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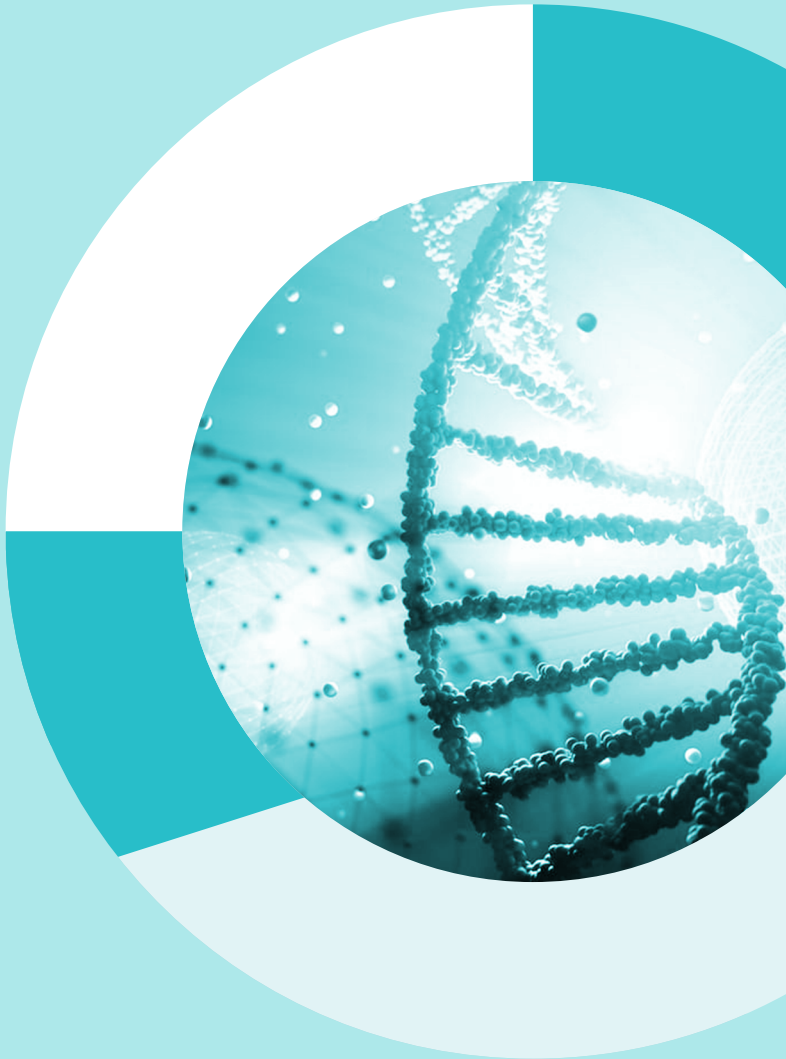
RESEARCHS ARTICLES

REVIEW



Official Journal of Cyprus Turkish Medical Association

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Volume: 6 | Issue: Supplement 1 | December 2021

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Volume: 6 | Issue: Supplement 1 | December 2021

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Volume: 6 | Issue: Supplement 1 | December 2021

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CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

ABOUT US

Cyprus Journal of Medical Sciences (Cyprus J Med Sci) is the official organ of Cyprus Turkish Medical Association. This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles published quarterly in March, June, September and December. The publication language of this journal is English.

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

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

The evaluation and publication processes of the Cyprus Journal of Medical Sciences are shaped in acceptance with the guidelines of ICMJE (International Committee of Medical Journal Editors), COPE (Committee of Publication Ethics), EASE (European Association of Science Editors), and WAME (World Association of Medical Editors). The journal also is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

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CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

INSTRUCTIONS TO AUTHORS

Peer Review, Publication Ethics and Malpractice Statement

Peer-Review

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

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

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

Human and Animal Rights

For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013, www.wma.net) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals, www.nap.edu.catalog/5140.html), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the Cyprus Journal of Medical Sciences (Cyprus J Med Sci) together with the manuscript.

The approval of the ethics committee, statement on the adherence to international guidelines mentioned above and that the patient's informed consent is obtained should be indicated in the "Material and Method" section and is required for case reports whenever data/media used could reveal the identity of the patient. The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

The author (s) should indicate in their articles that Informed Consent was received from the participating individuals in the studies conducted on people and send the approval document (s) received from the Ethics Committee or equivalent board of the institution where the study was conducted. In case reports, a document must be presented, indicating that each case is informed that their information will be used for publication. All work must have been done in accordance with the final amendments to the Helsinki Declaration. Patient information should be obtained in accordance with the Patient Rights Regulation published in the Official Gazette dated 01.08.1998 and numbered 23420. The European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purpose, by the Universal Declaration of Animal Rights, which reports results on animals, for the Protection of Vertebrates to be Used for Experimental and Other Scientific Purposes, T.C. The Regulation of the Ministry of Agriculture and Rural Affairs on the Production Areas of the Experimental Animals Used for Experimental and Other Scientific Purposes and the Regulation on the Establishment Operation Control Procedures and Principles of the Laboratory to Experiment, the Principles of Laboratory Animal Science, by the care and use of

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

laboratory animals. If it is available in accordance with the rules and principles contained in the relevant manuals and in the institution where the study is carried out, it should be made after approval from the Experimental Animals Ethics Committee. Ethics Committee approval must be submitted with the letter. In the articles, the information should be given about post-operative pain-relieving treatment methods used in human and animal studies.

PLAGIARISM AND ETHICAL MISCONDUCT

This journal uses "iThenticate" to screen all submissions for plagiarism before publication.

It is essential that authors avoid all forms of plagiarism and ethical misconduct as represented below.

Plagiarism: To Republish whole or part of a content in another author's publication without attribution.

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

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

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

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

We disapprove of such unethical practices as plagiarism, fabrication, duplication, data manipulation/falsification and salamisation and efforts to influence the review process with such practices as gifting authorship, inappropriate acknowledgements, and references in line with the COPE flowcharts.

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

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Duties of the Publisher

Handling of unethical publishing behaviour

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

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Scientific Misconduct

Cyprus Journal of Medical Sciences's publisher always takes all appropriate measures regarding fraudulent publication or plagiarism.

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

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B. DUTIES OF EDITORS:

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The editor of the journal keeps under control everything in the journal and strives to meet the needs of readers and authors. The editor is also responsible for deciding which articles submitted to the journal should be published and guided by the policies subjected to legal requirements regarding libel, copyright infringement, and plagiarism. The editor might discuss with reviewers while making publication decisions. The editor is responsible for the contents and overall quality of the publication. Editor ought to provide a fair and appropriate peer-review process.

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Articles that are submitted to the journal are always evaluated without any prejudice.

Confidentiality

The editor must not disclose any information about a submitted article to anyone other than editorial staff, reviewers, and publisher.

Conflicts of Interest and Disclosure

The Editor of Cyprus Journal of Medical Sciences does not allow any conflicts of interest between the parties such as authors, reviewers and editors. Unpublished materials in a submitted article must not be used by anyone without the express written assent of the author.

Fundamental Errors in Published Works

Authors are obliged to notify the journal's editors or publisher immediately and to cooperate with them to correct or retract the article if significant errors or inaccuracies are detected in the published work. If the editors or publisher learn from a third party that a published work contains a material error or inaccuracy, the authors must promptly correct or retract the article or provide the journal editors with evidence of the accuracy of the article.

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Reviewers evaluate manuscripts without origin, gender, sexual orientation or political philosophy of the authors. Reviewers also ensure a fair blind peer review of the submitted manuscripts for evaluation.

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All the information relative to submitted articles is kept confidential. The reviewers must not be discussed with others except if authorized by the editor.

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Contribution to editor

Reviewers help the editor in making decisions and may also assist the author in improving the manuscript.

Objectivity

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CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

Acknowledgement of Sources

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

D. DUTIES OF AUTHORS:

Reporting Standards

A submitted manuscript should be original, and the authors ensure that the manuscript has never been published previously in any journal. Data of the research ought to be represented literally in the article. A manuscript ought to include adequate detail and references to allow others to replicate the study.

Originality

The authors who want to submit their study to the journal must ensure that their study is entirely original. The words and sentences getting from the literature should be appropriately cited.

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Authors should not submit the same study for publishing in any other journals. Simultaneous submission of the same study to more than one journal is unacceptable and constitutes unethical behaviour.

Acknowledgement of Sources

Convenient acknowledgement of the study of others has to be given. Authors ought to cite publications that have been efficient in determining the study. All of the sources that used the process of the study should be remarked.

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

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

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CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

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Manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

INSTRUCTIONS TO AUTHORS

to prepare manuscripts under the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can be submitted through the journal's online manuscript submission and evaluation system, available at cyprusmedj.galenos.com. Manuscripts provided from another medium and sent by anyone other than one of the authors will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office will provide that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not comply with journal guidelines will be returned to the submitting author, along with technical correction recommendations.

Language

All manuscripts must go through a professional language editing process in the Cyprus Journal of Medical Sciences. Authors are required to submit the language editing certificate during initial submission. Editing service is provided by Enago.

Authors are required to submit the following:

· Copyright Agreement and Acknowledgement of Authorship Form, and

· ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.icmje.org.

Preparation of the Manuscript

Title page: A separated 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,

· ORCID IDs, name(s), affiliations, highest academic degree(s) of the author(s),

· Grant information and detailed information on the other sources of support,

· name, address, telephone (including the mobile phone number), and email address of the corresponding author,

· Acknowledgment of the somebody who contributed to the manuscript›s preparation but who does 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 1 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 and 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 should be accompanied by 3 to 5 "main points", which should emphasize the most significant results of the study and underline the principle statement that is addressed to the reader except letters to the editor. This section should be structured as itemized to give a general overview of the article. Since "Main Points" target the professionals and specialists of the field, each item should be written as plain and straightforward as possible.

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

INSTRUCTIONS TO AUTHORS

Manuscript Types

Original Articles: This is the most essential type of article because it provides new information based on original research. Acceptance of original papers will be based upon the originality and importance of the investigation. The main text of original articles should be structured as Introduction, Material and Methods, Results, and Discussion subheadings. An original article can be signed by a maximum of 6 authors unless it is a multi-center study or that it requires extensive labour. Please review Table 1 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, the 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 a minimum acceptable 24-item trial registration dataset.

• Authors must state a data sharing plan for the clinical trial registration. Please see details under the "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 1 January 2019, a data-sharing statement is required to register clinical trials. Authors are required to provide a data sharing statement for the articles that report a clinical trial result. 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 must register 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 if the authors do not share it.

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

INSTRUCTIONS TO AUTHORS

The journal's clinical trial and data sharing policy will be valid for the articles submitted from 1 February 2020.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted following the 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 used during the process must be specified.

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 a 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, 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. The journal may even invite these authors. 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.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

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

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 6 | Issue: Supplement 1 | December 2021

INSTRUCTIONS TO AUTHORS

Tables

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 the USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)."

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 shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

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

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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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REVISIONS

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CONTENS

RESEARCHS ARTICLE

REVIEW

RESEARCH ARTICLE

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Comparison of Cost, Risks, and Benefits of Robotic or Open Thyroidectomy on Thyroid Cancer

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Abstract

BACKGROUND/AIMS: This study aimed to raise awareness of the cost, risk, and benefits of robotic thyroidectomy (RT) and open thyroidectomy (OT) when deciding on the surgical method for thyroid cancer.

MATERIALS and METHODS: Complications, benefits, duration of operation, costs, and other risk factors in thyroid cancer cases, including robotic and OT of large case series followed up for a long time were comparatively analyzed, and results were evaluated.

RESULTS: The comparison of obtained results after a 5-year follow-up revealed significantly higher costs, operative times, and postoperative morbidity rates in RT than OT. The satisfaction of patients in cosmetic terms was higher in RT.

CONCLUSION: Our study results revealed that necessary outside logistics support, a necessary significant amount of operating room extra machines and materials, low patient circulation rate, and the medico-legal problems may arise, and we think that RT decision should be taken under limited conditions in thyroid cancers.

Keywords: Robotıc, thyroidectomy, risks, benefits, cost

INTRODUCTION

Robotic surgery was first used in 1985 to perform the biopsy in the field of brain surgery. Afterward, it has become widely used worldwide, especially in prostate cancer cases.[1] Robotic thyroid surgery has been extensively used in the Far East in the last 20 years;[2] but not in western countries. Since the time of Nobel Prize-winning scientist Theodor Kocher, one of the pioneers of modern surgery, open thyroid surgery has been successfully implemented in many countries worldwide without major changes.

Considering the basic criteria in surgical method selection for cases with surgical indication, such as cost, risk, and advantages,[3] robotic thyroidectomy (RT) and open thyroidectomy (OT) were compared in our study. Therefore, this study aimed to increase the awareness of the surgeons when deciding on the surgical method for thyroid cancers. Additionally, ethical and medico-legal problems that may arise in the selection of operations were evaluated.

MATERIALS and METHODS

Our study evaluated the breast, axillar, bilateral axillary breast, and facelift approaches within the scope of RT. Standard classical thyroidectomies that were not performed by remote control were evaluated as OT.

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Long-term follow-up and RT and/or OT studies, which consisted of a large number of cases compared the reported results with each other and statistically evaluated and revealed the cost, risk, and advantages. Criteria used to evaluate the advantages and risk factors include operative time, morbidity rates, recurrence rates, and cosmetic results.

Studies conducted by Cabot et al.[4], by Broom et al.[5], and in Turkey[6] compared the RT and OT costs and statistically evaluated results.

Russel et al.[7] conducted a study of total thyroidectomy in 216 RT and 419 OT cases, Lee et al.[8] in 68 RT and 110 OT cases, Kim et al.[9] in 69 RT and 138 OT cases, and Christine et al.[10] in 25 RT and 25 OT cases undergoing lobectomy, wherein mean operation times were compared and results were statistically evaluated.

The morbidity rate in 4751 patients who underwent RT in the study of Kim et al.[11] in the same institute, 1503 patients who underwent OT by Sciuto et al.[12] in the same institute, and 40,025 thyroid cancer cases by Caulley et al.[13] were compared and results were statistically evaluated.

Seul and et al.[14] conducted a study in 245 RT and 494 OT cases, Kim et al.[15] in 41 RT and 102 OT cases, and Billmoriave et al.[16] in 10,247 OT cases, wherein results were compared and statistically evaluated.

The study results of Lee et al.[17] in 66 OT and 62 RT cases and of Kyung et al.[18] in 75 RT and 226 OT cases were compared and statistically evaluated.

Statistical Analysis

Independent t-test between the samples at the α=0.01 level of significance was performed for large samples and the Wilcoxon-Rank-Sum test for samples of <30. Standard deviations and sample sizes were obtained from reference articles and t-statistics, and two-sided *p*-values were obtained for significance. When standard deviations were not given, range values (R) were used to estimate the standard deviation by using s = (max − min)/4.

Ethics Committee Approval

Ethics committee approval was received for this study from Girne American University Ethics Committee (approval date: 01.13.2020, approval number: 2020-009).

RESULTS

The results that compare the obtained data from the publications in which the costs were determined in RT and OT cases are presented (Table 1).

Table 1 shows the comparison of the costs in cases with RT or OT. A significant difference was determined in the cost between RT and OT (p <0.0001) in all cases; RT cases being significantly more costly compared to OT cases.

The results of the comparison of the mean operation times in the reported publications of RT and OT cases are shown in Table 2.

Table 2 shows the mean operation times compared in the reported publications of RT and OT cases. The RT times are significantly longer than that of OT in all cases.

Table 1. Comparison of costs in DTC cases with RT or OT

Study	Cost	RT	OT	*p*-value
Cabot[4]	Total cost	$13.670 ± $1384	$9.028 ± $891	<0.0001*
Broom[5]	Relative cost	$5.795	$2.668	<0.0001*
Turkey SUT + RA[6]	Relative cost	₺ 28.000	₺ 1.200	<0.0001*

DTC, Differentiated thyroid cancer; SUT, Turkey's Health Ministry communiqué health implementations; RA, Robotic arm; OT, Open thyroidectomy; RT, Robotic thyroidectomy; * statistically significant.

Table 2. Comparison of operation times in patients with RT and OT

Study	Type of operation	Mean surgical time RT (min)	Mean surgical time OT (min)	*p*-value
Russell[7]	Total thyroidectomy	170 (n=216) (R=398–100)	126.5 (n=410) (R=260–51)	<0.0001*
Lee H[8]	Total thyroidectomy	141.4±36.35 (n=68)	95.4±23.69 (n=110)	<0.0001*
Kim[9]	Total thyroidectomy	196 (n=69)	81 (n=138)	-
Christine[10]	Lobectomy	121 (n=25) (R=74–199)	68 (n=25) (R=41–112)	<0.0001*

OT, Open thyroidectomy; RT, Robotic thyroidectomy; *statistically significant.

Morbidity rates in patients with thyroid cancer undergoing RT and OT are shown in Table 3.

Table 3 shows the comparison of morbidity rates in patients with thyroid cancer undergoing RT and OT. The morbidity rates between the two groups were significantly different from each other, and morbidity rates were significantly higher in the RT group compared to the OT group.

Recurrence rates in patients who were followed for >5 years and underwent robotic total thyroidectomy (RTT) and open total thyroidectomy (OTT) (Table 4).

Table 3. Comparison of morbidity rates in patients with thyroid cancer undergoing RT and OT

Study	RT MR	OT MR	*p*-value
Kim[11]	24.1 (n = 4751)	-	<0.0001*
Sciuto[12]	-	12.6 (n=1503)	<0.0001*
Caulley[13]	-	7.74 (n = 40.025)	-

MR, Morbidity rate; OT, Open thyroidectomy; RT, Robotic thyroidectomy; *statistically significant.

Table 4 shows the recurrence rates in patients with thyroid cancer undergoing RTT and OTT. Results show no statistically significant differences between RTT and OTT in recurrence rates.

The comparison of cosmetic results of RT and OT is shown in Table 5.

Table 5 shows the comparison of cosmetic results in RT and OT cases. A significant difference was seen between the RT and OT cases, wherein RT cases were significantly more satisfied compared to OT cases.

The advantages and disadvantages of RT compared to OT in thyroid cancer cases (Table 6).

DISCUSSION

OT surgeries can be performed together with support staff with basic operating room knowledge and experience in all hospitals that can provide second-degree health services that do not require advanced technological logistic support. The patient can be taken to surgery immediately after surgical indication and complete routine preparations. RT operations require

Table 4. Recurrence rates in patients with thyroid cancer undergoing RTT and OTT

Study	Type of surgical tumor size	RT rec. rate (%)	OT rec. rate (%)	*p*-value
Seul GI[14]	Total, <1 cm	1.2 (n=245)	1.2 (n=494)	0.991*
Kim M[15]	Total, <1 cm	2.4 (n=41)	2.9 (n=102)	0.869*
Bilimoria[16]	Total, <1 cm	-	1.0 (n=10.247)	0.734*

RTT, Robotic total thyroidectomy; Rec rate, Recurrence rate; OT, Open thyroidectomy; RT, Robotic thyroidectomy; OTT, Open total thyroidectomy; Type of op., Type of operation; *statistically insignificant.

Table 5.

	Exteremely satisfied (1)		Satisfied (2)		Acceptable (3)		Dissatisfied (4)		Exteremely dissatisfied (5)		*p*-value
Study	OT	RT	OT	RT	OT	RT	OT	RT	OT	RT	
Lee et al.[17]	22	46	26	10	10	6	5	0	3	0	<0.0001*
Posop 6th month:	OT (n=66); RT (n=62)										
Kyung et al.18											<0.01
Posop 3rd month:	OT (n=226) 3.00+1.04; RT(n=75) 1.61+0.87										

OT, Open thyroidectomy; RT, Robotic thyroidectomy; *statistically significant.

Table 6. Advantages and disadvantages of RT according to OT in thyroid cancer cases

Advantages	Disadvantages
• Better cosmetic results	• Higher cost • Longer operation time, more dissection, more bleeding • Higher morbidity rates • The patient circulation process is long and cumbersome • Extra complications (such as drowsiness in the breast skin) • Medico-legal problems

RT, Robotic thyroidectomy; OT, Open thyroidectomy.

operator and support staff that passed the course with sufficient knowledge and experience.[19]

RT operations require approximately 3 million USD investments in operating theaters.[20]

Once these machines are supplied, establishing relations with companies for every logistic need before each operation is necessary. This situation makes the patient's circulation significantly difficult and cumbersome.[21]

The comparison of OT and RT surgery costs revealed a significant difference (Table 1). The robotic arm payment that needs to be changed in each operation is approximately ₺ 3,000. This charge is not payable by the National Insurance Institution (SGK).[6] SUT prices in OT operations are ₺ 1,200 in Turkey. It can be done with operating room materials in medium-sized hospitals without any extra logistic requirements. Hospitals, where RT surgeries can be performed, have quite high operating costs apart from the need for extra logistics and is approximately ₺ 25,000.[22] The evaluation of both surgical methods in "cost, risk, and benefits" revealed that RT was disadvantageous in "cost" compared to the OT.

Operation times under general anesthesia significantly increase morbidity. Myocardial infarction, renal failure, thromboembolic complications, arrhythmia, atelectasis, and other pulmonary complications can occur in the postoperative period. A meta-analysis conducted by Cheng et al.[23] revealed that an increased postoperative complication rate by 14% with every half-hour increased operation time. The comparison of operating times in RT and OT in patients with thyroid cancer revealed a significantly higher RT time than OT (Table 2). RT cases undergoing total thyroidectomy have approximately 40 min longer operating times. Few studies have reported a statistically insignificant difference between the cases with RT and OT.[24] The number of studies with higher operation times in RT is more.[7,8,10,19] According to these study results, longer operation times seem to be a major disadvantage of RT.

