitotic activity (1, 8). The tumor cells had dense lymphocytic infiltrate (1, 6, 9). LELSC was strongly positive for CK AE1/AE3, high-molecular-weight CK, p53, CK 5/6, and Cam5.2, and negative for CEA, S100, CK 20, CK 7, and EBV (1, 6, 9, 10).

The treatment methods for LELSC are wide local excision and detailed physical examination and imaging to rule out nasopharyngeal carcinoma (1, 8). Radiotherapy is better than surgical excision if the patient has lymph node metastasis or recurrence (1, 3, 8). LELSC has a low metastatic potential and better prognosis than other skin cancers, such as squamous cell carcinoma (SCC) and melanoma (1, 4, 8). However, some reports have discussed LELSC metastatic to lymph nodes at initial diagnosis (2, 9). At 1-year follow-up, no metastasis or recurrence was noted.

Main Points:

- LELSC is a rare, slow-growing malignant tumor with a low risk of metastasis and recurrence.
- It occurs more commonly in sunlight-exposed skin areas.
- We report the first case of LELSC in the Mediterranean region.

The differential diagnoses of LELSC include SCC, basal cell carcinoma (BCC), skin metastasis of lymphoepithelioma of the nasopharynx or other organs, melanoma, and lymphoma (1, 2, 7). Lymphoepithelioma of the nasopharynx is positive for EBV, but LELSC is not. In addition, lymphoepithelioma of the nasopharynx is more agressive than LELSC (3). SCC is located in the superficial dermis and has connections with the epidermis, unlike LELSC (3, 4). In the recent literature, LELSC is classified as a variant of SCC (3). LELSC, BCC, and lymphoma are histopathologically diffferent from each other. Malignant melanoma has a different immunohistochemical profile, which is CK (-), whereas S100 and Melan-A are (+).

Informed Consent: Consent form was taken from the daughter of the patient.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.Ö.; Design - H.Ö., İ.O.D.; Supervision - G.M.; Resource - H.Ö., G.M.; Materials - H.Ö., İ.O.D.; Data Collection and/or Processing - H.Ö., İ.O.D, G.M.; Analysis and/or Interpretation H.Ö., İ.O.D, G.M.; Literature Search - H.Ö.; Writing - H.Ö., G.M.; Critical Reviews - H.Ö., İ.O.D, G.M.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Letter to the Editor

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Rare Cause of Small Bowel Obstruction: Multiple Phytobezoars

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Dear Editor,

A 65-year-old male patient with abdominal pain, vomiting, and constipation for two days was admitted to the emergency unit. He had hypertension for ten years and an anamnesis of recurrent ileus. Additionally, he had two abdominal surgeries because of duodenal ulcer 30 years ago and fecaloid plug impaction because of ileus 3 years ago. There was abdominal distension without defense and rebound tenderness. His laboratory examination revealed slight leukocytosis with 13.4 μl/ml along with an increase in the levels of GGT (217 U/l), ALP (263 U/l), lipase (58 U/l), and CRP (34.5 g/l). He was clinically diagnosed with ileus and redirected to the radiology department for abdominal computed tomography (CT) examination. CT scans showed a well-defined, lobulated nodular intestinal lesion including millimetric air densities and intestinal content impaction at the pelvic entrance accompanied by diffuse intestinal wall thickening and mesenteric heterogeneity (Figure 1). Additionally, there was diffuse intestinal dilatation at the proximal part of small intestines. The site of this impaction was defined as the transition zone. There were also two similar nodular lesions in the fundus and antrum of the stomach (Figure 2). As the patient had duodenal ulcer surgery and anamnesis of recurrent ileus, these contents were diagnosed as phytobezoars. In follow-up visits, the patient's clinical symptoms and laboratory findings deteriorated and he was redirected to surgery. Enterotomy–gastrotomy along with phytobezoar resection surgery was administered on the patient (Figure 3). Macroscopic pathology evaluation detected three operation materials, which were green, colored, and spongiform consistent with the fissionable pattern. Microscopic evaluation revealed a homogeneous spongiform image. The histopathology results detected the operation materials as food-originated materials.

Phytobezoars are the accumulation of undigested or poorly digested fibers of fruits and vegetables in the gastrointestinal system (1). Their occurrence is common in patients with a history of gastric ulcer or gastric resection surgeries (2). Additionally, high-fiber diet digestion; other diseases and factors such as renal failure, diabetes mellitus, postoperative adhesions, Gulliain–Barré syndrome, myotonic dystrophy, and hypothyroidism; dental diseases, which causes insufficient chewing problems; and drugs, which slow the gastrointestinal motility, may result in the formation of phytobezoars (3, 4). A study has also reported the formation of idiopathic phytobezoars (4).

Mechanical small bowel obstruction commonly occurs in patients with phytobezoars. Because the diameters of the intestinal lumens are narrowed, proximal ileal segments and jejunum are the frequent transition zones of mechanical obstructions (2).