Postoperative morbidity rates were considered as an important risk factor in determining the surgical methods for thyroid cancers. Among the studies performed on RT and OT in thyroid cancers, especially those with a high number of cases were included in this study. The comparison of the morbidity rates in RT and OT cases revealed that morbidity rates are higher in RT cases (Table 3). The study conducted by Kim et al., where the largest case series with RT in thyroid cancers have been published so far, revealed the average morbidity rate of 24.1. Cases that were followed up for an average of 52.5 months were divided into 4 periods and revealed that morbidity rates were 25.8 in the first period, 23.2 in the second period, and 29.5 in the third period, which reduced to 14.7% in end-stage patients with 964 cases.[11] However, a large series of 40,025 cases with OT thyroid cancer cases published by Caulley et al. revealed an average of 7.74 morbidity rate.[13] There are small case series where the difference between the morbidity rates in heterogeneous patient groups performed RT and AT is meaningless.[7]

One of the most important reasons for higher postoperative complications in thyroid cancer cases with RT may be the longer operation time.[22] The high amount of dissection in RT causes more bleeding.[21] Comparative studies revealed significantly more bleeding in patients who performed RT than those who had OT.[8,21,25] Although not seen in cases with OT, some complications are seen in RT cases such as spinal accessory nerve palsy,[11] hypoglossus injury,[25] numbness in the brachial plexus distribution (breast skin) on the operation side,[10] induration due to dissection under the breast skin and suspicious image in related mammography,[21] and Horner syndrome.[11] The comparison of morbidity rates revealed that RT is riskier.

Some factors affected the recurrence rates in thyroid cancers, especially papillary thyroid cancers (PTC) are likely to be multicentric (MC) tumor and is approximately 20%.[26] Cervical lymph node metastases and tumor recurrence rates are high in MC PTCs.[27] Recurrence rates of tumors were higher in PTC cases with BRAFV600E mutation.[28] Results of studies in large differential thyroid cancer (DTC) series revealed increased recurrence rates after age 45 years and in males.[29] Tumor diameter is an important factor in increasing recurrence rates in differentiated thyroid cancers. Recurrence rates increase after the operation in cases of >1 cm.[30]

The series of thyroid cancer cases in our study with RT and followed for >5 years are very few. Current studies revealed no statistically significant difference between the recurrence rates in patients with RT of <1 cm in diameter and patients with RT and OT in thyroid cancer cases (Table 4). Many cases that are considered recurrences in thyroid cancers reported no relapse but residual tissue.[31] Considering approximately 20% of DTC cases are MC, thyroid cancers should remove all the thyroid tissue.[32] Removing the tissue completely by harmonic dissection especially at the level of the Zuckerkandl protrusion in RT is very difficult.[21] Recurrence rates were investigated in some non-homogeneous patients with DTC who underwent RT and OT and are followed for <5 years and revealed no significant differences.[9,32] Many studies compared RT and OT surgeries and do not recommend RT in risky cases because it increases morbidity and recurrence rates.[19,24] When risky patients are separated, the patient group suitable for RT decreases.

Mortality rates could not be compared as a risk factor in both surgical methods since the absence of case series in which 10 years of follow-up was reported in patients undergoing RT.

RT and OT studies that compared the results related to cosmetic satisfaction after the operation revealed a significantly higher

patient satisfaction in patients with RT (Table 5). This situation is an advantage in favor of RT. In patients who underwent OT without lateral neck dissection, scarring is avoided if incisions are made with the appropriate surgical technique parallel to the skin lines.[33] Thus, if the patient does not want any scar tissue on his neck, the higher risks of RT surgery than OT should be clearly explained to the patient for ethical reasons.[21] However, even if the patient prefers RT, it should be kept in mind that medical problems that may arise since RT may cause legal and criminal problems, despite the detailed consent form.

The advantages and disadvantages of RT are collectively shown in Table 6. According to these results, the only advantage of RT seems to be better cosmetic results.

CONCLUSION

According to our study results, RT decisions should be taken under limited conditions in thyroid cancers based on necessary outside logistic support, a significant amount of operating room extra machines and materials, low patient circulation rate, and the medico-legal problems that may arise.

Main Points

• RT is a new surgical method whose long-term follow-up results are unclear.

• RT is several times more expensive than OT and requires specialized personnel who are relatively trained, thus cannot be performed in every hospital.

• Operation time is significantly longer in RT than OT. Therefore, postoperative complication rates are higher than OT.

• RT has no obvious superiority over OT. When an appropriate operation technique is applied, very few scars remain in the neck in OT. Even without a scar on the patient's neck, numbness can occur on the breast skin, as well as stiffness under the breast skin, which may give false-positive results in future mammograms for tumor risk assessments.

• A patient who does not want any scar on her neck and if she insists on RT surgery, risks of RT should be clearly explained before surgery for medico-legal reasons.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from Girne American University Ethics Committee (approval date: 01.13.2020, approval number: 2020-009).

Informed Consent: It was obtained.

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Author Contributions

Concept: H.A.; Design: H.A.; Supervision H.A.; Resources: H.A.; Data Collection and/or Processing: H.A.; Analysis and/or Interpretation: A.Ü.; Literature Search: H.A.; Writing: H.A.; Critical Review: H.A.

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Conflict of Interest: The authors declare no conflicts of interest.

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RESEARCH ARTICLE

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Clinical, Demographic and Treatment Characteristics of Pediatric Psoriasis: A Multicenter Study of 150 Patients

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Abstract

BACKGROUND/AIMS: Many studies have focused on the epidemiological features of adult and childhood psoriasis. However, only a few studies have been conducted to demonstrate the clinical and demographic characteristics of pediatric psoriasis in Turkey. This study aimed to determine clinical, demographic, and treatment characteristics of childhood psoriasis in a multicenter series.

MATERIALS and METHODS: This study was conducted in four different centers that are located in four cities of Turkey between June 2016 and June 2020. The demographic parameters, possible triggering factors (emotional stress, physical trauma, infection, and medication), and clinical characteristics (psoriasis type, psoriasis area severity index, involved areas, nail involvement, joint involvement, subjective symptoms, disease duration, last treatments and duration of use, and history of accompanying diseases) of pediatric patients with psoriasis were retrospectively analyzed.

RESULTS: A total of 150 patients from four different centers were enrolled in the study, of whom 71 (47.30%) were males and 79 (52.70%) were females, with a mean age of 13.71±4.2 years (age range: 1–18 years). A family history of psoriasis was determined in 20 (13.33%) patients. Possible triggering factors included emotional stress (n=90, 60%), physical trauma (n=21, 14%), infection (n=14, 9.33%), and medication (n=1, 1.67%). The most common area of involvement was the trunk (n=69, 46%) followed by the scalp (n=42, 28%), hand (n=20, 13.33%), and face (n=19, 12.67%). The prevalence of clinical types was as follows: plaque (n=125,83.33%), guttate (n=10, 6.67%), palmoplantar (n=7, 4.67%), inverse (n=6, 4%), and pustular (n=2, 1.33%) psoriasis. Nail and joint involvement were observed in 30 (20%) and 15 (10%) patients, respectively. The last treatments received included topical treatment (n=101, 67.33%), phototherapy (n=23, 15.33%), acitretin (n=16, 10.67%), methotrexate (n=9, 6%), and cyclosporine (n=1, 0.67%).

CONCLUSION: In our cohort, the clinical types and treatments used for childhood psoriasis were similar to those of other studies, but the rate of family history was lower, whereas the incidence of emotional stress was higher. Addressing the psychological impacts of psoriasis along with its physical aspects may provide better treatment outcomes.

Keywords: Nail, children, treatment, psoriasis

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that is characterized by sharply circumscribed erythematous scaly plaques. Polygenic predisposition and environmental triggers play essential roles in etiopathogenesis.[1] Psoriasis has been reported to constitute 3.8% of all outpatient clinic visits in childhood and adolescence.[2] Recent epidemiological studies have shown that the prevalence of childhood and adolescent psoriasis varies between 0% and 1.37%.[3] The age of onset for pediatric psoriasis is unknown; however, psoriasis occurs before 10 years of age in 10% of the affected children and before 2 years in 2%.[4] Many studies focused on the epidemiological features of adult and childhood psoriasis. However, only a few studies have been conducted to demonstrate the clinical and demographic characteristics of pediatric psoriasis in Turkey.[2,5-10] This multicenter cohort study aimed to reveal the clinical and demographic features of pediatric psoriasis in Turkey.

MATERIALS and METHODS

Patients

This study was conducted in four different centers that are located in four cities of Turkey between June 2016 and June 2020 and included patients under 18 years old who were diagnosed with psoriasis. The relevant data were retrieved from a psoriasis registry system (PSORTAKSIS) integrated into the hospital electronic record system.[11]

Diagnosis

The diagnosis was principally made based on clinical features, but in cases where clinical findings were not typical, the diagnosis was histopathologically confirmed. The histopathological criteria for psoriasis were as follows: parakeratosis; hyperkeratosis; absence/reduction of the granular cell layer; rete ridge elongation; neutrophilic aggregates within the epidermis and dermis (microabscesses of Munro and pustules of Kogoj); dilatation of superficial dermal capillaries; and perivascular lymphocyte infiltration (Figure 1). Cases with suspicion in the diagnosis despite histopathological examination were excluded.

Parameters

The parameters that were retrospectively analyzed were as follows; 1) epidemiological data: age, gender, weight, height, body mass index (BMI), family history, and possible triggering factors (emotional stress, physical trauma, infection, and medication); 2) clinical features: psoriasis type, psoriasis area severity index (PASI), areas of involvement, nail involvement, joint involvement, subjective symptoms, disease duration, last medication and duration of use, and history of accompanying disease. The presence of at least one of the following changes observed by parents was considered an indicator of emotional stress: excessive worries, acting irritable or moody, withdrawing from activities that used to give pleasure, complaining more than usual about the school, and showing surprising fearful reactions.

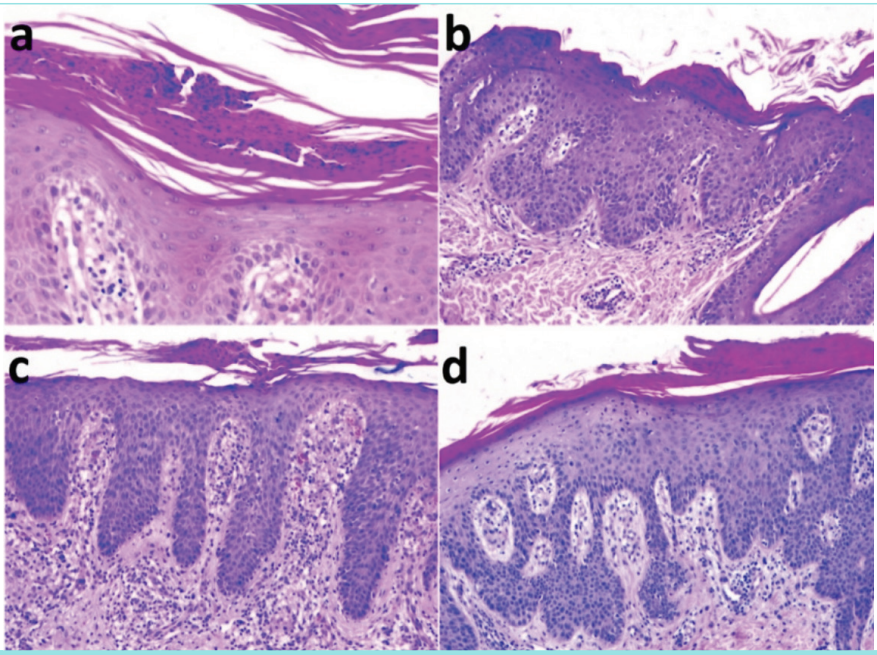

Figure 1. Histopathological microphotographs of four pediatric patients diagnosed with psoriasis vulgaris. Biopsies demonstrate microabscesses of Munro (a, b) (H&E, ×200; H&E, ×100), parakeratosis, hyperkeratosis, hypogranulosis, elongation of the rete ridges, and dermal perivascular lymphocyte infiltration (c, d) (H&E, ×100; H&E, ×100).

H&E: Hematoxylin and eosin stain.

Statistical Analysis

The data obtained were analyzed using International Business Machines Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, IL, USA) package program. Descriptive statistics were used, with categorical variables that are summarized using numbers and percentages and continuous variables using mean, standard deviation, minimum, and maximum. The normality of distribution was analyzed using the Shapiro-Wilk test. Relationships between variables were analyzed via the chi-square test, the Spearman correlation test, the logistic regression, and the multiple logistic regression. The findings were evaluated at a 95% confidence interval and 5% significance level. A *p*-value of <0.05 was considered statistically significant.

Ethics Approval

All the procedures followed the Helsinki declaration, and the study was approved by the local institutional review board (decision date and number: 2020-09/78).

RESULTS

A total of 150 patients from four different centers were enrolled in the study, of whom 71 (47.30%) were males (mean age: 12.74 years) and 79 (52.70%) were females (mean age: 14.57 years). The boy/girl ratio was 0.89/1. The ages of patients ranged from 1 to 18 years with a mean age of 13.71±4.2 years. The mean weight, height, and BMI were 47.44 (17.98) kg (range: 9–90), 1.5 (0.19) (range: 0.88–1.83) meters, and 20.15 (4.17) (range: 5.91–33.46) kg/m^2, respectively. The mean disease duration was 3.65 (3.84) (1–34) months and the mean PASI score was 1.85 (2.29) (0–19). All clinical and demographic features of patients are shown in Table 1. Twenty patients (13.33%) had a family history of psoriasis. Possible triggering factors included emotional stress (n=90, 60%), physical trauma (n=21, 14%), infection (n=14, 9.33%), and medication (n=1, 1.67%). The most common areas of involvement were the trunk (n=69, 46 %) followed by the scalp (n=42, 28%), hand (n=20, 13.33 %), and face (n=19, 12.67%). The prevalence of clinical types was as follows: plaque (n=125, 83.33%), guttate (n=10, 6.67 %), palmoplantar (n=7, 4.67%), inverse (n=6, 4%), and pustular (n=2, 1.33%) psoriasis. Nail involvement was observed in 30 (20%) patients including pitting (n=16), subungual hyperkeratosis (n=5), leukonychia (n=5), onycholysis (n=2), oil spot (n=1), and discoloration (n=1). Fifteen patients (10%) showed joint involvement. Comorbidities included aortic stenosis (n=1), diabetes mellitus (n=1), familial Mediterranean fever (n=1), chronic renal failure (n=1), Henoch Schoenlein purpura (n=1), liver cirrhosis (n=1), and hypothyroidism. As treatment, 101 (67.33%) patients were on topical, 23 (15.33%) on phototherapy, 16 (10.67%) on acitretin, 9 (6%) on methotrexate, and 1 (0.67%) on cyclosporine. The mean duration of the last treatment received was 4.67 (5.24) months. No statistically significant difference was found between any parameters in comprehensive statistical analysis.

DISCUSSION

Psoriasis is a polygenic and multifactorial papulosquamous disease, which is estimated to affect approximately 1%–3% of the population.[1,12] The epidemiological data on pediatric psoriasis are limited. The prevalence of pediatric psoriasis has been reported in a range of 0.7% to 3.8% in different studies, and several studies have reported a mild female dominance.[5,7,10,13-16] Similarly, our cohort also showed a mild female dominance (female/male: 1.11/1).

The etiopathogenesis of psoriasis is not fully known; however, evidence on the etiopathogenetic role of genetic factors has recently strengthened. The relevant literature has reported different rates of family history in psoriasis, varying from 4.5% to 89%.[6,7,9,10] Our study revealed a lower rate of family history than the majority of the reported rates in previous studies. Kumar et al.[6] found the rate of family history as 4.5% and suggested that this low rate is related to the single center-limited design of their study. The low rate of family history in our multicenter series may indicate that the role of environmental factors in the etiopathogenesis of pediatric psoriasis is stronger than known. Contrarily, the low rate of family history in our series may be associated with the ignorance of family members concerning the presence of the disease. Additionally, the actual absence of the disease in family members at the time of diagnosis may have subsequently occurred.[17] Environmental factors, including smoking, alcohol, emotional stress, climate, trauma, medicines, and infections, have played roles in the pathogenesis of psoriasis and are considered triggering factors for its emergence.[18-20] Triggering factors play a more prominent role in pediatric cases compared to those of adults.[5,6,14,17,18,20] Studies have suggested that 30%–40% of cases are linked with emotional stress.[19] Our study revealed that 60% of patients had emotional stress, whereas a history of physical trauma, infection, and medication was present in 14%, 9.33%, and 1.67% of patients, respectively. Psoriasis affects the social and personal lives of patients, reduces the quality of life, and causes anxiety. Myths that psoriasis is a contagious disease stigmatize and exclude patients from social lives and schools.[21] The high incidence of emotional stress that is observed in our series may be associated with these factors. Contrarily, our study results may support the role of the brain-skin axis in the pathogenesis of psoriasis.

Pediatric psoriasis may present with various clinical types, such as plaque, guttate, pustular, erythrodermic, inverse, palmoplantar plaque, palmoplantar pustular, and sebopsoriasis. These clinical types may show different

Table 1. Demographic and clinical features of childhood psoriasis patients

	Number of patients (n=150)	Percentage (%)
Female	79	52.70
Male	71	47.30
Age (mean ± SD, min-max)	13.71±4.2 (1–18)	
Weight (mean ± SD, min-max)	47.44±17.98 (9–90)	
Height (mean ± SD, min-max)	1.5±0.19 (0.88–1.83)	
BMI† (mean ± SD, min-max)	20.06±4.17 (5.91–33.46)	
Family history positivity	20	13.33
Clinical types (n)	Plaque (125) Guttate (10) Palmoplantar (7) Inverse (6) Pustular (2)	83.33 6.67 4.67 4 1.33
Localization (n)	Trunk (69) Scalp (42) Hand (20) Face (19)	46 28 13.33 12.67
Disease duration (mean ± SD, min-max)	3.65±3.84 (1–34)	
Nail involvement (n)	Pitting (16) Subungual hyperkeratosis (5) Leukonychia (5) Onycholysis (2) Oil spot (1) Discoloration (1)	10.66 3.33 3.33 1.33 0.67 0.67
Joint involvement	15	10
Accompanying diseases (n)	Aortic stenosis (1) Diabetes Mellitus (1) FMF‡ (1) CRF§ (1) HSP¶ (1) Cirrhosis (1) Hypothyroidism (1)	0.67 0.67 0.67 0.67 0.67 0.67 0.67
Triggering Factors (n)	Stress (90) Trauma (21) Infection (14) Medicine (1)	60.00 14.00 9.33 1.67
Last treatment (n)	Topical therapy (101) Phototherapy (23) Acitretin (16) Methotrexate (9) Cyclosporine (1)	67.33 15.33 10.67 6 0.67
Duration of last treatment (mean ± SD, min-max)	4.67 ± 5.24 (1–19)	
PASI Score# (mean ± SD, min-max)	1.85 ± 2.29 (0–19)	

†Body mass index; ‡Familial Mediterranean fever; §Chronic renal failure; ¶Henoch Schoenlein purpura; #Psoriasis area severity index; SD, standard deviation; min, minimum; max, maximum; n, number.

prevalence in different ethnic groups. Epidemiological studies have shown that the most common type of psoriasis in childhood is plaque type, as it is in adults.[22] A series of pediatric psoriasis (n=277) reported by Fan et al.[7] revealed that the most common type was plaque psoriasis (68.6%) followed by guttate (28.9%), arthropathic psoriasis (2.9%), erythrodermic (1.4%), and pustular psoriasis (1.1%). Another study by Moustou et al.[8] revealed that 82.1% of 842 children had plaque-type psoriasis, whereas 20.2% and 7.5% had inverse and guttate psoriasis, respectively. Another study that involved 280 patients with pediatric psoriasis revealed that 68% had plaque type, whereas 12.5% and 11% had guttate and palmoplantar types, respectively.[23] Our study revealed that the most common type of psoriasis was plaque type (n=125, 83.33%), followed by guttate (n=10, 6.67 %), palmoplantar (n=7, 4.67 %), inverse (n=6, 4 %), and pustular (n=2, 1.33%) psoriasis. Erythrodermic psoriasis and arthropathic psoriasis are rare in childhood.[24-26] In our series, psoriatic arthritis was accompanied by other clinical types in 10% of patients, whereas none had erythrodermic psoriasis.

A series of 207 cases that compared the clinical characteristics of European and Asian children with psoriasis revealed that the scalp was the most common location.[27] However, Fan et al.[7] reported that the most common locations were leg extensors, arms, and scalp, whereas Kwon et al.[16] found that the most common area of involvement was the trunk. In our series, the lesions were mostly located in the trunk (n=69, 46 %) followed by the scalp (n=42, 28%), hand (n=20, 13.33 %), and face (n=19, 12.67 %).

Nail involvement can be observed in 7%–40% of patients with pediatric psoriasis.[5,18] Relevant literature reported that the most commonly reported nail finding is pitting. Subungual hyperkeratosis, onycholysis, oil spot, and longitudinal streaking are also relatively common.[7,18,25,26] In our series, 10.66% of patients had nail pitting, whereas other findings included subungual hyperkeratosis, leukonychia, onycholysis, oil spot, and discoloration.

Recent studies showed that psoriasis is a chronic systemic inflammatory disease rather than a skin-limited condition.[28] Patients with psoriasis, compared to the healthy population, have a higher incidence of hyperlipidemia, obesity, hypertension, diabetes mellitus, ischemic heart disease, rheumatoid arthritis, Crohn's disease, and ulcerative colitis.[19,29] Our series revealed that seven patients had accompanying disorders including aortic stenosis (n=1), diabetes mellitus (n=1), Familial Mediterranean Fever (n=1), chronic renal failure (n=1), Henoch Schoenlein purpura (n=1), liver cirrhosis (n=1), and hypothyroidism. The low number of patients with comorbidities in our series makes it difficult to understand the causal relationship between these comorbidities and psoriasis.

No standardized evidence-based treatment protocols are available for pediatric psoriasis, mainly due to the paucity of randomized and controlled studies. However, the vast majority of studies consider topical agents as the first step in mild to moderate psoriasis.[18,24,29] Phototherapy, particularly narrowband UV-B, maybe the first option for patients who are unresponsive to topical therapies and those with moderate to severe psoriasis.[29,30] The adverse effects profile and the lack of large-scale studies that are focused on childhood psoriasis limit the use of systemic drugs. Our series revealed that the last treatments received included topical treatment (n=101, 67.33%), phototherapy (n=23, 15.33%), acitretin (n=16, 10.67%), methotrexate (n=9, 6%), and cyclosporine (n=1, 0.67%). The main limitations of our study include its retrospective nature and the relatively small number of included patients, which could have biased statistical analyses.

To sum up, our series showed similar results regarding the clinical types and treatments used for childhood psoriasis (Table 2). However, comparing the previous studies, the rate of family history was found to be lower, whereas the frequency of emotional stress was higher. We believe that addressing the psychological impact of psoriasis along with its physical aspects may provide better treatment outcomes.

Main Points

- In a multicenter series, we tried to evaluate the clinical, demographic, and treatment features of childhood psoriasis.
- A total of 150 patients from four different centers were enrolled in the study.
- This cohort is the largest recently conducted the study in our country.
- In our cohort, the clinical types and treatments used for childhood psoriasis were similar to those of other studies, but the rate of family history was lower, whereas the incidence of emotional stress was higher. Addressing the psychological impacts of psoriasis along with its physical aspects may provide better treatment outcomes.

Table 2. Comparisons between epidemiological studies on childhood psoriasis

Study	Country	n	Male:Female ratio	Family history (%)	Type (%)	Nail involvement (%)
Current study	Turkey	150	0.89:1	13.33	Plaque 83.3 Guttate 6.67 Palmoplantar 4.67 Invers 4 Pustular 1.33	20
Tovar-Garza, et al.[21] (2017)	Mexico	280	1:1.5	5.0	Plaque 68.0 Guttate 12.5 Palmoplantar 11.0	5.0
Moustou, et al.[8] (2014)	Greece	842	1:1	16.7	Plaque 82.1 Inverse 20.2 Guttate 7.5	11.8
Fan, et al.[7] (2007)	China	277	1:1.13	34.3	Plaque 68.6 Guttate 28.9 Erythroderma 1.4	5.6
Seyhan, et al.[10] (2006)	Turkey	61	1:1.6	23.0	Plaque 83.6 Erythroderma 16.9	21.3
Kumar, et al.[6] (2004)	India	419	1:0.9	4.5	Plaque 60.6 Plantar 12.8 Guttate 9.7	31.0
Morris, et al.[5] (2001)	Australia	1,262	1:1.14	71.0	Plaque 34.0 Inverse 21.6 Guttate 6.4	-
Nanda, et al.[2] (1990)	India	112	1:0.9	9.8	Plaque 69.6 Guttate 25.9 Erythroderma 1.8	39.3

n, Number.

ETHICS

Ethics Committee Approval: All the procedures followed the Helsinki declaration, and the study was approved by the Clinical Research Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine (decision date and number: 2020-09/78).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: Ö.F.E., Design: A.K., Supervision: K.Ö., Ü.E., Data Collection and/or Processing: K.Ö., M.S.M., Analysis and/or Interpretation: A.D., Literature Review: Ö.F.E., Writing: A.D., Critical Review: M.A., T.L.

DISCLOSURES

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Conflict of Interest: The authors declared no conflict of interest.

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RESEARCH ARTICLE

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The Level of Knowledge About Human Papillomavirus and Attitude Towards Vaccination Among Young Women in Turkey

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Abstract

BACKGROUND/AIMS: Human papillomavirus (HPV) is a virus that may cause cancer, and it is important to protect against HPV. This study was carried out to determine the young women's knowledge and attitudes toward the HPV and HPV vaccine.

MATERIALS and METHODS: This descriptive and cross-sectional study was completed with 533 young women in Turkey. A questionnaire form consisting of a total of 26 questions investigating the socio-demographic characteristics of the students and their knowledge and attitudes toward the HPV and HPV vaccine used. Data were analyzed using the Statistical Package for the Social Sciences for Windows SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS: While 57% of the participants stated that they knew what HPV is, 66% stated that they learned this information during the course. While 54% of the participants stated that they knew the routes of HPV transmission, 98% stated that HPV is sexually transmitted, and 59% stated that HPV is transmitted through the blood. In the study, half of the participants heard of the HPV vaccine. However, there was no participant who received the HPV vaccine among them. A significant difference was determined between having knowledge of HPV and knowing the routes of HPV transmission, having heard of the HPV vaccine, intention to receive the HPV vaccine, intention to receive the HPV vaccine if it is freely available, and intention to receive the HPV vaccine if it is recommended by the doctor ($p<0.05$).

CONCLUSION: This study revealed the need for education due to the lack of knowledge about the HPV and its' vaccine.

Keywords: HPV; student health; cervical cancer; young women

INTRODUCTION

Human papillomavirus (HPV) is a double-stranded, non-enveloped DNA virus from the parvovirus family.[1] This virus causes benign proliferations, such as warts, epithelial cysts, hyperkeratosis, anogenital, oropharyngeal and laryngeal papilloma, or invasive malignancies.[2] Furthermore, its association with the cervical cancer has been precisely determined.[1] It is known that there are >200 defined types of HPV.[1-3] It is known that HPV types such as 6–11 that are known to be low-risk cause genital warts while the *HPV* types such as 16–18 that are known to be high-risk cause cervical or other anogenital cancers.[1-3]

Human papillomavirus affects 30%–50% of sexually active young women and is among the most common sexually transmitted infections worldwide.[4,5] This leads to a significant public health problems.[5] It is estimated that approximately 290 million women worldwide are infected with the HPV.[6] In the analyses performed

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by the International Agency for Research on Cancer-IARC, HPV has been determined to be responsible for 5%–10% of female cancers. According to the Turkish Cancer Research data for 2015, cervical cancer is among the top 10 most common types of cancer in women.[7]

Attention is paid to the importance of protection before transmission with the HPV to avoid the human papillomavirus outbreak.[8] The protection strategies against HPV primarily include the elimination of the risk factors and prophylactic vaccination. In addition to the protection measures against HPV to reduce the mortality and morbidity associated with the HPV infection, attention is paid to the spread of screening programs and early treatment.[9-11]

The World Health Organization (WHO) recommends the HPV vaccine for girls in the 9–13 age group.[12] According to the American College of Obstetricians and Gynecologists, the vaccine provides protection close to 100%, when it is administered before the first sexual intercourse. The completion of the vaccine series is important before the sexual life begins to ensure the highest level of prophylactic efficacy against the cancer that may develop.[12,13] According to the International Federation of Gynecology and Obstetrics-FIGO, women aged between 9–26 years are recommended to receive the vaccine whether they are sexually active or not.[14] The WHO recommends the inclusion of the HPV vaccine in the national immunization protection program if vaccination strategy and financial support are appropriate for the country and the region. There are differences in terms of vaccination rates around the world.[10] The HPV vaccine is included in the national immunization programs of approximately of 45 countries, including Denmark, England, France, Germany, Sweden, and the United States.[15,16]

In our country, the Turkish Society of Gynecologic Oncology recommends the usage of HPV vaccine.[17] In Turkey, it is not yet included in the vaccine schedule.[13,17] Therate of vaccination against the HPV is observed to be very low despite the presence of HPV vaccines in Turkey. In the studies conducted, it was determined that the reasons for not receiving the vaccine were the lack of sufficient evidence for protection against cancer, expensiveness of the vaccine, and the fears of negative effects of the vaccine and infections.[8] According to a study carried out by Unutkan and Yangin[13], it is indicated that the fact that long-term efficacy and side effects of the vaccines have not been proven, and they are not included in the national immunization program in Turkey, affects the society's perspective on the vaccine despite of obtaining a new evidence on HPV vaccines every day.

In Turkey, there are studies published between 2010 and 2018 in which young women's levels of knowledge on HPV, its' vaccine, and their attitudes toward the vaccine were evaluated.[2, 8,13,18-20] In those studies, it was determined that the level of knowledge about the HPV was moderate (24.1%–55.7%) and the rate of the vaccination against HPV was very low (0.3%–1.9%) among young women in Turkey.[2,8,13,18-20] No study was conducted in Istanbul was found among those studies conducted in different provinces of Turkey.

This research was carried out as a descriptive study to determine the knowledge and attitudes of the young women, who are in a period during which primary protection could be achieved, regarding the HPV and HPV vaccine, and whether the rate of vaccination against the HPV varied among them. The results obtained are considered to contribute to an educational planning and political arrangements required for protection against the HPV.

MATERIALS AND METHODS

Research design

This is a descriptive and cross-sectional study.

Time of Data Collection

Data were collected between 18–30 June, 2018.

Study Samples

The study was carried out in female students studying in the midwifery, Physical Therapy and Rehabilitation, Healthcare Management, Social Services, and Gerontology departments at the Faculty of Health Sciences of a public university in İstanbul. All female students at the faculty (n=1,214) constituted the population of the study. Sample selection was not performed in the 1st, 2nd, 3rd, and 4th grades of all the departments of the faculty, and it was aimed to reach the entire population by a random sampling method. A total of 533 (44%) female students who agreed to participate in the study, were 18 years and older, were in the class on the day of conducting the questionnaire, and completed the questionnaires were included in the study.

Data Collection Tool Used in the Study

The questionnaire form was prepared by the researchers in accordance with the literature.[1-4,8,13,18-20] This form was submitted for an expert opinion assessment and necessary corrections were made. Then, a pilot study was conducted on 10 people to evaluate the questionnaire form. The form that was arranged because of the pilot study was finalized. A questionnaire form consisting of a total of 26 questions investigating the socio-demographic characteristics (16 questions) of the students and their knowledge (5 questions) about and attitude (5 questions) toward the HPV and HPV vaccine was used. Nine, fifteen and two of the answers to the questions in the questionnaire form were prepared as optional, yes/no, and open-ended, respectively.

The data were collected between 18–30 June, 2018 using the face-to-face interview method with the students in all grades of

the faculty departments. It took approximately 5–10 mins to fill in the questionnaire form. Students were briefly informed about the study.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean, number, and percentage in the data analysis. Comparisons were evaluated using the chi-square test.

Ethical Approval and Consent to Participate

Ethics committee approval was received for this study from İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval date: 25.06.2018, approval number: 2018-12-14). All procedures performed in the studies involving the human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable to the ethical standards. Informed consent was obtained from all the individual participants included in the study. All participants gave written consent to participate in the study. Filling in the questionnaire was anonymous.

RESULTS

A total of 533 (44%) students out of 1214 female students were included in the study. There was no student who received the HPV vaccine among the participants.

The mean age of the young women participating in the study was 20.37±1.50 (18–28 years), and it was determined that 39% of them were in the midwifery department, 35% were in the second grade, 92% were unemployed, 89% had health insurance, 56% had income equal to the expenses, 96% were single, and 6% graduated from a medical vocational high school (Table 1).

While 57% of the participants stated that they knew what HPV is, 66% of them stated that they learned this information during the course. While 54% of the students stated that they knew the routes of the HPV transmission, 98% stated that HPV is sexually transmitted, and 59% stated that HPV is transmitted through the blood, and 10% stated that HPV is transmitted through the skin contact, and 5% stated that HPV is transmitted through breathing. Of the students participating in the study, 78% reported that they did not consider themselves to be at risk of HPV (Table 2).

Of the participants, 50% heard of the HPV vaccine. While the rate of receiving information about the vaccine was 85%, only 48% of them stated that they intended to receive the vaccine. While 87% of the participants stated that they could receive the vaccine if it was recommended by the doctor, 68% of them stated that they could receive the vaccine if the HPV vaccine was freely available (Table 2).

A significant difference was determined between having the knowledge of HPV and knowing the routes of HPV transmission, considering herself to be at risk of HPV transmission, having heard of the HPV vaccine, intention to receive the HPV vaccine, and intention to receive the HPV vaccine if it is freely available, and recommended by the doctor ($p<0.05$) (Table 3).

DISCUSSION

Protection against the HPV, early diagnosis, and the treatment are of social importance in the prevention of cervical cancer which is the third most common cancer after the corpus and ovarian cancers in Turkey.[8,16] Informing the students about HPV and HPV vaccine is considered to be an important strategy for the prevention of HPV.[21] In this study, it was aimed to determine the young women's knowledge and attitudes toward the HPV and HPV vaccine.

State of Having Knowledge of HPV

A bit more than half of the students participating in this study stated that they had knowledge of HPV (Table 2). In other national

Table 1. Analysis results of the participants' socio-demographic characteristics (n=533)

		n	%
Department	Midwifery	209	39
	PTR	130	24
	Healthcare management	92	17
	Social services	67	13
	Gerontology	35	7
Grade	1st grade	162	30
	2nd grade	185	35
	3rd grade	160	30
	4th grade	26	5
Working status	Employed	45	8
	Unemployed	488	92
Health insurance	Yes	476	89
	No	57	11
Marital status	Married	5	1
	Single	512	96
	She has a sexual partner	16	3
Level of income	Income less than expense	150	28
	Income equal to expense	299	56
	Income higher than expense	84	16
School graduated	Medical vocational high school	30	6
	Other	503	94

PTR, Physical Therapy and Rehabilitation; n, Number.

Table 2. Knowledge about human papillomavirus and its vaccine (n=533)			
		n	%
Having knowledge of HPV	Yes	304	57
	No	229	43
Where did you hear about HPV*	Course subjects	199	66
	The internet	103	34
	Healthcare personnel	77	25
	Books	75	27
	Friends	41	14
	Media	40	13
Knowing the routes of HPV transmission	Yes	286	54
	No	247	46
Routes of HPV transmission*	Sexually	279	98
	Through blood	169	59
	Through skin contact	28	10
	Through breathing	5	2
Considering herself to be at risk of HPV	Yes	97	18
	No	413	78
	No idea	23	4
Having heard of the HPV vaccine	Yes	265	50
	No	268	50
Intention to receive information about the HPV vaccine	Yes	452	85
	No	81	15
Intention to receive the HPV vaccine	Yes	258	48
	No	246	46
	Undecided	29	5
Receiving the HPV vaccine if it is freely available	Yes	362	68
	No	156	29
	Undecided	15	3
Receiving the HPV vaccine if it is recommended by the doctor	Yes	464	87
	No	69	13

*More than one option was indicated among those knowing the routes of transmission.

HPV, Human papillomavirus; n, Number.

studies carried out with university students, it is observed that the rate of having the knowledge of HPV varies between 24.1% and 55.7%.[2,13,18,19] These results are like the results of our study. In some studies carried out abroad, similarly to the present study, it is observed that the level of having knowledge does not exceed 60%.[22-24] However, there are also overseas study results revealing the high levels of having the knowledge of HPV compared to this study.[21,25,26] It is obvious that the young women in this study need knowledge. The fact that these young individuals, who are the health care professionals of the future, have knowledge of HPV is important primarily in terms of their own health, and then the health of the community they will consult.

In this study, a bit more than half of the students stated that they knew the routes of HPV transmission (Table 2). In the study of Kavanagh et al.[23], it was observed that one-quarter of the participants knew the routes of HPV transmission. The fact that the rate of knowing the routes of HPV transmission was high in this study compared to the study of Kavanagh et al.[23] is since this study was carried out in a health-related faculty.

The participants of this study also stated that they mostly obtained information about the transmission during the courses (Table 2). The fact that the participants' main source of information was the courses is like the study result obtained by Shetty et al.[21]. This similarity is thought to be caused by the fact that the participants of both the studies were students. In the study conducted by Basnyat and Lim[27], the importance of the social and interpersonal networks in realizing HPV-related preventive health behavior was revealed. Therefore, it should not be ignored that the use of other means of communication, together with the courses, will be beneficial in increasing the level of knowledge among the young womens.

In this study, almost all the students who knew the routes of HPV transmission knew that it is sexually transmitted (Table 2). In the study carried out by Shetty et al.,[21] the knowledge that HPV is a sexually transmitted disease was on the first rank, which is like the result of this study. It is an expected result that those with knowledge of HPV also have a high level of awareness of transmission routes.

Three out of four students participating in our study reported that they did not consider themselves to be at a risk of HPV (Table 2). In the study of Leung and Law,[26] a bit more than half of the students stated that they thought they could be infected with HPV in the future. It is thought that this difference between the two studies was due to a high level of knowledge of HPV in the study carried out by Leung and Law.[26]

Situation Related to the HPV Vaccine

In this study, the fact that half of the participants heard of the HPV vaccine (Table 2) is like the study result obtained by Shetty et al.[21] In a study carried out by Yilmaz and Griffin[8] in Turkey, the number of students who heard of the HPV vaccine was found to be higher compared to this study. This difference is thought to be so since the participants of the study were only nursing students. In the studies carried out by Borlu et al.[20] and Durusoy et al.[18] in Turkey, it is also observed that the rate of having heard of the *HPV* vaccine is lower compared to this study. This difference is thought to be so since the studies also included university students apart from the health sciences students. In the studies carried out with the same age group abroad by Kasymova et al.[25] and Leung and Law[26], it was reported that the vast majority of the participants had knowledge of the HPV vaccine. The difference here is thought to be due to a high level of knowledge of HPV mentioned in the results of this study carried out abroad, and its inclusion in the national immunization schedule.

It was determined that more than three-quarters of the students intended to have a knowledge of the vaccine (Table 2). This situation suggests that information-seeking behavior increases as the awareness increases. In domestic[18,20] and international[26] studies carried out with the similar groups, the rate of asking for information about the vaccine was also found to be same like the result of this study. A high level of information-seeking behavior is thought to be so, since the study was carried out with individuals from a younger age group.

In this study, only half of the participants intended to receive the *HPV* vaccine (Table 2). In the studies carried out by Borlu et al.[20] and Durusoy et al.[18] with the university students in Turkey, it was observed that the ratio of those who intended to receive the HPV vaccine was far less compared to this study. The difference between this study and other studies is thought to be so since the other studies included non- health-related departments. In the study carried out by Shetty et al.[21] abroad, the rate of intention to receive the vaccine was higher compared to this study. Since there is a similarity between the two studies in terms of the age group and the education levels, this difference is thought to be due to a high level of knowledge of HPV in the study carried out by Shetty et al.[21] It is stated that the acceptability of the HPV vaccine is more possible when the people receive written educational information about the risks and benefits.[21]

It was observed that the rate of intention to receive the vaccine increased by one and a half when the vaccine is freely available (Table 2). In the study conducted by Kasymova et al.[25] in the United States, where HPV was included in the national immunization schedule, the ratio of those who received the vaccine was found to be higher compared to this study. In a study carried out by Basnyat and Lim[27] in Singapore, it was indicated that the confidence in the Government's health policies increased the rate of the confidence in the vaccine. This also suggests that it is important to receive the Government's support in the acceptance of the HPV vaccine.

In the present study, it was found out that the number of people who stated that they could receive the vaccine if it was recommended by the doctor increased by the two times (Table 2). It is known that health care providers play an essential role in the patient education regarding the benefits of the HPV vaccine and offering a strong recommendation.[21] Indeed, in the study by Kasymova et al.[25] in which the vaccination rate was found to be high, it was determined that three-quarters of those with the vaccination received the vaccine with the doctor's recommendation. In the studies by Basnyat and Lim[27] and Leung and Law[26], it was also indicated that the health care providers play an essential role in the vaccination decision. In the study carried out by Durusoy et al.[18], it was determined that being aware of the vaccine was an important determinant of a positive attitude toward the vaccination. This reveals that health care providers' recommendation and having knowledge of the vaccine are important factors in the increase of vaccination acceptance.

It was observed that those with the knowledge of HPV mostly intended to receive the HPV vaccine (Table 3). In the study by Zhuang et al.[28], the lack of knowledge was determined to be the biggest obstacle in receiving the HPV vaccine. In the study by Shetty et al.[21], it was determined that a more positive attitude toward

Table 3. Comparison of having knowledge of human papillomavirus and some parameters (n=533)

Having knowledge of human papillomavirus*					
		Yes	No	χ^2	p
Knowing the routes of HPV transmission**	Yes	247 (46%)	39 (7%)		
	No	57 (11%)	190 (36%)	219.881	**0.000**
Considering herself to be at risk of HPV transmission	Yes	75 (14%)	22 (4%)		
	No	221 (42%)	192 (36%)	23.028	**0.000**
	No idea	8 (1%)	15 (3%)		
Having heard of the HPV vaccine	Yes	221 (42%)	44 (8%)	149.449	**0.000**
	No	83 (15%)	185 (35%)		
Intention to receive the HPV vaccine	Yes	172 (32%)	86 (16%)		
	No	115 (21%)	131 (25%)	20.420	**0.000**
	Undecided	17 (3%)	12 (2%)		
Receiving the HPV vaccine if it is freely available	Yes	225 (42%)	137 (26%)	12.324	**0.002**
	No	73 (14%)	83 (15%)		
	Undecided	6 (1%)	9 (2%)		
Receiving the HPV vaccine if it is recommended by the doctor	Yes	274 (51%)	190 (36%)	5.945	**0.015**
	No	30 (6%)	39 (7%)		

*Knowing that HPV causes cancer, knowing the ways of prevention from HPV etc.