Endoscopic methods along with open or laparoscopic surgeries are the treatment options for this disease (5). Surgery is preferred after the failure of endoscopic treatment (5). Laparoscopic surgery requires optimal preoperative radiological evaluation and technical experience (5). Although laparoscopic surgery is more frequently performed, open surgery is still the most common treatment method (5). Enterotomy is administered in patients who had bezoar in the proximal parts of gastrointestinal tract (5).

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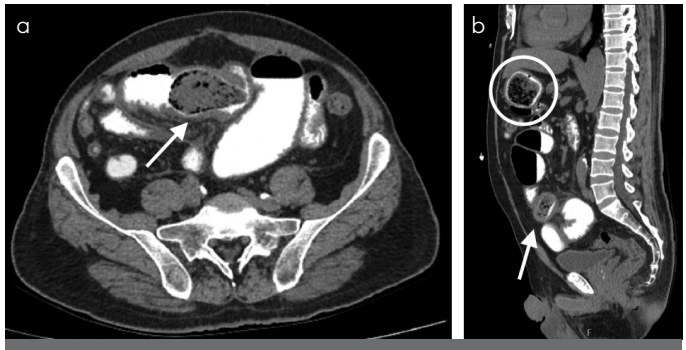

FIGURE I. a, b. a. Axial b. Sagittal CT examinations with oral positive contrast material show a well-defined, lobulated nodular intestinal lesion including millimetric air densities compatible with phytobezoars and intestinal content impaction at the proximal part of small intestines accompanied by diffuse intestinal wall thickening and mesenteric heterogeneity (Arrow). The site of this impaction was defined as the transition zone of mechanical intestinal obstruction. Additionally, similar nodular density is observed in the stomach lumen (Circle)

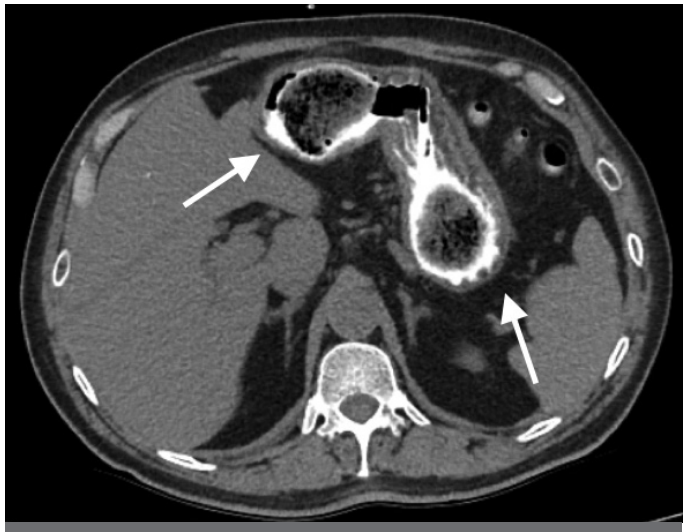

FIGURE 2. Axial CT image with oral positive contrast material shows two phytobezoars filling the defects at the fundus and antrum of the stomach

In conclusion, phytobezoars must be considered in the diagnosis of patients especially with gastric surgery for peptic ulcer and anamnesis of recurrent mechanical intestinal obstruction. CT provides an optimal evaluation of the location of phytobezoars and assists in planning and choosing the surgical method.

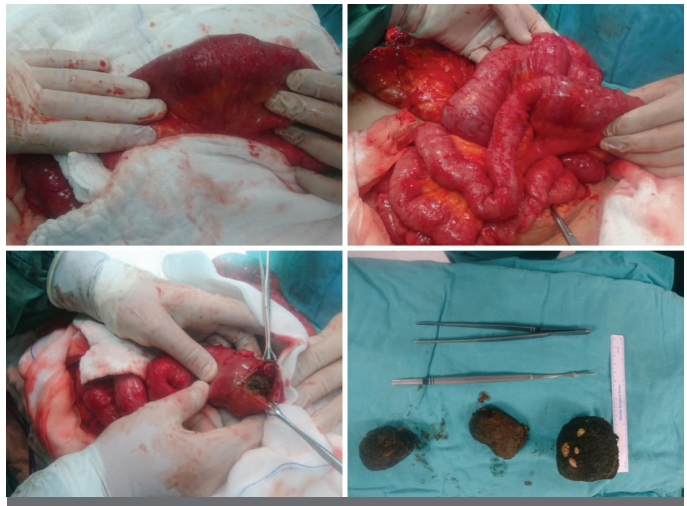

FIGURE 3. Surgical procedures compatible with enterotomy and gastrotomy. Three resected and different phytobezoars are seen

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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CUMHURBAŞKANLIĞI

"The best of people are those that bring most benefit to the rest of mankind."

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