**Sexually, through blood etc.

p <0.05; HPV, Human papillomavirus; n, Number.

the vaccination was associated with the intention to receive the HPV vaccine. In the study carried out by Leung and Law[26], it was determined that those with the knowledge of HPV had positive attitudes toward the HPV vaccine. Devarayasamudram et al.[24] indicated that a structured curriculum would be effective in the increasing young women's knowledge about and attitudes toward HPV. Therefore, it is important to raise the awareness of HPV and its vaccine. Furthermore, information is an important variable in increasing the acceptability of the vaccine.

In this study, there was no one who received the vaccine. In the studies carried out with university students in Turkey, the vaccination rate was found to be three per thousand by Borlu et al.[20] and four per thousand by Durusoy et al.[18] It is an expected result that the vaccination rate is too low while the level of knowledge of HPV and HPV vaccine was so low[18,20] and the HPV vaccine is not included in the country's routine vaccination policy.[17] In the study carried out by Leung and Law[26] abroad with the female students in Hong Kong, it was observed that approximately half of the students were vaccinated. It is thought that such a high rate of vaccination was caused by discounting the HPV vaccine to female university students.[26]

CONCLUSION

Half of the students did not have knowledge of HPV. There was no one who received the vaccine among the participants. Most of the students intended to have a knowledge of the vaccine. Students' primary source of information is the courses.

When other studies on HPV and HPV vaccine carried out in Turkey were considered, in those studies, the level of knowledge about the HPV did not vary, there was no individual who received the vaccination against HPV, intention to receive the information about the vaccine did not vary among most young women, the rate of those who intended to receive the vaccine increased, and the rate of those who intended to receive the vaccine increased if the vaccine was freely available. It could be interpreted that young women's knowledge about the HPV was still moderate. However, there were positive attitude changes toward the HPV vaccine, even if they did not receive the vaccine.

This study reveals the need for education to increase the awareness of HPV and its vaccine. It is important that the Faculty of Health Sciences students, as health care providers in the future, have knowledge of HPV and its vaccine. To increase students' awareness, elective courses to raise awareness of the cancer could be added, brochures could be prepared, informative meetings could be held, and they could be provided with the opportunities to receive consultancy service in this regard.

Recommendations

It may be recommended to provide the education for increasing the levels of knowledge about the HPV and its vaccine and

arrange the curriculum, carry out studies including men, add the HPV vaccine to the national immunization schedule, include it in the current government policies, provide the flow of accurate information about the HPV through the social media.

Limitations of the Study

This study has limitations, such as the fact that it was a descriptive and cross-sectional study and was carried out in a single center and included only the female students. Our results cannot be generalized since the study was carried out in a single center. Since the HPV is a sexually transmitted infection, men's knowledge, and attitude toward the vaccination are also important. Men's knowledge and attitudes were not evaluated in this study.

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ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Date: 25.06.2018, number: 2018-12-14).

Informed Consent: All participants gave written consents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: T.Y., H.D., S.G., Ü.G.; Design: T.Y., H.D., S.G., Ü.G.; Data Collection and/or Processing: T.Y., H.D., S.G., Ü.G.; Analysis and/or Interpretation: T.Y., H.D., S.G., Ü.G.; Literature Review: T.Y., H.D., S.G., Ü.G.; Writing: T.Y., H.D., S.G., Ü.G.; Critical Review: T.Y.

DISCLOSURES

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RESEARCH ARTICLE

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The Effect of Breathing Exercise on Stress Hormones

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Abstract

BACKGROUND/AIMS: The aim is to determine the acute effects of breathing exercise on stress hormones in young women.

MATERIALS and METHODS: The study was conducted with the voluntary participation of 15 healthy young women who were working as coaches in the fitness and swimming branches. At the beginning of the study, the body compositions of the participants were determined, and 45-minute natural and connected breathing exercise was applied under the supervision of a breathing coach after having a standard breakfast. Cortisol and epinephrine hormone analyses from the serums was obtained from the blood samples taken before and after the breathing exercise were determined through a Chemiluminescence measurement method. Whether the data showed a normal distribution was analyzed through Kolmogorov-Smirnov test and paired t-test, since parametric test conditions were fulfilled. The relationship between the variables were determined with a Pearson correlation analysis.

RESULTS: At the end of an acute breathing exercise, a significant decrease was determined in the mean cortisol hormone levels of the participants ($p < 0.05$). A decrease was observed in the epinephrine hormone levels; however, this change was not found to be statistically significant ($p > 0.05$). In addition, it was determined that there was a positive and considerably weak insignificant relationship between the mean cortisol and epinephrine of the participants following the breathing exercise ($r=0.039$; $p > 0.05$).

CONCLUSION: It could be stated that natural and connected breathing exercise has a reducing effect on stress hormones, and accordingly, breathing exercises could be used as a relaxation technique.

Keywords: Breathing exercise; cortisol; epinephrine

INTRODUCTION

Life is the period between the first breath and the last one. While breathing is behavioral and respiration is reflexive; therefore, breathing and respiration are not the same phenomenon.[1] Breathing is based on the energy flow by moving downward/upward, expanding/narrowing of the chest and abdomen area in the physical body, and how this flow affects our bodies physically, mentally and spiritually.[2]

According to Greek mythology" PNEUMA," (i.e., breath, is our primary activity that accompanies us in every aspect of our lives and enables us to survive healthily for quality life).[3] Behavioral or voluntary control of breathing is located on the cerebral cortex. While voluntary breathing requires the amount of focus, attention is not necessary to maintain an automatic (metabolic) breathing.[4] While breathing regulates pH, electrolyte balance, blood flow, hemoglobin chemistry, and kidney function, it also has a significant effect on other behaviors such as motivation, strength, emotion, focus, perception, and memory role.[5]

Breathing techniques, which are expressed as pranayama applied in different variations in the form of conscious, intermittent, nasal, and abdominal breathing where upper, middle, and

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lower parts of the lung are used.[6] Breathing techniques are regularly applied for relaxation, stress management, control of psycho-physiological states, and to improve the organ functions.[7] Although there are many sources for stress, it also varies from individual to individual.[8] Psychological studies revealed breathing practice as an effective non-pharmacological intervention for emotional improvement including anxiety, depression, and stress.[9] In addition, breathing practices are also commonly applied in the clinical treatments for mental disorders such as post-traumatic stress disorder,[10] movement disorders,[11] phobias, and other stress-related emotional disorders.

Prana is particularly associated with an energy production processes in the body. There is a direct connection between the breathing energy and energy release from the body.[12] With a proper breathing, improvements could be experienced in energy centers of the body. The first energy center is located below the abdomen near the center of the gravity, and this center controls vital energy and certain hormones. The proper functioning of this center strengthens the immune system and increases the overall life energy.[13] Scientists have been reported that the daily energy needs could be met by taking the deep breaths for 15 mins. However, most people use energy potential in a limited way because they do not know use the power of breath that will enable them to achieve these benefits.[14] Studies report that slow and rapid breathing types have different physiological effects in the healthy subjects.[15]

Epinephrine and cortisol hormones known as stress hormones, are secreted by the adrenal glands. Epinephrine hormone alerts the body by being secreted in the dangerous situations such as exercise, lack of oxygen, excitement, fear, excessive heat decrease, anger, and sudden decrease in the blood sugar levels. The roles of epinephrine are to increase the blood pressure, heart rate and the blood circulation, depth of respiration, and blood glucose level. Cortisol hormone, which belongs to the glucocorticoid class, increases the blood glucose level by accelerating the synthesis of glucose from the protein and fat in the liver. It accelerates the burning of triglycerides and causes an increase in the concentration of free fatty acids in the blood, and it also has anti-inflammatory effects.[16]

Stress caused by the physiological or psychological conditions could be expressed as the sum of reactions of a person to the various mental and physical difficulties.[8] Nervousness, impatience, anger, hostility, anxiety, panic, restlessness, sadness, tension, poor memory, difficulty in taking the decisions, hypersensitivity, change in the sexual life, frequent daydreaming, frequent repetitions of death and suicidal thoughts, sleep disorders, depression, increase in the alcohol intake and substance use, decrease in the self-esteem and productivity are the psychological symptoms of the stress.[17]

Stress may have many psychological and physiological causes. The environment in which we live, our body and even our world of thoughts could be a trigger factor for stress. However, people physiologically tend to cope up with the stress and react to it. In this context, the cortisol hormone plays a very important role in a stress response. One of the important hormone response systems to stress is cortisol -hypothalamic-pituitary-adrenal (HPA) axis, especially the glucocorticoids.[18] Within this context, stressors stimulate cortisol secretion from the adrenal gland by affecting the hypothalamus. With the mixing of cortisol into the blood, a stress response occurs in the body.[19] Stressors have a huge impact on the mood, sense of well-being, behavior, and health. In the presence of a physical or psychological threat, cortisol levels fluctuate to provide the energy needed to cope up with the stress-inducing stimuli or escape danger.[20]

Stress in daily life could cause physical, emotional, behavioral, and psychological problems as well as chronic illness. Therefore, it is very important for individuals to learn how to live with stress, and to know how to manage the stress to minimize its negative effects. In the study, answers to the questions such as "what is the effect of breathing exercise on stress hormones," "Does the stress hormone level decrease with breathing exercise?" were sought. The limited number of studies in the literature conducted on how breathing exercises affect the stress hormone levels motivated us to carry out this study. This research aimed to determine the acute effects of breathing exercises applied to young women on epinephrine and cortisol hormones.

MATERIALS AND METHODS

Research Group

A total of 15 healthy and voluntary young women aged between 20–35 and working as coaches in the different branches in Konya province, Selçuklu Municipality Social Facilities participated in this research. Prior to the study, the subjects were informed about the study and their written informed consents to participate in the research were obtained. The questionnaire prepared by the researcher was applied to determine the demographic characteristics, physical activity levels, and general health conditions of the participants. For this study, approval was obtained from Selçuk University Faculty of Sports Sciences Non-Interventional Clinical Research Ethics Committee on December 20, 2018.

Inclusion criteria: Having no health problems that would prevent the participant from doing breathing exercises. Being in the age range of 20–35. Exclusion criteria: Having a systemic pathology. Using medication/drugs that may affect the hormone levels.

General Design of the Research

All measurements and breathing exercise were made on January 23, 2019 at the Selçuklu Municipality Gazalya Hatun Social Facility. Body composition measurements of the subjects were performed after a standard breakfast while the blood samples

were taken before and after the acute exercise under the equal conditions. To reveal the effect of an exercise on biochemical variables, subjects were warned not to perform heavy physical activities at least 48 hours before, and not to use any drug or liquid food that could affect the values.

Determination of Body Composition

The body weights (kg) of the subjects were measured with Tanita device and their heights (cm) were measured with a metal meter with 0.01 cm precision. Participants' body mass index (BMI) was calculated by dividing the body weight (kg) in the square of height (m).[21] Participants' fat mass, lean body mass, and fat percentage values were measured with BC-418 MA model Tanita device (1-14-2, Maeno-cho, İtabashi-ku, Tokyo, Japan) through the bio-electrical impedance analyzer technique.

Breathing Exercise

One week before the acute breathing exercise planned for the research, the participants were informed by a breathing coach who had received the training on natural and connected breathing, and a practice session was performed to apply the technique correctly. One week after this application, all the participants were subjected to a breathing session on the same day and at the same time. Breathing session was started after the participants were in the sitting position with their soles on the grounds, knees bent, and bodies back at a 45º angle. With the guidance of the coach, the participants were enabled to stay in a natural and connected breathing without a break in an uninterrupted and continuous way. The participants were enabled to breathe through the mouth for 45 mins by using the diaphragm and chest, respectively.

Biochemical Blood Analyses

All participants of the research were asked to have a light standard breakfast at least 2 hours before coming for the exercise. Blood samples were taken from the forearm elbow vein into the vacutainer blood collection tubes with a gel and anticoagulant (6 cc) by the health personnel at 08:00 a.m. before and after the breathing exercise. Blood samples were centrifuged at + 4ºC and 4,000 rpm for 10 mins and their serums were obtained, and they were frozen at -20 ºC until the analyses is being done. From the serum samples, cortisol and epinephrine hormone levels were determined with Chemiluminescence measurement method in Abbott Architect I2000 analyzer (Abbott Labs, Chicago, Illinois, USA) and epinephrine hormone levels were determined with the same method but in Shimadzu LC-20A HPLC device (Shimadzu Corp, Kyoto, Japan).

Figure 1. Breathing exercise.

Statistical Analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) packaged program was used in the analysis of the data. Arithmetic means and standard error mean of all the variables obtained in the study were calculated. Kolmogorov-Simirnov test was used to determine whether the data showed a normal distribution. As a result of the test, it was determined that the data showed a normal distribution and paired t-test was applied to reveal the differences between the measurements performed on the same group at two different times. The relationship between the variables was determined through Pearson correlation analysis and the results were evaluated at 95% confidence interval and p <0.05 significance level.

RESULTS

The mean age of the participants was found to be 29.06±4.26 years, height 163.66±3.81 cm, body weight 54.98±4.97 kg, fat percentage 24.20±4.23, and mean BMI 20.55±1.78 kg/m² (Table 1).

A significant decrease was observed in the mean cortisol hormone levels of the participants before and after the breathing exercise (p <0.05). When the responses of epinephrine hormone were examined, it was seen that there was a decrease in the hormone levels, but this decrease was not found to be statistically significant (p >0.05) (Table 2).

A positive and considerably weak insignificant relationship was determined between the mean cortisol and epinephrine of the participants following the breathing exercise (r=0.039; p >0.05).

Table 1. Results related to the participants' mean age, height, body weight, and body mass index

Variables	n	Min	Max	$\bar{X}$	SD
Age (year)	15	24.00	35.00	29.06	4.26
Height (cm)	15	159.00	171.00	163.66	3.81
Body weight (kg)	15	47.60	62.50	54.98	4.97
Fat (%)	15	16.70	31.20	24.20	4.23
BMI (kg/m²)	15	17.00	23.50	20.55	1.78

Min, Minimum; Max, Maksimum; SD, Standard deviation; n, Number.

Table 2. T-test result of the mean 1st and 2nd measurements of cortisol and epinephrine hormones of the participants

Variable	Test	n	Min	Max	$\bar{X}$	SD	t	*p*-value
Cortisol (µg/dL)	1	15	5.70	15.91	9.48	2.91	4.609	0.000*
	2	15	3.25	13.09	6.28	2.20		
Epinephrine (mg/dL)	1	15	11.06	179.30	115.79	53.43	0.524	0.608
	2	15	45.29	175.51	109.55	40.83		

*p <0.05; Min, Minimum; Max, Maksimum; SD, Standard deviation; n, Number.

DISCUSSION

The most important finding of this study conducted to determine the effects of the breathing exercises on some stress hormones, is that epinephrine and cortisol hormone levels decreased after an acute breathing exercise; however, while this change was significant in cortisol hormone, it was not found in epinephrine hormone. Moreover, there was a positive and highly weak insignificant relationship between the stress hormones.

The control mechanisms of the body are the nervous system and endocrine system. These two systems are responsible for the regulation of the body's physiological and psychological processes. Like the increase in the happiness hormone levels when feeling happy and stress hormone levels when feeling stressed and nervous, mood state may also change with the effect of hormones psychologically. Stress is accepted as a condition in which emotional and psychological components are no longer in harmony with the physical components of health. If this condition is perceived and evaluated by the brain as danger, stress reaction begins to function. Some subcortical areas are activated in the brain, and they try to regulate the normal function of the body. The first activated system is the hypothalamus, and it immediately begins to secrete hormones. The effects of stress are not only limited to psychological components; stress also changes the levels of various hormones.[22]

Cortisol hormone is a reliable indicator stress.[23] In addition, cortisol is a hormone that could involuntarily control some of the mental processes including metabolism, immunity, memory, and emotional evaluation, and is easily affected from the breathing excercises.[24] The second system is the secretion of epinephrine hormone from the adrenal medulla through the sympathetic nervous system. Both systems are useful in managing the temporary stress, protective and supportive in the tissues.[8]

Janakiramaiah et al.[25] interpreted that the plasma cortisol level remained stable after the first yoga breathing session applied to the dysthymic patients, and the breathing experience was not stressful. It is foreseen that sudarshan kriya yoga, which is a special series of respiration techniques, may relieve anxiety, depression, daily stress, post-traumatic stress, and stress-related medical diseases, and may be a useful, low-risk, and low-cost supplementary treatment for substance abuse and the rehabilitation of the criminals (26). Evidence obtained from the randomized controlled study shows that a seven-day intensive yoga program with pranayama, (i.e., breathing exercises), reduces anxiety and depression in patients with a chronic low back pain.[27] Like this study, Kharya et al.[28] concluded that controlled breathing exercises, including the Sudarshan Kriya and Prana-Yoga, positively changed stress coping with the behavior and initiated an appropriate balance in the cardiac autonomic tone.

Veerabhadrappa et al.[29] detected a significant decrease in the Beck Depression Inventory score after a two-week breathing exercise to determine the antidepressant efficiency and hormonal effects of the yogic breathing technique on alcohol addicts. As a result of this study, it was stated that this improvement in the psychological condition may have been caused by the significant decrease in the cortisol levels. In another study, it was reported that a breathing exercise of five minutes and 30 sessions per day could significantly reduce the anxiety in pregnant women who experienced preterm labor.[30] Salyers et al.[31] emphasized that a one-day breathing exercise relieved an emotional exhaustion, and depersonalization caused by occupational burnout. In a study conducted to determine the effects of the diaphragmatic respiration on exercise-induced oxidative stress and the potential role of the cortisol hormone in this stress condition, it was found that diaphragm breathing applied after an intensive training increased the antioxidant defense status, and this situation resulted from the decrease in the cortisol level.[32] Naik et al.[22] reported that there was a significant decrease in the resting heartbeat rate, systolic and diastolic blood pressure, and perceived stress conditions of 100 male volunteers who performed slow and deep breathing exercise for 30 minutes 5-times a week for 12 weeks, and it was effective in the improvement of the cardiovascular parameters.

It is emphasized that a rhythmic and controlled breathing type, which includes cyclic breathing where medium and short breath followed by a long breath, may play an important role in promoting the healthy lifestyle by improving the immune system, antioxidant condition, hormonal condition, and the brain function.[33] The mechanism through which breathing exercises are thought to reduce stress is a decrease in the serum cortisol levels as well as a direct decrease in the sympathetic

activity which enables the domination of a parasympathetic tone. Decreased cortisol levels are related with an increased sense of happiness, decreased anxiety, and an increased threshold for stress perception.[34]

When the above-mentioned studies are examined, it is observed that the studies examining the responses of the breathing exercises to stress hormones mostly include special yoga breathing sessions for psychological and therapeutic purposes.[15,25,27,28,30] In the present study, unlike the other studies, an acute effect of a breathing exercise performed by the healthy individuals on epinephrine and cortisol hormones was examined. Our study differs from other studies in this respect.

Limitations of the Study

This research has some limitations; all female participants included in this research were examined in terms of stress hormones because of only one breathing exercise; however, the effects of the age groups, gender, and different breathing exercises could not be examined. The absence of a control group is one of the limitations of this study, as there were not enough participants with the same conditions in the study, and therefore, it was not possible to compare the breathing exercise group with a control group. The pre-exercise values of the experimental group were accepted as the basic values by making a comparison within the group. In the new studies to be carried out, experiment and control groups could be formed and the difference between the groups may be evaluated. Furthermore, blood samples were taken as a single sample before and after the exercise at the morning hours. However, since the day and night rhythms of the hormones differ during the day, not taking samples at certain intervals may have been affected the results of the study.

CONCLUSION

Cortisol is secreted in a pulsatile manner. In humans, cortisol secretion has a circadian rhythm, and the cortisol concentration reaches its peak level during the morning hours.[35] Later, cortisol gradually declines in the body during the day until evening. Since our research aim was to determine the effect of an acute breathing exercise on the stress hormones, cortisol levels during the day could not be measured. This is one of the limitations of the research. Therefore, considering this limitation, the morning hour, which is stated to have a high cortisol secretion, was preferred to see the effect of the breathing exercise. The significant decrease in the cortisol levels after 45 mins of breathing exercise is thought to have stemmed from breathing exercise. As a matter of fact, cortisol is a hormone that is easily affected by breathing.[24] In other studies, indicating that breathing exercises reduces the cortisol levels, there have been references supporting our study results.[25,29,32,34]

As a result, it was determined that an acute breathing exercise decreased stress hormone levels. Considering the long-term effects of breathing exercise, it could be stated that it has healing effects in non-pharmacological areas in terms of balancing the emotions and managing stress.

Main Points

• Breathing is based on an energy flow that is much more than moving downward/upward, expanding/narrowing of the chest and abdomen area in the physical body and how this flow affects our bodies physically, mentally, and spiritually. As a vital function, respiration is not regulated by the certain hormones but is affected by a wide variety of hormones. Breathing techniques are regularly applied for relaxation, stress management, control of psycho-physiological states and to improve the organ function.

• The aim of this study is to determine the acute effects of breathing exercise on stress hormones in young women.

• It could be stated that natural and connected breathing exercise has a reducing effect on stress hormones, and accordingly, breathing exercises could be used as a relaxation technique.

ETHICS

Ethics Committee Approval: For this study, approval was obtained from Selçuk University Faculty of Sports Sciences Non-Interventional Clinical Researches Ethics Committee on 20.12.2018 with the decision number of 65.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Ö., S.K., Ş.A; Design: D.Ö., S.K., Ş.A.; Supervision: D.Ö., S.K.; Fundings: S.K.; Materials: D.Ö.; Data Collection and/or Processing: D.Ö.; Analysis and/or Interpretation: S.K.; Literature Search: D.Ö., S.K., Ş.A.; Writing: D.Ö., S.K., Ş.A.; Critical Review: Ş.A.

DISCLOSURES

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Conflict of Interest: The authors declare no conflict of interest.

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RESEARCH ARTICLE

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Results Muscle Strength and Thickness After Anterior Cruciate Ligament Reconstruction with Hamstring Tendon Autografts: An Ultrasonographic and Isokinetic Evaluation

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Abstract

BACKGROUND/AIMS: This study aimed to compare the muscle strength and thickness of individuals who underwent anterior cruciate ligament (ACL) reconstruction using a hamstring tendon graft for at least 12 months with uninvolved limbs and healthy controls.

MATERIALS and METHODS: This study included 25 individuals who underwent ACL reconstruction [age: 29.56±8.25 years; Body Mass Index (BMI): 27.27±3.89 kg/cm^2] and 25 healthy participants (age: 27.12±5.94 years; BMI: 24.70±3.03 kg/cm2). Muscle thicknesses of the vastus medialis oblique (VMO), rectus femoris (RF), biceps femoris (BF), and semitendinosus-semimembranosus (SS) muscles were evaluated by ultrasonographic measurement. Muscle strength measurements using an isokinetic system were performed.

RESULTS: VMO (p<0.001) and RF (p<0.001) muscle thickness were higher in the uninvolved limb than in the surgical limb. The concentric quadriceps muscle (p=0.029), eccentric quadriceps muscle (p=0.012), and eccentric hamstring muscle strengths (p=0.001) were significantly higher in uninvolved limb, which was similar concentric hamstring muscle strength (p>0.05). Muscle thickness and muscle strength of the control group and the surgical limbs were similar (p>0.05).

CONCLUSION: An average of 3 years has passed since the operation; however, VMO and RF muscle atrophy and decreased hamstring and quadriceps muscle strength continued. These results revealed that the use of the limb, which has not fully achieved its functionality, is limited, and individuals try to compensate for this situation by the uninvolved limb.

Keywords: Anterior cruciate ligament; muscle thickness; muscle strength; ultrasonographic measurement; isokinetic evaluation

INTRODUCTION

Injuries of the anterior cruciate ligament (ACL), which play an important role in joint stability,[1] are the most common knee injuries due to sports-related lower extremity injuries. These injuries can jeopardize athletic careers by reducing physical activity in athletes.[2] Following ACL injury, varying degrees of atrophy and strength are observed in the lower extremity

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muscles.[3] Therefore, the most important part of rehabilitation after ACL surgery is the restoration of the quadriceps and hamstring muscle strengths.[4] The quadriceps muscle has an important role in knee joint stabilization and the quadriceps muscle strength is associated with functional performance and development of osteoarthritis in the long term, thus the rehabilitation after ACL surgery should primarily focus on the treatment of this muscle.[5] Several treatment approaches have been developed to strengthen the quadriceps muscle after the ACL reconstruction; however, the literature has reported that muscle strength cannot be restored to pre-injury level.[6]

The hamstring muscle plays a synergistic role with the ACL.[7] The strength and neuromuscular function of the hamstring muscle group is important in ACL injury prevention. Therefore, the ACL must be preserved.[8] Hamstring activity relatively decreases quadriceps activation and leads to injury risk in the ACL.[8] Following surgery, the decreased strength in the hamstring muscles is due to neural inhibition that occurs in this area due to grafting of the hamstring muscle and changing mechanics in musculotendinous structures.[9] Therefore, in the postoperative period, the thigh muscles should especially be evaluated in detail for atrophy.[10]

The literature has reported that atrophy of the quadriceps muscle may be present both in the early term and at the return-to-sport phase, which is considered to be postoperative 6 months after ACL reconstruction surgery.[11] Studies have investigated the effects of hamstring and quadriceps muscles after ACL reconstruction; however, the results of hamstring muscles, in particular, are controversial.[12-14] Additionally, many studies compared the surgical limb with the uninvolved limbs. However, deficits in muscle strength are also seen in the knee after surgery, and this condition is attributed to cross-over inhibition or insufficient fitness.[15,16] This shows that comparing the muscle strength on the surgical limb with the uninvolved limb does not yield accurate results.[16] Therefore, studies must conduct comparisons with a healthy control group to achieve more accurate results. Based on this information, this study aimed to examine the quadriceps and hamstring muscle thickness and strength of participants who underwent ACL reconstruction surgery at least 12 months ago via ultrasonography and isokinetic system and compare the results with that of healthy participants.

MATERIALS and METHODS

Participants

This study evaluated 77 patients who underwent ACL reconstruction surgery using hamstring tendon grafts between 2013 and 2016 for eligibility criteria. Inclusion criteria are ACL surgery, ages 18–45 years, unilateral ACL reconstruction surgery with a hamstring tendon autograft at least 12 months before the study initiation, and no injuries for at least 12 months in both lower limbs. Patients with accompanying posterior cruciate ligament, lateral collateral ligament, or medial collateral ligament and meniscus injury in the same knee, biopsy, tibial plate fracture, joint movement range restriction, quadriceps or patellar tendon graft, cartilage injury, previous surgery on the lower limbs, and accompanying systemic or neurological problems were excluded from the study. This study included 25 patients.

The control group evaluated 28 healthy individuals aged 18–45 years who did not have any knee injury or surgery in the last 12 months, were not diagnosed with a disease, and who voluntarily agreed to participate in the study. Individuals in the control group were selected from those with similar age, gender, and physical activity level to those who underwent ACL reconstruction. An International Physical Activity Questionnaire short form was used to determine the level of physical activity.[17,18] The study included 25 healthy participants. The flowchart of the individuals is shown in Figure 1.

Before initiating the study, all participants were informed about the study, and written consent with their agreement to participate in the study was obtained. Ethics committee permission was obtained from the ethics committee of the university with the decision dated 06.13.2016 and numbered 326.

Procedure

The age, height, body weight, and dominant limb were recorded for all participants. Additionally, the limbs with ACL injuries, the dates of ACL injury and surgery, pre-existing musculoskeletal injuries, post-surgical treatment, and duration of treatment were also evaluated.

Before the assessments for the study, individuals were given a 5-min warm-up of 5 minutes of walking on the treadmill at self-selected speeds.

Tests were performed starting from the uninvolved limb in individuals who underwent ACL surgery and from the dominant limb in the control group.[19,20] The dominant limb was determined by evaluating the limb the individuals used in kicking a ball or jumping.

Ultrasonographic muscle thickness measurements were performed with B-mode ultrasonography using the 7.5–12 MHz linear probe (LOGIQ 7 Pro; GE Yokogawa Medical System, Tokyo, Japan). The Vastus medialis oblique (VMO) and rectus femoris (RF) muscle thicknesses were measured in the supine position. For the VMO muscle thickness measurement, the probe was placed 4 cm proximal and 3 cm medial to the superomedial border of the patella, parallel to the muscle fibers, in the oblique-sagittal plane.[21] For the RF muscle thickness measurements, the distance between the superior border of the patella and Spina iliaca anterior superior were measured and marked, and the probe was placed at the midpoint.[22,23]

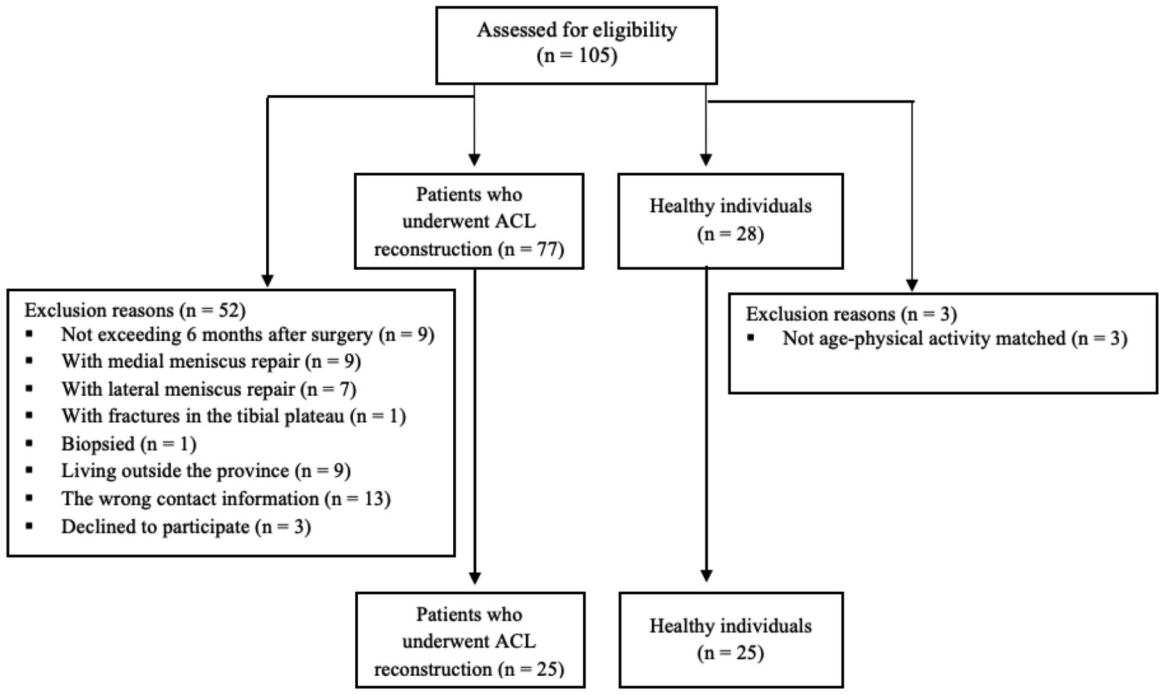

Figure 1. The follow diagram of patients who underwent ACL reconstruction and healthy individuals in the study

Muscle thickness measurements of the biceps femoris (BF) and semitendinosus-semimembranosus (SS) muscles were performed in the prone position. For the BF muscle thickness measurement, the midpoint of the distance between the lateral condyle of the femur and the ischial tuberosity were determined and the midpoint of the distance between the medial condyle of the femur and the ischial tuberosity were used to measure the SS muscle thickness.[22] The water-soluble permeable gel was used to provide acoustic contact between the probe and the skin. The obtained ultrasonographic images determined the muscle-subcutaneous fat interface and muscle-bone interface. The distance between the interfaces was used to measure the muscle thicknesses of VMO, RF, BF and SS.

Muscle strength measurements were performed in a sitting position using the isokinetic system (Cybex NORM®, Humac, CA, USA). Individuals were fixed with a strap from the shoulders, waist, and thighs to prevent compensatory movements during the test. For the ankle, the strap was placed 3 cm proximal to the malleolus.[19,20] Simultaneously, both verbal and visual feedback was given during the tests for individuals to achieve maximum effort.[19] Concentric strength evaluation of the quadriceps femoris and hamstring muscles was performed in the knee flexion ranging 0–90 degrees at 60º/s velocity. The tests were initiated from 90 degrees of knee flexion. Before the test, three submaximal warm-up repetitions were performed. After 1 minute of rest, five maximal test repetitions were performed.[24] The eccentric muscle test was performed with five repetitions at a speed of 60º/s in the knee flexion range 20–90 degrees. After two attempts, a 1-minute rest period was given. The test of the quadriceps femoris muscle was initiated at 20 degrees of knee flexion, whereas the hamstring muscle was initiated at 90 degrees knee flexion position.[25] During all tests in the isokinetic system, peak torque/body weight values were obtained for hamstring and quadriceps muscles from both limbs.

Statistical Analysis

Statistical analyses were conducted using the statistical package for social sciences version 22.0 (SPSS INC, Chicago, IL, USA) software. The normal distribution of variables was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov test). For descriptive statistics, mean ± standard deviation or median and range of values, and interquartile range were calculated. The difference between the limbs of individuals who underwent ACL surgery and the control group was analyzed using the "Independent groups t-test" in cases of normal distribution and the "Mann-Whitney U test" in the absence of normal distribution. For the comparison between the limbs in the group that underwent ACL surgery, the "Paired t-test" was used for normally distributed variables. Without normal distribution, the "Wilcoxon test" was used. *P*-values below 0.05 were evaluated as statistically significant results.

RESULTS

The demographic characteristics of participants were presented in Table 1. A mean of 34.08±14.97 months had passed since

Table 1. Demographic characteristics of participants

		ACL groups (n=25, mean ± SD)	Control groups (n=25, mean ± SD)	*p*-value
Age (years)		29.56±8.25	27.12±5.94	0.502
Body weight (kg)		84.22±13.35	78.09±12.67	0.402
Height (cm)		175.64±8.04	177.48±7.31	0.102
BMI (kg/m²)		27.27±3.89	24.70±3.03	0.012*
Physical activity level (MET/min)		2,034.80±1,858.46	2036.48±1599.23	0.946
Sex, n (%)	Female	4 (16%)	5 (20%)	
	Male	21 (84%)	20 (80%)	
Dominant limb, n (%)	Right	18 (72%)	25 (100%)	
	Left	7 (28%)	0 (0%)	
Surgery limb, n (%)	Right	12 (48%)		
	Left	13 (52%)		

*Statistically significant association (p <0.05).
ACL, Anterior cruciate ligament; BMI, Body mass index; MET, Metabolic equivalent task; SD, Standard deviation; n, Number

the individuals underwent ACL surgery (12–60 months). Rehabilitation after surgery was received by 16 (64%) patients, whereas 9 (36%) did not. The mean duration of rehabilitation following the surgery was 8.12±3.89 weeks (2–16 weeks).

In the control group, data were compared obtained from the dominant and non-dominant limbs to determine the limb to be used for comparison, which revealed no difference between the two limbs (p>0.05). Therefore, the comparisons were performed by matching the limbs that underwent surgery with the same side limb of the control group.

The comparison of VMO, RF, BF and SS muscle thickness of the surgical limb and the uninvolved limb of the individuals revealed that the muscle thickness of VMO (p <0.001, Table 2) and RF (p <0.001, Table 2) to be significantly greater in the uninvolved limb. However, the values of the BF and SS muscle thicknesses of the surgical and uninvolved limbs were similar (p >0.05). The comparison of the surgical limb and the matching limb of the control group revealed that the muscle thicknesses are similar both groups (p >0.05, Table 2).

The comparison of the two limbs of the group that underwent surgery revealed a significantly higher concentric quadriceps muscle (p=0.029, Table 2), eccentric quadriceps muscle (p=0.012, Table 2), and eccentric hamstring muscle strength (p=0.001, Table 2) in the uninvolved limb, which was similar to the concentric hamstring muscle strength (p >0.05, Table 2). The comparison of the surgical limb and the control group revealed similar muscle strength measurement results (p >0.05, Table 2).

DISCUSSION

The study results that examined individuals who underwent ACL reconstruction surgery at least 12 months ago revealed that atrophy of VMO and RF muscles and weakness in the hamstrings and quadriceps muscles continued even though an average of 3 years had passed since the surgery.

Volume changes occur in the affected muscles after the ACL reconstructive surgery.[26] The literature reported that in the postoperative period, after an ACL injury, decreases are observed in the activity and corresponding mechanical stimulation, which reduces the load on the surgical extremity. Arthrogenic muscle inhibition is associated with pain, inflammation, swelling, and damage to joint proprioceptors and leads to the atrophy of the quadriceps muscles.[27] Ten patients who underwent ACL reconstruction surgery using hamstring tendon grafts were evaluated 9–10 years after surgery with magnetic resonance imaging (MRI). Their MRIs revealed semitendinosus muscle atrophy and BF muscle hypertrophy.[28] These results suggest that the morphological changes due to ACL surgery occur not only in the grafted muscles but also in other peripheral muscles.[26] The quadriceps muscle mass was evaluated using MRI in the preoperative and postoperative periods in a study with 25 patients who had undergone ACL reconstruction surgery and revealed that the muscle mass decreased in the surgical limb at the preoperative assessment and the assessments performed in the fourth and twelfth postoperative weeks. Therefore, quadriceps atrophy was largely related to the quadriceps muscle weakness.[27] Another study conducted with 22 individuals who underwent surgery evaluated the quadriceps muscle mass using MRI and concluded that a lower cross-sectional area of the quadriceps muscle in the surgical limb. Therefore, muscle atrophy has been associated with the loss of muscle strength. Additionally, treatment approaches were emphasized to prevent muscle strength loss and atrophy after surgery.[29] The study performed by Williams et al.[13] examined the preoperative and

Table 2. The comparison of muscle thickness and muscle strength

		Surgical limb (mean ± SD)	Uninvolved limb (mean ± SD)	*p*-value Surgical vs. uninvolved limb	Control groups limb (mean ± SD)	*p*-value Surgical vs. controls limb
Cross-sectional area (cm)	VMO	2.44±0.54	2.72±0.53	0.000*	2.46±0.47	0.894
	RF	4.58±0.67	4.94±0.68	0.000*	4.64±0.75	0.535
	BF	4.69±0.52	4.87±0.63	0.121	4.54±0.58	0.312
	SS	5.64±0.60	5.81±0.56	0.092	5.76±0.73	0.510
Concentric strength PT/BW (N/kg)	Quadriceps	147.44±45.17	159.56±44.08	0.029*	173.96±58.48	0.079
	Hamstring	79.16±24.66	82.56±28.02	0.413	89.28±33.33	0.228
Eccentric strength PT/BW (N/kg)	Quadriceps	195.04±61.57	220.28±57.82	0.012*	205.44±67.62	0.572
	Hamstring	104.88±27.62	118.16±28.07	0.001*	110.92±30.77	0.469

*Statistically significant association (p <0.05).
VMO, Vastus medialis obliqus; RF, Rectus femoris; BF, Biceps femoris; SS, Semitendinosus-semimembranosus, PT/BW, Peak torque/body weight; SD, Standard deviation

postoperative (after the subject had returned to sports) MRI results of eight individuals who underwent ACL reconstruction surgery using hamstring tendon grafts and revealed a decreased volume of the semitendinosus muscle in the surgical limb, and BF and semimembranosus muscle hypertrophy was evident compared with the uninvolved limb. Results that were interpreted as atrophy might be ongoing as tendon regeneration processes and are incomplete.

The MRI results before surgery and at the third and twelfth postoperative months concluded that semitendinosus muscle atrophy continued after surgery in all nine patients who underwent ACL reconstruction surgery using a hamstring tendon graft compared with the uninvolved limbs. This study revealed that the loss of hamstring muscle strength continued in addition to the atrophy. Additionally, most study participants neither received enough physiotherapy nor participated in at-home exercise programs. The presence of atrophy has been interpreted with these concerns.[14] The gracilis and semitendinosus tendons that are preferred as autografts in ACL reconstruction procedures explain the semitendinosus muscle atrophy. However, a different study stated that the MRI results of 22 individuals who underwent ACL reconstruction surgery at least 5 months ago (range: 4–91 months), and 22 healthy controls showed no difference in the volume in their knee flexor muscles (SS and BF). Additionally, despite the neurologic dysfunction in the quadriceps muscle, no neurologic dysfunction was found in the hamstring muscles.[12]

Our study revealed similar BF and SS muscles thicknesses of the surgical limb and the uninvolved limb. The thicknesses of VMO and RF muscles on the uninvolved limb were higher than the surgical limb. This finding might be because the uninvolved limb is used more during the activities of daily living, and exercises and thereby are more activated. Given the similarity of the results with the uninvolved limb, because of the fear of re-injury, the use of the surgical limb may have been avoided leading to the overuse of the uninvolved limb, thus, causing an increased muscle strength of the uninvolved limb. Additionally, the individuals who received physiotherapy after ACL reconstruction were generally given bilateral strengthening training, causing an increased uninvolved limb muscle strength, thus the uninvolved limbs may be higher than their surgical limbs. The comparison of the surgical limb with the healthy controls revealed similar muscle thicknesses of all muscles.

After ACL surgery, muscle function decreases, and abnormal functional movement patterns occur that may persist for a long time.[30] Following knee surgery, permanent weakness may affect the quadriceps muscle, which is the basis for normal knee functions.[31] Thus, one of the first goals after ACL surgery is quadriceps muscle strength restoration.[32] The weakness of the hamstring muscles may lead to problems during the rehabilitation process and re-injury because they have a crucial role in protecting the ACL and must compensate for the loss of stability in the knee in the presence of an ACL injury.[33] The medial (SS) and lateral (BF) hamstring muscles contribute differently to knee stability.[8] The SS muscles are responsible for the internal rotation and varus stresses in the knee, whereas the BF is responsible for external rotation and valgus stresses.[8] The weakness of the hamstring muscles and the low co-activity regarding the quadriceps muscle also increase the risk of an ACL injury.[33] Therefore, strength measurements following ACL surgery and rehabilitation are important objective results.[34]

A study that evaluated individuals who underwent ACL reconstruction surgery using hamstring tendon grafts after six years revealed no strength deficits in the hamstring and quadriceps muscles according to the muscle strength

measurement results using the isokinetic system.[35] Another study in individuals who underwent ACL surgery and were evaluated after 51 months considered rehabilitation strategies as ineffective in quadriceps function improvement. However, their study participants were operated on by different surgeons and with different rehabilitation programs, therefore whether quadriceps weakness was caused by the rehabilitation programs or arthrogenic muscle inhibition was unclear.[20] Our study revealed that both the eccentric and concentric muscle strength of the quadriceps muscle and the eccentric muscle strength of the hamstring muscle was lower than those of the uninvolved limb in the comparison between the surgical and uninvolved limbs. Many studies have emphasized the relationship between the presence of muscle strength and atrophy. Our study results reflected the atrophies in the VMO and RF muscles in the strength results. The comparison of the surgical limb with the matching limb of the control group revealed similar muscle strength results.

CONCLUSION

Our study investigated the rates of rehabilitation and revealed that nine patients (36%) did not receive rehabilitation after surgery. The period of rehabilitation examination revealed the mean duration of rehabilitation as 8.12±3.89 weeks (range: 2–16 weeks). The ideal rehabilitation program should last approximately 6 months after an ACL repair, thus this period is insufficient. In our opinion, the treatment duration was very short for some patients, and these treatment periods were not long enough to eliminate the deficits that occurred after surgery. These differences related to the rehabilitation process may have led to different results. The atrophy and muscle strength losses may continue despite an average of 3 years after surgery because of insufficient rehabilitation periods.

The limitations of our study include the different rehabilitation programs in our study participants in the postoperative period. Additionally, ACL injuries are problems that are mostly seen in females; however, our low number of female cases might be another limitation. Moreover, we do not have preoperative measurement data of individuals who underwent ACL reconstruction.

This study revealed that after having ACL reconstructive surgery, participants returned to their daily lives or sports activities with muscular strength imbalances and morphological differences in VMO and RF muscles. Therefore, the use of the limb, which has not fully achieved its functionality, is limited and individuals try to compensate for this situation by over-using the uninvolved limb. An adequate and well-planned physiotherapy program after ACL surgery is required for lower limb functionality. Determining the current problems by evaluating the individuals in detail in the long term after surgery is important and rehabilitation programs should be developed to provide solutions to these problems.

Main Points

• Individuals who underwent ACL reconstruction had muscle strength imbalances and morphological changes in the VMO and RF muscles even with an average of three years since the surgery.

• The use of the limb, which has not fully achieved its functionality, is limited and individuals try to compensate for this situation by over-using the uninvolved limb.

• Determining the current problems by evaluating the individuals in detail in the long term after surgery is important and rehabilitation programs should be developed to provide solutions to these problems.

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ETHICS

Ethics Committee Approval: Ethics committee permission was obtained from the Ethics Committee of Gazi University with the decision dated 06.13.2016 and numbered 326.

Informed Consent: Before initiating the study, all participants were informed about the study, and written consent with their agreement to participate in the study was obtained

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: S.S.K.; Design: S.S.K., Supervision: N.G., N.K., M.B.A.; Data Collection and/or Processing: S.S.K., G.Ç., Z.G.; Analysis and/or Interpretation: S.S.K., N.G., G.Ç., N.K.; Writing: S.S.K.

DISCLOSURES

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Conflict of Interest: The authors declared no conflict of interest.

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RESEARCH ARTICLE

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Analysis of Knowledge, Beliefs, and Attitudes of Patients in the Emergency Service Toward Rational Drug Use

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Abstract

BACKGROUND/AIMS: Irrational drug use results in the inability to get the expected outcome from the treatment and inappropriate demands of patients stemming from overuse of drugs and drug addiction, and these factors lead to an increased number of applications to health institutions. This study aimed to identify the factors that affect the knowledge, beliefs, and attitudes of patients presenting to the emergency department in terms of rational drug use.

MATERIALS and METHODS: This is descriptive cross-sectional research that includes patients who applied for treatment to the emergency department of a state hospital in Turkey between 01.08.2019–31.12.2019. The study sample was composed of 262 patients who agreed to participate in the study. The study used the Rational Drug Use Scale (RDUS) and Drug Use Health Belief Scale (DUHBS) as data collection tools.

RESULTS: The mean scores of participants from RDUS (32.37±6.56) and DUHBS (144.37±19.68) were at a good level. A positive and significant relationship was found between RDUS and DUHBS mean score of patients (p <0.01). Knowledge of rational drug use differed according to age, gender, economic status, educational level, and reasons for applying to the emergency department variables (p <0.05), and health beliefs regarding drug use varied according to the gender variable (p <0.01).

CONCLUSION: Study results are significant since they revealed the factors that affect the patients' knowledge of rational drug use and their related health beliefs, as well as the relationship between these factors.

Keywords: Attitude; emergency department; health belief model; knowledge; rational drug use

INTRODUCTION

Emergency departments are special units where health services are provided every hour daily, and many patients with urgency are quickly evaluated and given medical services.[1] However, inappropriate use of the emergency department leads to an excessive number of patients and consequent serious problems in health service delivery.[2] Moreover, patients' improper emergency applications result in excessive examination and treatment use.[3] The use of emergency departments by patients without urgency is a universal health problem, and many reasons arise that emergency departments are preferred instead of primary healthcare services.[4,5] Health and disease-related behaviors are affected by a variety of factors, such as the habits of the society in which the individual lives, knowledge and health literacy level, health inequalities, mental capacity and social media.[6] Rational drug use, which has a great impact on outcomes, such as compliance with treatment and health costs, is an important aspect of the health management system.[7,8] Today, irrational drug use leads to inappropriate use of resources, thereby reducing drug access and causing many health, economic, social, and political problems.[9] Rational drug use ensures that individuals can easily obtain the suitable drug according to their clinical symptoms and individual characteristics in a suitable time and dosage at the most reasonable cost. However, many

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countries experience problems that are related to the overusage of drugs.[10]

Rational behavior is affected by correct and sufficient knowledge, as well as beliefs and attitudes. Health Belief Model (HBM) explains the attitudes and beliefs that affect and facilitate individuals' behaviors in their health and disease status.[11] According to the HBM, for the individual to acquire positive health behavior or quit negative health behavior, first of all, identifying the beliefs and attitudes that prevent the individual and the group from adopting that behavior is necessary.[12]

Irrational drug use results in negative outcomes, such as not receiving any benefits from the treatment, inappropriate patient demands caused by drug overusage, and drug addiction, and these factors cause several applications to health institutions to increase. Identifying the patients' knowledge and behaviors regarding rational drug uses, which is a multi-factor process, will guide the improvements in this field in the future.[13] This study aimed to identify the factors that affect rational drug use behavior by examining the knowledge, beliefs, and attitudes of patients who present to the emergency department of a state hospital in rational drug use. Thus, in line with the obtained findings, it was aimed to inform the patients and raise their awareness about rational drug use.

MATERIALS and METHOD

Study Design and Setting

The study has a descriptive and cross-sectional design, which aimed to analyze the knowledge, beliefs, and attitudes of the patients presenting to the emergency department regarding rational drug use.

Study Sample

The study population consisted of patients who applied for treatment to the emergency department of a state hospital in Turkey between 01.08.2019–31.12.2019. The study sample was composed of 262 who applied to the emergency department of the relevant hospital.

Sample Selection Criteria:

- 18 years of old and above
- literate
- voluntary participation
- received examination and healthcare services

This study aimed to address the following questions:

Q1: What are the demographic characteristics of patients who present to the emergency department?

Q2: What is the knowledge level of patients who present to the emergency department regarding rational drug use?

Q3: What are the health beliefs of patients who present to the emergency department regarding rational drug use?

Q4: What is the relationship between the demographic characteristics of patients who present to the emergency department and their knowledge level and health beliefs regarding rational drug use?

Q5: What is the relationship between the knowledge level of patients present to the emergency department regarding rational drug use and their health beliefs?

Data Collection

Data were collected from individuals who voluntarily participated in the research in the waiting room of the emergency service. Data collection periods were the available and preferred time of patients while waiting for the test results or after all their procedures in the emergency service ended. The data were collected in 15 min on average through the face-to-face interview method.

Data Collection Tools

In the collection of the data, "Identifying Information Form", "Rational Drug Use Scale" and "Drug Use Health Belief Scale" was employed.

Identifying Information Form

The identifying Information Form used in the data collection was developed by the researcher who reviewed the literature.[14,15] The form, which investigates the identifying information about the patients, includes 8 questions that determine demographic characteristics (age, gender, and marital status), socioeconomic characteristics (economic status and educational level), and information about diseases (chronic disease, drug use, and the reason for the emergency department visit).

Rational Drug Use Scale (RDUS)

The validity and reliability study of the RDUS, which assesses the knowledge level of rational drug use, was performed by Demirtaş et al.[14] in 2018. The scale consists of a total of 21 statements, of which 10 are correct and 11 are incorrect. Each statement is assessed with three options as "correct," "incorrect," and "don't know." The "correct" answer gets a score of 2, "do not know" as 1, and "incorrect" as 0. As the level of knowledge increases, the score obtained from the scale also increases. The scale, which is used in Turkey to determine the knowledge level regarding rational drug use, is a scale whose validity and reliability studies have been completed. The validity and reliability study conducted by Demirtaş et al.[14] revealed that Cronbach's alpha coefficient of the scale was 0.789. The present study revealed Cronbach's alpha

coefficient as 0.804. The obtained result revealed the reliability of the scale.

Drug Use Health Belief Scale (DUHBS)

The DUHBS structured following the HBM was developed by Çiçek[16] (2012) to evaluate the health belief perceptions regarding drug use. Consisting of 36 items, the scale has six subdimensions, which include Perceived Susceptibility, Perceived Severity, Health Motivation, Perceived Benefit, Perceived Barriers, and Self-Efficacy. Perceived Susceptibility (items 1 to 6) determines the risks perceived by individuals related to unconscious and unprescribed drug use. Perceived Severity (items 7 to 12) indicates how seriously harmful the outcomes that occur due to unconscious drug use are perceived in terms of physical health. Health Motivation (items 13 to 18) identifies internal/external resources and willingness that determine responsible drug use behavior. Perceived Benefit (items 19 to 22) demonstrates perceived benefits due to conscious drug use. Perceived Barriers (Items 23 to 28) determine the barriers perceived by individuals in conscious drug use. These items are considered negative, and scores are reversely calculated. High scores obtained from the subdimension of Perceived Barriers suggest that the individual evaluates the barriers related to rational drug use as reasonable. Self-Efficacy (items 29 to 36) encompasses the individual's self-belief, determination, and will in the realization of conscious drug use behavior.[15]

Each item is scored as 1–5 and is evaluated on a 5-Point Likert-type scale. The item scoring is as follows: Strongly disagree as 1, Disagree as 2, Neither Agree Nor Disagree as 3, Agree as 4, and Strongly Agree as 5 points. A higher score obtained on the scale indicates a higher level of health belief in terms of conscious and prescribed drug use. Cronbach's alpha coefficient of the scale developed by Erci and Çiçek[15] (2017) was 0.910. The Cronbach's alpha of the scale in the present study was 0.916. This result showed the reliability of the scale.

Ethical Considerations

Ethics Board of the hospital approval (decision no: 2019-9/9) and hospital permission were obtained for the study. Permission was also taken from the authors of the scale used in the study. Care was taken to observe ethical principles at all stages of the study.

Statistical Analysis

Data were analyzed through Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA) package program. The study calculated the scale scores, and The Skewness and Kurtosis coefficients were examined to determine the normally distributed scores. As the scores displayed normal distribution, parametric test techniques were used. T-test and analysis of variance (ANOVA) were used to analyze whether the scale score varied according to demographic characteristics. The t-test was used for the analysis of 2-group demographic variables, whereas ANOVA was employed for the analysis of variables with the k (k >2) group. Additionally, the relationship between the scale scores was analyzed with the Pearson correlation test.

RESULTS

Distribution of the Demographic Characteristic of Patients Who Presented to the Emergency Department

The evaluation of the distribution of participants according to demographic characteristics revealed that 32.8% (n=86) were between the ages of 13 and 31 years, 79.4% (n=208) were females, and 67.2% (n=176) were married. Of the patients, 35.9% (n=94) had primary school education, whereas 71% (n=186) had medium level of economic status. While 61.1% (n=160) of patients presented to the emergency department had no chronic diseases, 42.7% (n=112) were determined to use drugs regularly. The evaluation of the reasons for patients to present to the emergency department revealed that the highest percentage was related with pain due to digestive or urological problems with 40.5% (n=106), followed by respiratory system with 20.6% (n=54), and cardiovascular complaints with 13% (n=34), respectively (Table 1).

Findings Related to the Distribution of RDUS and DUHBS Item Mean Scores of Patients Who Presented to the Emergency Department

RDUS total mean score of patients who presented to the emergency department was 32.37±6.56 (Table 2).

DUHBS total mean score was 144.37±19.68. The evaluation of the subdimensions of the HBM revealed that the Self-Efficacy mean score was 29.79±5.27, Health Motivation was 25.45±4.91, Perceived Susceptibility was 25.10±5.10, Perceived Severity was 24.77±4.71, Perceived Barriers was 21.95±7.35, and Perceived Benefit was 17.29±3.04 (Table 2). Item mean scores of the scale subdimensions from the highest to the lowest were found as Perceived Benefit (4.32±0.76), Self-Efficacy (4.26±0.74), Health Motivation (4.24±0.81), Perceived Susceptibility (4.18±0.85), Perceived Severity (4.12±0.78), and Perceived Barriers (3.65±1.22), respectively (Table 2).

The Relationship Between the Individual Characteristics of Patients Who Presented to the Emergency Department and RDUS and DUHBS Total Mean Scores

Study results revealed no statistically significant difference between RDUS total mean scores and marital status, presence of chronic diseases, and drug use status of patients who presented to the emergency department (p >0.05). Contrarily, a statistically significant relationship was determined between RDUS total mean scores and the patients' age, gender, economic status, and reasons for presenting to the emergency department (p <0.05) (Table 3).

Table 1. Distribution of the demographic characteristics of the patients who presented to the emergency department (n=262)

Characteristics	Min-Max	Mean ± SD (median)
Age (years)	18–79	42.13±16.75
	n	%
Age groups		
18–31	86	32.8
32–45	66	25.2
46–59	62	23.7
60–79	48	18.3
Gender		
Female	208	79.4
Male	54	20.6
Marital status		
Married	176	67.2
Single	86	32.8
Economic status		
Good	50	19.1
Medium	186	71.0
Poor	26	9.9
Educational level		
Literate	24	9.2
Primary school	94	35.9
High school	92	35.1
University and above	52	19.8
Chronic disease		
Yes	102	38.9
No	160	61.1
Regular drug use		
Yes	112	42.7
No	150	57.3
Reasons for presenting to the emergency department		
1. Pain (GIS or urology)	106	40.5
2. Respiration	54	20.6
3. Cardiovascular	34	13.0
4. Psychiatric	26	9.9
5. Trauma	16	6.1
6. Allergy	12	4.6
7. Other*	14	5.3
Total	262	

*Other problems are neurological, eye, otolaryngology, and gynecological problems. Min, Minimum; Max, Maximum; SD, Standard deviation; GIS, Gastrointestinal system; n, Number.

Table 2. Distribution of RDUS and DUHBS item mean scores of the patients who presented to the emergency department (n=262)

Scale and subdimensions	Min	Max	Mean	SD	
RDUS (total score)	15.00	42.00	32.37	6.56	
Scale and subdimensions	Min	Max	Mean	SD	Item Mean Score
DUHBS (total score)	74.00	175.00	144.37	19.68	
Perceived susceptibility	6.00	30.00	25.10	5.10	4.18±0.85
Perceived severity	11.00	30.00	24.77	4.71	4.12±0.78
Health motivation	6.00	30.00	25.45	4.91	4.24±0.81
Perceived benefit	4.00	20.00	17.29	3.04	4.32±0.76
Perceived barriers	6.00	30.00	21.95	7.35	3.65±1.22
Self-efficacy	11.00	35.00	29.79	5.27	4.26±0.74

RDUS, Rational Drug Use Scale; DUHBS, Drug Use Health Belief Scale; Min, Minimum; Max, Maximum; SD, Standard deviation; n, Number.

No statistically significant difference was found between DUHBS total mean scores and the patients' age, marital status, educational level, presence of chronic disease, drug use, and reasons for presenting to the emergency department (p >0.05). A statistically significant relationship was identified between the patients' gender and DUHBS total mean scores (p <0.01). Health belief perceptions of females regarding drug use were found to be higher than those of males (Table 3).

The Relationship Between the Patients' RDUS Total Mean Scores and DUHBS Subdimensions Total Item Mean Scores

Study results revealed a positive and significant relationship between the patients' RDUS total mean scores and DUHBS total and Perceived Susceptibility, Health Motivation, and Perceived Barriers subdimensions item mean scores (p <0.01) (Table 4).

No significant relationship was determined between RDUS total mean scores and Perceived Severity, Perceived Benefit and Self-Efficacy subdimensions item mean scores (Table 4).

DISCUSSION

The evaluation of RDUS total mean scores of patients who presented to the emergency department revealed a good patients' level of knowledge regarding rational drug use (32.37±6.56). A study conducted by Aslan et al.[17] (2019) revealed that RDUS mean score at a medium level (24.19±5.16) Another study by Ekici et al.[18] (2019) found RDUS mean score of 29.75. This difference was thought to have stemmed from the hospital where the study was conducted, the region, and the patients' characteristics.

Table 3. Comparison of RDUS and DUHBS total mean score of the patients who presented to the emergency department (n=262)

		RDUS (total score)		DUHBS (total score)	
Characteristics	n	Mean ± SD	X^2/Z/p	Mean ± SD	X^2/Z/p
Age groups					
18–31	86	32.83±6.79		143.93±17.59	
32–45	66	34.33±5.18	4.270	142.12±20.65	2.375
46–59	62	30.90±6.90	0.006	149.87±19.26	0.071
60–79	48	30.75±6.74		141.16±21.52	
Gender					
Female	208	32.86±6.27	**2.398**	146.31±17.98	3.190
Male	54	30.48±7.36	**0.017**	136.88±23.95	0.002
Marital status					
Married	176	31.82±6.53	−1.930	144.38±20.27	0.014
Single	86	33.48±6.53	0.055	144.34±18.54	0.988
Economic status					
Good	50	34.32±5.73	3.693	141.04±21.66	0.889
Medium	186	31.68±6.88	0.026	145.11±18.80	0.412
Poor	26	33.53±4.79		145.46±21.98	
Educational level					
Literate	24	32.75±6.97		144.25±18.47	
Primary School	94	32.14±4.60	4.846	146.61±20.00	1.134
High School	92	30.93±7.35	0.003	144.39±20.55	0.336
University	52	35.15±7.19		140.34±17.88	
Chronic disease					
Yes	102	31.84±5.56	−1.045	144.47±21.70	0.063
No	160	32.71±7.12	0.297	144.31±18.36	0.950
Regular drug use					
Yes	112150	31.75±6.02	−1.331	146.76±21.11	1.707
No		32.84±6.92	0.184	142.58±18.42	0.089
Reason for presenting					
1.Pain (GIS/Urology)	106	32.20±5.94		146.60±17.81	
2.Respiration	54	30.96±7.31		139.88±20.98	
3.Cardiovascular	34	33.00±5.54		140.52±16.48	
4.Psychiatric	26	30.61±7.61	2.210	146.69±30.75	1.316
5.Trauma	16	34.50±8.26	0.043	146.75±17.01	0.250
6.Allergy	12	36.16±3.15		140.50±16.84	
7.Other	14	35.14±6.43		150.42±10.34	

Significant values are shown in bold.
RDUS, Rational Drug Use Scale; DUHBS, Drug Use Health Belief Scale; SD, Standard deviation; n, Number.

Our study results revealed a significant relationship between age, gender, economic status, educational level, and reasons for presenting to the emergency department, and rational drug use knowledge (p <0.05) (Table 3). Patients with the highest level of rational drug use knowledge in terms of age variable were participants between the ages of 32 and 45 years, whereas the lowest was in the 60–79 age group. As one gets older, his/her access to knowledge and understanding and utilizing knowledge decreases.[19] Therefore, rational drug use knowledge mean scores significantly differed in terms of age. The study revealed that the female participants' mean score related to rational drug use knowledge (32.86±6.27) was higher compared to males. Contrarily, other studies revealed no significant difference between the gender variable and rational drug use

Table 4. The relationship between RDUS and DUHBS item mean scores of patients who presented to the emergency department

Variable	RDUS (total score)	
	r	*p*-value
DUHBS (total score)	**0.249****	**0.000**
Perceived susceptibility	**0.260****	**0.000**
Perceived severity	−0.119	0.055
Health motivation	**0.262****	**0.000**
Perceived benefit	−0.004	0.950
Perceived barriers	**0.386****	**0.000**
Self-efficacy	0.004	0.954

***p* <0.01 RDUS, Rational Drug Use Scale; DUHBS, Drug Use Health Belief Scale; Significant values are shown in bold.

RDUS, Rational Drug Use Scale; DUHBS, Drug Use Health Belief Scale.

knowledge.[11-17] Pirinççi and Bozan[20] determined in their study that rational drug use behaviors of male nurses developed more than female nurses, contrary to our study results. Likewise, a study conducted by Kaya et al.[21] revealed that rational drug use behavior of male students developed more than female students. A study conducted by Beggi and Aşık[22] (2019) revealed that women were using their prescribed drugs more regularly, in parallel with our study findings. This difference in research results was thought to be caused by the difference in other demographic characteristics of male and female participants (age, educational level, profession, etc.). The evaluation of rational drug use knowledge according to economic status revealed that RDUS mean scores of participants in good economic condition statistically significantly differed. Therefore, as individual's income increases, their access to health-related knowledge will be easier and they will use this knowledge more easily. However, the study conducted by Aslan et al.[17] revealed no significant difference between the participants' economic status and their knowledge of rational drug use. The evaluation of the participants' knowledge levels of rational drug use concerning their educational level revealed that as their educational levels increased, their RDUS mean scores also increased. The study revealed that use of drugs knowledge of participants with a university degree was higher (35.15±7.19). The study conducted by Aslan et al.[23] revealed no significant difference between the participants' educational levels and their knowledge of rational drug use. Macit et al.[23] found a significant difference between educational levels and knowledge of rational drug use in their study in individuals' knowledge level of rational drug use. As individuals' educational levels increased, they could easily access health information and understand and make use of this information, thereby having higher levels of knowledge related to rational drug use. Within the scope of the study, participants' reasons for presenting to the emergency department were also evaluated, which revealed a significant relationship between their reasons for applying to the emergency department and their knowledge level of rational drug use (p <0.05). Additionally, RDUS mean scores (36.16±3.15) of patients who presented to the emergency department for allergic problems were higher. Macit et al.[23] (2019) reported that participants with food or drug allergy informed the doctor or health professional about their condition during the examination at quite high rates. Allergic complaints have a determining effect on the personal attitude and behavior of the patient toward his/her health/disorder in the long term. The high awareness levels of patients with an allergic history are suggested to affect their knowledge levels of rational drug use.

The DUHBS total mean score of the study participants was 144.37±19.68. DUHBS identifies individual perceptions, which are believed to affect the use of drugs. The study revealed that participants have a high level of health belief regarding rational drug use when the maximum obtained score was considered. The total mean score of health belief regarding drug use obtained in the study shows similarity to other conducted studies.[24,25] The evaluation of the subdimensions of DUHBS revealed that while the subdimensions of Perceived Benefit (4.32±0.76) and Self-Efficacy (4.26±0.74) had the highest item mean scores, Perceived Barriers (3.65±1.22) subdimension had the lowest item mean score. Perceived Benefit subdimension refers to the individuals' perception of the outcomes and benefits of conscious drug use. Individuals with a high level of Perceived Benefit know that conscious and prescribed drug use provides recovery, prevents complications, and protects his/her legal rights. Contrarily, Self-Efficacy is one of the effective factors on how an individual will think how s/he will behave and be motivated for taking action. Individuals with a high level of Self-Efficacy have high self-confidence and competence in realizing conscious drug use behavior.[16] Teke and Arslan[25] found high levels of Self-Efficacy in their study to determine the levels of Self-Efficacy and compliance with pharmaceutical treatment in individuals with hypertension. Similar to our study, Özer[24] determined that the Perceived Benefit and Self-Efficacy mean score in patients with chronic diseases was high, whereas the Perceived Barriers level was low.

Our study results revealed that the patients' perceptions of health belief regarding drug use (DUHBS) did not statistically significantly different in terms of their age, marital status, economic status, educational level, presence of chronic disease, drug use, and reasons for presenting to the emergency department (p >0.05). However, a significant relationship was identified between the patients' gender and their DUHBS mean scores (p <0.01). This result indicates that females had higher levels of health beliefs regarding drug use compared to those of males (Table 3). Therefore, beliefs, such as susceptibility, benefit, severity, and motivation, were more effective on the behavior of females regarding rational drug use than on males. A meta-analysis conducted by Abegaz and friends revealed that drug conformity of males was lower than that of females but

was not statistically significant.[26] Studies showed that the belief and conformity of females to the treatment are better than that of males.[27] A study conducted by Kahraman et al.[28] revealed no significant difference between the variables of gender and marital status and the attitude and belief development toward obesity. The study conducted by Nişancı Kılınç et al.[11] revealed that the patients' health beliefs significantly differed in terms of age variable, but no significant difference in terms of gender, educational level, and employment status. Gender significantly determines attitudes, behaviors, preferences, and tendencies. This situation significantly affects both the mental and physical attitude of females and males, as well as their perception of health/disease and their way of being exposed to the disease.[29] Our study results support these results.

No significant relationship was found between the patients' RDUS total mean score and item mean scores obtained from the subdimensions of Perceived Severity, Perceived Benefit, and Self-Efficacy in the health belief scale (Table 4). A study conducted by Nişancı Kılınç et al.[11] revealed no significant difference between the individuals' educational level and health belief perception. The reasons for realized/unrealized behaviors related to health cannot be explained by a single cause. Contrary to study results, it is believed that individual variables, such as educational level, have an impact on behavior.[30] A positive and significant relationship was found between the patients' RDUS and DUHBS total mean scores and Perceived Susceptibility, Health Motivation and Perceived Barriers subdimensions item mean scores (p <0.01) (Table 4). The results obtained showed a positive and significant relationship between the individuals' knowledge level of rational drug use and health beliefs for drug use. HBM explains why a recommended/unrecommended health behavior was displayed, refused, or postponed by an individual.[12] In the drug use health belief scale, individual perceptions, which are assumed to affect health behaviors, are revealed. The study revealed that as the knowledge level of rational drug use increased, health belief perceptions were positively affected. The knowledge level is effective on critical thinking, being responsible, and health-seeking behaviors. Therefore, as the knowledge level of rational drug use increased, susceptibility, motivation, and benefit related to the use of drugs outweighed barriers, and that Perceived Barriers increased. Perceived susceptibility, severity, benefit, and motivation reduce the effect of Perceived Barriers in the HBM, behavior develops.[30] This obtained result is significant as it reveals the relationship between susceptibility, health motivation, and Perceived Barriers, which are effective in the development of health behavior and increased knowledge level of rational drug use.

CONCLUSION

Non-rational drug use increases undesired adverse effects while decreasing the expected efficiency in the treatment. Inappropriate emergency applications of patients and excessive examination cause treatment usage and increased costs. When emergency services are not utilized according to their purpose, an excessive patient intensity was found in hospitals, and accordingly, quality is negatively affected. Therefore, the study was conducted with patients who visited the emergency service. Determining the rational drug use information, health beliefs, and affecting factors in the patient population who apply to the emergency service is important. Adopting rational drug use in increasing the quality of healthcare services, reducing costs, and especially, ensuring patient safety will also reduce inappropriate emergency applications.

This study revealed that the health beliefs of patients who presented to the emergency department in terms of rational drug use knowledge and use of drugs were at a high level. The knowledge of rational drug use differed according to age, gender, economic status, educational level, and reasons for presenting to the emergency department and their health beliefs differed according to the variable of gender. A positive relationship was found between health belief perceptions, which describe individual perceptions and are assumed to affect drug use behaviors and their knowledge of rational drug use.

Numerous factors affected health-seeking behavior. Therefore, our study results are important in terms of revealing the relationship between the knowledge of rational drugs and the factors affecting health beliefs related to drug use. Behavioral and psychological factors should be considered, beliefs should be identified, and accordingly, training and consultation should be provided to raise public awareness about rational drug use and increase public consciousness.

ETHICS

Ethics Committee Approval: Ethics Board decision (Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee decision no. 2019-9/9) and hospital permission were obtained for the study.

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

Peer-review: Externally peer-reviewed.

DISCLOSURES

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RESEARCH ARTICLE

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Could Theophylline Be First-Line Treatment for Post-Spinal Puncture Headache in Postpartum Mothers?

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Abstract

BACKGROUND/AIMS: Theophylline is a drug proven safe to use during the lactation period. This study retrospectively evaluates the efficacy of theophylline infusion administered under a standard protocol in the treatment of post-spinal puncture headache (PSPH) following a cesarean delivery, and discusses its role in the treatment measures in regard to its effects on the postpartum mother and infant.

MATERIALS and METHODS: A total of 33 patients who underwent a designated treatment algorithm at our Algology department were included in the study. Information on patient age, level of spinal block administration, and needle diameter were recorded from the patient records. Examination findings, analgesic drugs used before the hospital admission, onset of headache following a spinal block, time from the onset until theophylline administration, number of theophylline infusions, and Visual Analogue Scale (VAS) scores before and after the treatment were questioned in headache evaluation. Regarding drug safety, changes in the blood pressure and heart rate before and after the drug administration were evaluated.

RESULTS: Seventeen (51.5%) patients did not receive the additional drug treatment before our evaluation, and only received bed rest and fluid therapy. Mean standing VAS score was 6.1±1.8 before a theophylline infusion and 1.3±1.2 45 mins after the end of the infusion ($p < 0.05$). Infusion was administered once in 22 (66.7%) of the patients. Headache had resolved in all the 31 (93.9%) patients who arrived for an evaluation 24 and/or 48 hours after the theophylline administration.

CONCLUSION: Theophylline infusion provided a rapid and effective treatment of PSPH in postpartum mothers. Despite the limitations, we believe our study contains valuable findings that may be helpful in studies on planning a "PSPH treatment algorithm" for postpartum mothers.

Keywords: Post-spinal puncture headache; theophylline; postpartum; mother; infant

INTRODUCTION

Post-spinal puncture headache (PSPH) is one of the most common complications of spinal anesthesia. Pregnant women have several risk factors associated with the PSPH development due to the gender and age distribution.[1] While its incidence following a spinal anesthesia is reported between 3%–10%, this number may rise to 32% after a cesarean delivery.[1,2]

There are serious debates on the effectiveness of the bed rest and fluid therapy as conservative treatment options of PSPH. Among the drug options, only caffeine, theophylline, gabapentin, and hydrocortisone have been determined to be effective,[3] in which only caffeine and theophylline have been listed as safe, to use during the lactation period.[4] There are also studies indicating that theophylline infusion could be used for PSPH prophylaxis following a cesarean delivery.[5]

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Pain while standing up is one of the most prominent features of PSPH diagnosis, and the reason patients avoid mobilization. Prolonged immobilization in the postpartum period increases the maternal risk of deep vein thrombosis and pulmonary embolism. Pain and limited mobility reduce the mother's daily activity and delay in caring for her infant. There is currently no treatment algorithm for PSPH which takes these events under a consideration.

Our department practices a standard protocol consisting of theophylline infusion for PSPH treatment. In this study, we aim to conduct a retrospective analysis of the patients who were administered with theophylline infusion to treat PSPH after a cesarean delivery to evaluate efficacy of the drug and discuss the order of the treatment steps for a lactating mother in context to the literature.

MATERIALS AND METHODS

After obtaining ethics committee approval (date: 10.05.2018; decision: 2018/202), the follow-up and treatment files of 33 patients who underwent the treatment algorithm at our Algology department due to PSPH between 2009–2018 were examined. Since our study was retrospective, informed consent was not obtained. Information on patient age as well as additional diseases, spinal block injection level, and the needle diameter were recorded. Examination findings, analgesic drugs used before the hospital admission, onset of headache following a spinal block, time from onset until the theophylline infusion, number of theophylline applications, and Visual Analogue Scale (VAS) scores before and after the treatment were questioned in headache evaluation. Regarding the drug safety, changes in the blood pressure and heart rate before and after the drug administration were also recorded.

PSPH Evaluation and Treatment Algorithm

According to the algorithm, patients diagnosed with PSPH with VAS of <4 were recommended with a conservative treatment. Neurological examination was repeated 24 and/or 48 hours with a follow-up when deemed necessary by the doctor. Patients with VAS ≥4 at follow-up examination or admission were administered with 200 mg IV theophylline as 45 min infusion with a hemodynamic monitorization. Forty-five minutes after the infusion, patients were asked to sit, and VAS scores were reassessed. Patients whose symptoms regressed or were able to be mobilized were discharged and called for follow-up 24 and/or 48 hours later after the discharge. Patients decided to have a repeated theophylline infusion were hospitalized and closely monitored. Patients with change in type of headache, increased severity, presence of pathological findings in neurological examination (such as cranial nerve examination pathology, motor-sensory deficit, visual field examination), history of cerebrovascular accident, and previous intracranial surgery underwent cranial and/or spinal magnetic resonance imaging (MRI). Patients with the intracranial hypotension findings in cranial MRI and VAS ≥4 despite passing of 48 hours were planned with an epidural patch. Theophylline may be re-administered to reduce the symptoms until blood patch procedure.

Unlike the other patients, the lactating mother is informed that breastfeeding must be postponed two hours after a theophylline infusion.

Statistical Analysis

For statistical analysis, data was input into "Statistical Package for the Social Sciences" version 24 (SPSS v.24) SPSS Inc., Chicago, IL, USA) and "e-PICOS" program was used for calculations based on "Medicres Good Biostatistical Practices." Descriptive statistics were used for the categorical variables and frequency calculations were expressed as percentage. Comparisons of means were performed with independent t-test. *P*-value <0.05 was considered as statistically significant.

RESULTS

Mean patient age was 31.6±4.6 years. Of the PSPH patients, 32 (96.7%) were evaluated at the gynecology and obstetrics department, and one (3.3%) with neurology consultation.

Lumbar puncture was performed at L_3-L_4 level in 17 (51.5%) patients and L_4-L_5 in nine (27.3%) patients. Seven (21.2%) patients did not have the available records on lumbar puncture level.

22G needle was used for lumbar puncture in 27 (81.8%) patients. Information on needle diameter was unavailable in six (18.2%) patients.

The number of patients with orthostatic headache in examination was 21 (63.6%). Twelve (36.3%) patients had more than two additional complaints (Table 1). There were no complaints of fever or neck stiffness.

Table 1. Additional complaints in patients with an orthostatic hypotension

Complaint	Number	Percentage (%)
Nausea	6	18.18
Tinnitus	6	18.18
Dizziness	4	12.12
Vomiting	2	6.06
Diplopia	2	6.06
Photophobia	3	9.09
Phonophobia	3	9.09
Numbness in left arm	2	6.06
Prickling/tingling	1	3.03
Ear fullness	1	3.03

Onset of headache was <23 h in 21 (67.7%) patients and 24–120 h in 12 (32.3%) patients. Before our evaluation, a total of 17 patients (51.5%) did not receive any additional drug treatment, but they were only on bed rest and fluid intake. Eleven (33.3%) patients received paracetamol (500 mg)-codeine (10 mg) combination; five patients (15.2%) received paracetamol (300–500 mg) treatment.

Mean time from headache onset until theophylline administration was 85.2±54.2 h (min: 24/h; max: 264/h). Theophylline infusion was initiated 24–120/h after the onset in 27 patients (81.4%) and >121 hours in five (15.6%) patients. Time record of theophylline administration was unavailable in one patient.

VAS score was ≥4 in all the patients (100%). Mean standing VAS score was 6.1±1.8 before theophylline the infusion, and 1.3±1.2 45 minutes after ending the infusion (p=0.001) (Figure 1).

Patients with complaints in addition to orthostatic headache did not have a significant difference in mean VAS score before and after the theophylline infusion compared to those who did not (6.10±1.2, 6.16±2.1; 0.8±1.3, 1.6±1.1, respectively; p >0.05 all).

Mean heart rate was 74.8±10.4 bpm before theophylline infusion and 78.0±11.1 bpm after the infusion (p <0.05). Mean diastolic blood pressure was 73.1±9.6 mmHg before the infusion and 71.4±6.4 mmHg after the infusion (p >0.05).

Theophylline infusion was administered only once in 22 (66.7%) patients. As for the remaining patients, theophylline was administered twice in seven (21.2%) and three times in four (12.1%) patients. Two of the patients who were administered theophylline three times were decided to receive an epidural blood patch. During the time until the patch procedure, infusions were repeated to reduce the symptoms.

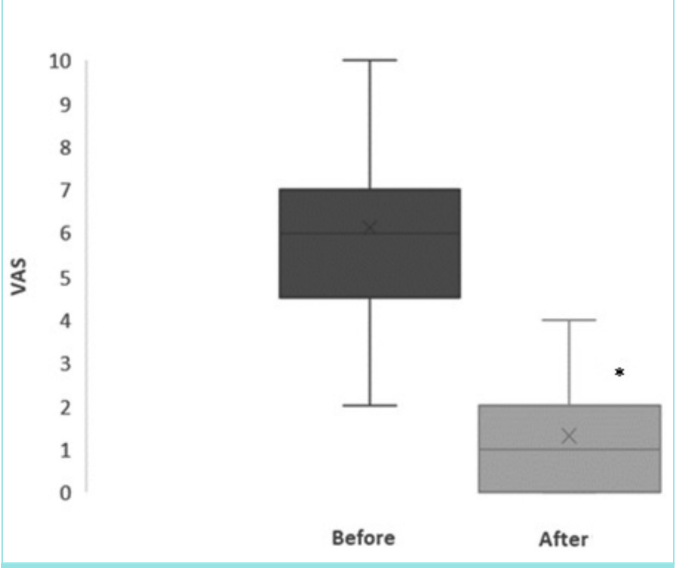

Figure 1. VAS scores before and after theophylline infusion. Mean VAS score after theophylline infusion was significantly lower compared to mean VAS score before infusion (*p=0.001). VAS, Visual analogue scale.

Adverse effects associated with the theophylline were not reported in any of the records.

Headache had resolved in all the 31 patients (93.9%) who arrived for follow-up evaluation 24 and/or 48 hours after the theophylline infusion. In the two patients who received blood patch (6.1%), headache had resolved but diplopia continued. Records showed that ophthalmologic consultation was requested for these patients for follow-up and treatment.

DISCUSSION

This study was the first retrospective study on theophylline administration for PSPH treatment in the postpartum period within the framework of a designated algorithm. Success rate with a single theophylline infusion was 66.7%. This rate increased to 87% after the second infusion. While VAS scores of all the patients were "severe pain" level at admission, they improved to "no pain" level after the infusion. We believe this change is significant, especially regarding mothers taking care of themselves and their infants in as short period as possible.

According to The International Classification of Headache Disorders (ICHD)-3 beta version, PSPH is defined as an orthostatic headache that occurs within five days of a Dural puncture.[6] All patients in our study had headache that developed within five days after the Dural puncture. Theophylline administration time varied between 1–11 days.

There are some critical studies on the use of the drugs that are effective in the treatment of PSPH. Caffeine has been shown to provide temporary relief but requires repeated doses and does not reduce the need for epidural blood patch.[3,7] Although the efficacy of the hydrocortisone has been shown, the authors emphasize that the alternatives with a higher efficacy and broader presence in the literature should be prioritized.[3,7-9] Gabapentin is a moderately safe drug option during the lactation period. However, there is a reluctance to use the drug with the newborns due to concerns that it may cause neonatal neurotoxicity caused by slow drug clearance.[10,11] Although the use of NSAIDs, acetaminophen, and oxycodone, which are also among the drug treatments of PSPH, are safe during the lactation period, their efficacy in PSPH treatment has been found to be low.[7,8] In our patients, 48.5% had received a conservative drug therapy which they did not benefit from.

There are studies that demonstrate the efficacy of theophylline in the PSPH treatment. Ergun et al.[12] conducted a study on 20 patients and reported a significant improvement in the VAS scores, 30 minutes after the administration in 47.1% and 60 minutes after in 61.9% of the patients. Another study on 35 patients which compared theophylline to a placebo found

that the group which received only 200 mg theophylline showed a significant improvement in the VAS scores after 40 minutes.[13] In the same study, patients with <50% decrease in the VAS score received the repeated infusion of theophylline at the same dose and time and significantly improved.[13] In our study, 66.7% (n=22) of patients had significantly less pain after the first infusion. The remaining seven patients (21%) did not require any additional treatment after the second infusion.

There are also studies that associate needle diameter of the puncture and severity of pain in PSPH. It has been indicated that the use of needles with larger diameter cause a larger lesion and more CSF leakage in the dura mater.[14] 22G spinal needles had been used in 81.8% of our patients. Even in these 22G needle blocks, defined as a large diameter, theophylline treatment reduced the other neurological symptoms in addition to VAS values, and we believe this may be considered as another finding indicating the efficacy of the drug.

Theophylline requires monitorization during the administration due to its cardiac effects. Andreas et al.[15] reported in 2004 that intravenous theophylline infusion raised systolic blood pressure and heart rate in the congestive heart failure patients, but this was not statistically significant. In our study, there was no statistically significant difference in systolic and diastolic blood pressure before and after the theophylline infusion. Although there was a statistically significant difference in the heart rate, it was not clinically significant. One study that investigated the kinetics of maternal theophylline transfer to breast milk reported that <1% of maternal theophylline dose transferred into a breast milk. In the same study, theophylline peak breast milk levels manifested immediately after the IV administration and decreased over a time, indicating that the amount of theophylline consumed by the infants would depend on the volume of breast milk and the concurrent plasma concentration of the mother.[16] In another study, no adverse effects were observed in four out of five breastfed three-day-old infants who were administered 200 mg intravenous aminophylline treatment every six hours for an asthma treatment, and had no time limitation for breastfeeding. Irritability and sleep disturbance were observed in one infant and the symptoms completely disappeared when the drug treatment was discontinued.[17] The main reason breastfeeding time was specified as two hours from the theophylline infusion was that we believe the drug concentration will decrease considerably in this period.[18]

Limitations of the Study

While our study was conducted according to the protocol, there were also some limitations. Limited mobilization was not evaluated with a standardized score, theophylline levels were not assessed in infants, and the drug was not followed up for adverse effects, preventing more concise findings. We believe prospective studies may consider these points in the future.

CONCLUSION

In conclusion, theophylline infusion provided rapid and effective treatment of PSPH in postpartum mothers. We believe our study contains valuable information that may be helpful in prospective studies planning a "PSPH treatment algorithm" in postpartum mothers.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Mersin University (date: 10.05.2018; decision no: 2018/202).

Informed Consent: Since this study was retrospective, informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: Ş.R., M.A.; Design: Ş.R., G.G.T.; Supervision: Ş.R., M.B.; Data Collection and/or Processing: G.G.T.; Analysis and/or Interpretation: Ş.R., G.G.T.; Literature Review: M.B., M.A.; Writing: G.G.T., M.B., M.A.; Critical Review: Ş.R., G.G.T., M.B., M.A.

DISCLOSURES

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Conflict of Interest: The authors declare no conflict of interest.

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RESEARCH ARTICLE

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Students' Opinions on the Theoretical Aspects of Nursing Education in Turkey

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Abstract

BACKGROUND/AIMS: In recent years, nursing education has attempted to transition to a student-centered curriculum; however, the nursing education system needs to renew itself and adapt to changing conditions. Therefore, the perceptions, opinions, and recommendations of the students, who are the cornerstones of education, in the changing process are important. This study aimed to reveal the opinions of nursing students on the theoretical aspect of nursing education.

MATERIALS and METHODS: This descriptive qualitative study with a holistic single-case design was conducted with a total of 14 students. Interviews were conducted using a semi-structured interview form. The thematic descriptive and content analysis method was used to analyze the obtained data.

RESULTS: Thematic analyses revealed that the most important theme was that a theoretical lesson is conducted 8 hours a day. Among the 14 metaphors produced by the students about the theoretical aspect of nursing education, a positive feature was mentioned only in one.

CONCLUSION: Study results may guide decisions, such as planning course catalogs and curriculums. Additionally, students' views can contribute to the conducted studies to improve and develop nursing education.

Keywords: Nursing education; theoretical course; case study

INTRODUCTION

Nursing education and practice have passed through various stages so far in Turkey. Despite improvements in nursing education, some problems are determined in this process. Nursing education has problems in finding qualified and sufficient teaching staff, using modern teaching methods in the courses, and objectively evaluating the learners.[1,2] This study aimed to understand the perceptions of final year students on theoretical education and the problems they experienced in learningand put forward suggestions for solutions.

Recently, nursing education is changing toward a student-centered curriculum, thus the education system has to respond to the self-renewal, changing conditions, needs, and expectations. However, globally, nursing education is reported as inadequately competent due to insufficient strategic leadership, the static and rigid curriculum of nursing faculties, and inadequate resources.[3-6]

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Therefore, nursing education, management, accreditation, and learning systems need to be developed worldwide.[5] Additionally, revealing the students' views on the experiences of nursing students could contribute to the re-construction of nursing education.

The results of this study are expected to contribute to the proposals for theoretical nursing education. Therefore, the following questions were sought to answer:

- What are the experiences of students in theoretical courses?
- What are the problems that students face regarding theoretical courses?
- What are students' recommendations for the development of theoretical courses?
- What do the students think theoretical courses are like? Why?

Background

The nursing workforce has a key role in the functioning of the health care system. Health care workers provided great support to health and development in the last century. However, the changing needs of health care in the 21st century suggest that nursing education should be subjected to different developments.[5] Improvements in nursing education are considered as the basis for increasing the quality of health and care systems.[5,7,8] Nursing education should provide the students with the knowledge, skill, attitude, behavior, decision making, and application ability, which form the basis of nursing practice and factors that constitute the nursing profession, such as evaluation and monitoring of innovations.[9]

In nursing education programs, theory and practice are integrated conducted. Students get the necessary theoretical information at school; however, they also try to improve their clinical judgment ability by transferring the theoretical knowledge to practice to transform the information to the behavior and learn the whats, whys, and hows.[8,9] Experiences, expectations, and recommendations of the students about theoretical and practical education can contribute to the more effective nursing educational processes. However, knowledge and researches in the education of health professionals are insufficient.[5]

Nursing education in Turkey is based on a 4-year or 4,600-h theoretical and clinical training. At least one-third of the total educational period is theoretical and the rest is clinical. In Turkey, 124 are in nursing undergraduate programs and 71,538 students are registered to those programs. Similar problems are experienced in nursing education in Turkey with the rest of the countries worldwide. Solving those problems will impact the development and maintenance of community health, as well as contribute to the nursing profession.[10]

The review of related literature identified limited qualitative studies on the theoretical aspect of nursing education. Thus, study results can contribute to the planning, implementation, and evaluation of the theoretical aspect of nursing education.

MATERIALS and METHODS

Design

This study is a qualitative study with a descriptive and holistic single-case design. Descriptive case studies are one of the most common qualitative studies, which can provide an understanding of individuals' world perceptions and seek insights.[11] Case studies can establish cause and effect by observing effects in real contexts, recognizing that context is a powerful determinant of both causes and effects. Further, case studies investigate and report the complex dynamic and unfolding interactions of events, human relations, and other factors in a unique instance.[12]

Participants

This study consisted of 977 nursing students who study in the Faculty of Nursing in a university in the academic year 2017. The sample selection was based on a purposeful sampling method, and two volunteer participants were selected from each major department (surgical nursing, internal medicine nursing, obstetrics and gynecology nursing, child health and diseases nursing, psychiatric nursing, public health nursing, and management nursing), making a total of 14 participants. An equal number of students from each gender in the final year was also taken into consideration to determine the participants. Thus, interviews were done with those 14 volunteer students from the final year.

Data Collection

Data were collected by researchers from April–May 2017. An interview form consisting of four open-ended semi-structured questions was used. This included 45-min recorded interviews with participants using initial interview questions. Participants were encouraged to freely express their own opinions during the interview. The in-depth interview technique was conducted in the qualitative data collection, and a suitable environment was created for students to freely express their experiences and views related to their theoretical education. All interviews were conducted in a separate room, and participants' experiences, thoughts, and feelings were recorded in a taped diary after obtaining the participant's verbal and written consents.

Data Collection Tools

Individual information form: An individual information form prepared by researchers involving nine questions related to

the socio-demographic characteristics (age, educational status, family information, etc.) of the study participants was used.

Semi-structured interview form: A conceptual framework was created from the conducted field study to prepare the semi-structured interview form. Later on, preliminary discussions wereheld and opinions of experts were obtained and questions, which were taken into account in preparing the final question form, were selected. The questions were open-ended and semi-structured for them to be answered and re-configured with the received responses to lead to new questions. The semi-structured interview form with four questions was based on the experiences of the nursing education in theoretical aspects and problems that are experienced and how they coped with those problems and their suggestions. Semi-structured interviews were used because they would provide an in-depth exploration of the topic and allow the researchers flexibility, e.g., to change the order of questions, simplify the questions, and probe the interviews.[12]

Statistical Analysis

Data analysis started with repeated readings of interview transcripts from interviews with the nursing students to determine the essence of the phenomenon and structures of experiences of nursing students related to theoretical aspect and understand the influences of this kind of training on final year nursing students. During data analysis, the data were categorically and chronically organized, repeatedly reviewed, and continually coded. Interview transcripts were regularly reviewed, themes were arranged, and findings were interpreted.[12]

Additionally, the data analysis process was aided using a qualitative data analysis computer program called NVIVO11. These kinds of computer programs do not perform the analysis but facilitate and assist it by organizing data and recodes and nodes, etc.[12]

Validity and Reliability

Five steps were followed to ensure reliability and validity of the study: (i) data were collected from semi-structured interviews based on related literature and data were categorically and chronically organized, repeatedly reviewed, and continually coded, (ii) data were used as direct quotations from the interviews without making any comments on them, (iii) a purposive sampling method based on voluntarism was used to get opinions and experiences of nursing students, (iv) data were coded by two independent researchers and Cohen's Kappa coefficient was calculated to determine the inter-rater reliability of themes coded as -0.773 perfect agreement for inner reliability, and (v) records of interviews were kept for outer reliability.

Ethical Consideration

The study was initiated with the permission of the Faculty of Nursing and the approval of the ethics committee of clinical researches. Participants were briefed about the research aims, kept informed at all stages, and offered anonymity. A consent form was signed between the researcher and each participant on the use of data for analysis to be reported and disseminated. The researcher was careful not to impose their belief on others and wassecondary, and the participants' opinion was required.

RESULTS

Of the 14 participants, seven were females, the average age was 22.21±0.69 years (min: 21, max: 24), eight had a mother and seven had a father who was a primary school graduate, and seven had two brothers. Of them, nine resided in dormitories and 11 had incomes that equaled their expenses. The Grade Point Average of students was 2.68±0.269 (min: 2.30, max: 3.10).

Based on the qualitative findings from the interviews with the participants, the problems, factors, recommendations, and metaphors associated with theoretical education consisted of main themes and their sub-themes.

Problems in Theoretical Education

The thematic frequency of nursing students' opinions regarding the problems experienced in theoretical education was categorized to find out the response to the problems in theoretical education. As seen in Table 1 from the opinions of the students on the problems they experienced in theoretical education; 13/14 (92.86%) students complained about block-scheduling of courses (theoretical courses 8 hour a day). Some participants' views on that are as follows:

It is difficult, it is difficult. We come in the morning and return in the evening. We become very tired in the evening and we can't do anything, we just go to sleep. We get up early and again, does the same thing (K3,1,1).

Compressed. I mean, it's too compressed for normal lesson hours. You know, you want to get all of it, but I can't seem to keep up with this... I know, I sleep a lot in class in most of the courses (K4,1,1).

Complains about the problems with teaching courses were expressed by 8/14 (57.14%) students as follows:

I think that the lecture notes are very inadequate as a way of expression... There are no cases in course notes. What is missing is the fact that the information in the lecture notes is not visualized in my eyes (K8,1,2).

Moreover, if the lecturer can get a little more into the student level, it will be very good too... They know a lot of information, but there are problems with teaching what they know (K10,1,2).

Complaints about physical conditions were expressed by 7/14 (50%) students. One of the participants' views is as follows:

Other problems... When the class is crowded, there is noise. We cannot hear much when we sit on desks far from the board and the instructor. These things happen... Sometimes, things can be a problem, while using projectors, technical problems can occur, and fixing it up takes time (K2,1,3).

Problems originating from the students were mentioned by 6/14 (42.9%) students. One of the participants' views on that is as follows:

We are 270 students but we are not united. If we want to do something here, to reflect modern nursing, I must do it with the support of my friends, but I can't find it (K1,1,4).

Instructors' insufficient effective class management is expressed by 5/14 (35,71%) students. Some participants' views on that are as follows:

Our problem is that the number of students is too many. I think the lecturers should have more control over the classes (K11,1,5).

Some of our lessons were very boring since some lecturers have taught in a boring way, making us bored (K14,1,5).

Maybe, the lecturers need to develop themselves in this regard. The lectures in class should neither control students too much nor ignore students in class. The lecturer must be both be loving, with humor, and make students listen (K6,1,5).

The problems with measurement and evaluation of students were mentioned by 4/14 (28.6%) students. One of the participant's views on that is as follows:

We are also expecting that nursing care should be asked during exams; however, generally, among the 50-exam questions, 15 are on nursing care, the rest are on illnesses (K1,1,6).

Problems, such as inadequate and expensive textbooks, nursing education are being far from making the students enjoy the nursing profession, the course hours' being divided among different teaching staff, and the insufficiency of nursing aspect in the subjects of courses was mentioned by 1/14 (7.1%) student. Some participant's views on those are as follows:

... First of all, we do not have a source to study on, apart from the course notes, few nursing notebooks are on sale and are very expensive (K14,1,7).

A difference is observed between senior lecturers and lecturers in theoretical courses. That is to say if, in a program, there are too many senior lecturers, lecturers do not have many courses and usually, the courses they teach are the courses that senior lecturers do not want to teach (K1,1,9).

When we generally interpret the participants' views on the theoretical education problems, it is understood from the participant's view that the block-scheduling of courses is the main problem to be resolved. Additionally, problems related to teaching courses and problems due to physical setting were also emphasized more than others.

Table 1. Thematic analysis of problems at theoretical education

n	Problems at theoretical education	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10	K11	K12	K13	K14	f	%
1	Block-schedulling of courses	√	√	√	√	√	√	√	√		√	√	√	√	√	13	92.86
2	Problems with teaching courses	√			√	√			√	√		√	√		√	8	57.14
3	Problems due to physical setting	√	√	√			√			√		√		√		7	50.00
4	Problems originating from the students	√		√		√			√		√				√	6	42.86
5	Instructors' lack of managing the class effectively	√					√		√					√	√	5	35.71
6	Problems with measurement and evaluation of students	√			√									√	√	4	28.57
7	Inadequate and expensive textbooks														√	1	7.14
8	Nursing education's being far from making the students enjoy nursing profession				√											1	7.14
9	The course hours' being divided among different teaching staff	√															7.14
10	The insufficiency of nursing aspect in the subjects of courses	√														1	7.14

n, Number.

Factors Facilitating Theoretical Education

The thematic frequency of nursing students' opinions regarding the factors that facilitate theoretical education was categorized to find out its response. As seen in Table 2 from the opinions of the students on factors facilitating theoretical education, 5/14 (35.7%) students mentioned theoretical education completion with laboratory practice. Some participants' views on that are as follows:

In other words, the immediate practice of theoretical courses makes it easier to understand (K6, 2,1).

I am pleased that what is taught is practiced in the lab. This is good (K7,2,1).

I see the lab as the biggest step before the internship... I think that if I go out of the laboratory without doing modeling, I will have difficulty in my internship (K13, 2,1).

Laboratory practices are certainly very useful... For example, we have the process steps in the laboratory, or even they are really useful for our clinical practice (K14,2,1).

Attending theoretical courses before the clinical practice was mentioned by 2/14 (14.2) participants. Some participants' views on that are as follows:

And I think it's a good thing that before we start practicing, we should first attend courses in theory (K1,2.2).

As I said, since theoretical courses are presented before we start practicing, it makes me more comfortable during practice, and of course, I also learn things that I do not know (K14,2,2).

The description of clinical experiences by lecturers in the course, classification of the curriculum according to the principle from simple to complex, the sufficiency of physical conditions and technical equipment, and using remarkable methods in teaching was mentioned by 1/14 (14.2) participant as follows:

While the lecturers tell their experiences with the patients, I directly see myself in the stories they tell. At that moment, when I put myself in that feeling, I realize that I am really in a sacred profession (K10,2, 3).

I think it's helpful to attend the courses at these stages…I think that it is very good and logical to go on first, the fundamentals of nursing, then internal medicine nursing, surgical nursing, etc. (K14,2,4).

When we generally interpret the participants' views on factors that facilitate the theoretical education, they stressed the practice aspect of nursing education, such as theoretical training completion with laboratory practice and clinical experiences description by lecturers in the course. Then they were also concerned with the technical and physical conditions of the theoretical courses, classification of the curriculum according to the principle from simple to complex, and remarkable methods in teaching.

Recommendations for Theoretical Education

The thematic frequency of nursing students' recommendations for theoretical education was categorized to find out recommendations for theoretical education (Table 3).

As understood from participants' recommendations for theoretical education, 11/14 (78.57%) participants suggested

Table 2. Thematic analysis related to factors facilitating theoretical education

n	Factors facilitating theoretical education	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10	K11	K12	K13	K14	f	%
1	Completion of theoretical education with laboratory practice					√	√				√			√	√	5	35.7
2	Attending theoretical courses before clinical practice	√												√		2	14.2
3	Description of clinical experiences by lecturers in the course											√				1	7.14
4	Classification of the curriculum according to the principle from simple to complex														√	1	7.14
5	Sufficiency of physical conditions and technical equipments	√														1	7.14
6	Using of remarkable methods in teaching													√		1	7.14

n, Number.

that some teaching methods should be used to enhance learning.

Some participants' views on that are as follows:

I still think that some information in courses has not been updated for us. On some slides, we find some differences among the suggested references... The education in the theoretical courses should be a little more updated (K1,3,1).

Sometimes expressions are insufficient, we use our imagination, that is, images in the courses are more effective... it can be a video or a photo. Things like that... I think it's much improved with laboratory. The lecturers should discuss with the students what they teach, otherwise, we don't learn but memorize (K5,3,1).

I want teachers to do things like a 5-min role-play to attract students' attention in courses (K13,3,1).

Block-scheduling of courses should be given up as suggested by 9/14 (64,3%) participants. Some participants' views on that are as follows:

It will be better to have longer breaks. Because having a class for 8 h is a bit difficult (K1,3,2).

The number of laboratory practices should be increased... I think it is necessary to put the theories into practice (K13,3,3).

Laboratory practices should be more effective as suggested by 6/14 (42,9%) participants. One of the participants' views on that is as follows:

Because in laboratory practices, we feel that we learn more. What is taught in theoretical courses in 2 h can be taught in laboratories about in 10 min in all details. It is more didactic. Thus, practices in laboratories are better (K9,3,3).

The number of students per classroom should be reduced as suggested by 4/14 (28.6%) participants. One of the participants' views on that is as follows:

My suggestion for the effectiveness of theoretical courses is that the number of students perclass should be reduced (K1,3,4).

Positive feedback should be given to students in the courses as suggested by 3/14 (21.4%) participants. One participant's view on that is as follows:

Unlike some lecturers, some are very open-minded to our ideas. They say that they will considerwhether our ideas are appropriate or not, which positively motivates us (K11,3,5).

The teaching of course topics should be carried out with case reports as suggested by 2/14 (14.3%) participants. One of the participant's views on that is as follows:

I think courses should be carried out with case reports. There must be a case report at the end of each course, I mean, while explaining a topic of a course. Thus, we learn much better with it (K8,3,6).

Courses should be summarized at the end, that there should be no obligation for course attendance, and that courses should have standardized measurement and evaluation as suggested by 1/14 (7.1%) participants. One of the participant's views on that is as follows:

During the last 10 min of the course, summarizing the whole course and revisions by lecturers are very useful instead of checking

Table 3. Thematic analysis of recommendations for theoretical education

n	Recommendations for theoretical education	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10	K11	K12	K13	K14	f	%
1	Using methods to enhance learning	√	√	√	√	√	√	√		√	√	√		√		11	78.57
2	Giving up block-scheduling of courses	√	√		√	√				√	√	√	√	√		9	64.29
3	Making laboratory practices more effective				√		√			√		√	√	√		6	42.86
4	Reducing the number of students in classrooms	√									√		√	√		4	28.57
5	Giving positive feedback in the courses	√									√	√				3	21.43
6	Teaching of course topics through case reports	√							√							2	14.29
7	Summarizing at the end of each course														√	1	7.14
8	No obligation of course attendance				√											1	7.14
9	Standardizing measurement and evaluation in all courses	√														1	7.14

n, Number.

students by questions whether they have learned ornot (K14, 3, 7).

When we generally interpret the participants' suggestions on theoretical education, they first stressed on the importance that some teaching methods should be used to enhance the effectiveness of learning in class. Additionally, they also forwarded suggestions for longer breaks among courses instead of scheduling, that the number of students per classroom should be reduced, and that there should be more laboratory practice, which is a bridge between theoretical and practical in nursing education.

Thematic Analysis of Metaphors on Theoretical Education

As seen in Figure 1, according to metaphors on the theoretical education of students in the nursing faculty, four were under plants theme including tree, snowdrop, the tree half of which leaves fell and pomegranate; three under machine theme including non-stop watch, projection and machine; two under the cybernetic theme including computer software and robot; animal theme including the bird in cage and sheep flock; one under the human theme including clown ;and under other theme including disposable goods.

When generally analyzed, the students reported eight negative metaphors about the theoretical aspect of nursing education, four no positive or negative judgment, and one positive. For instance, thestudent who produced the positive metaphor used the "snowdrop" flower that grows even in hard a condition just as to train nursing students is a long and hard process.

DISCUSSION

This study qualitatively analyzed the problems, factors, and recommendations for theoretical education in nursing and metaphors by nursing students for their opinions based on their perspectives via thematic, descriptive, frequency, and content analysis.

This study understood that the block-scheduling of courses was the most important problem based on the results of the participant's views on the problems in theoretical education. This finding is consistent with the studies by Bagcivan et al.[7] and Burnard et al.[12] that revealed that intensive and day-long course hours are an important source of stressors for nursing students.

Additionally, problems with teaching courses and physical settings were of priority. Accordingly, in the study on nursing faculty students by Bagcivan et al.[7], monotonous, boring courses, and problems originating from the physical setting were the factors that were mentioned as sources of stress by nursing students. One of the problems mentioned in the 2017 nursing education workshop that was reported by the Council of Higher Education,[9] was that the development of students' advanced cognitive talents, such as analysis, synthesis, and evaluation, is limited due to the theoretical courses that are taught with expository instruction method without question and answer, and discussion techniques instead of interactive teaching methods, which are parallel with our study results. Contrarily, participants mentioned the experiences related to the problems that originate fromstudents, which showed that they self-criticize themselves.

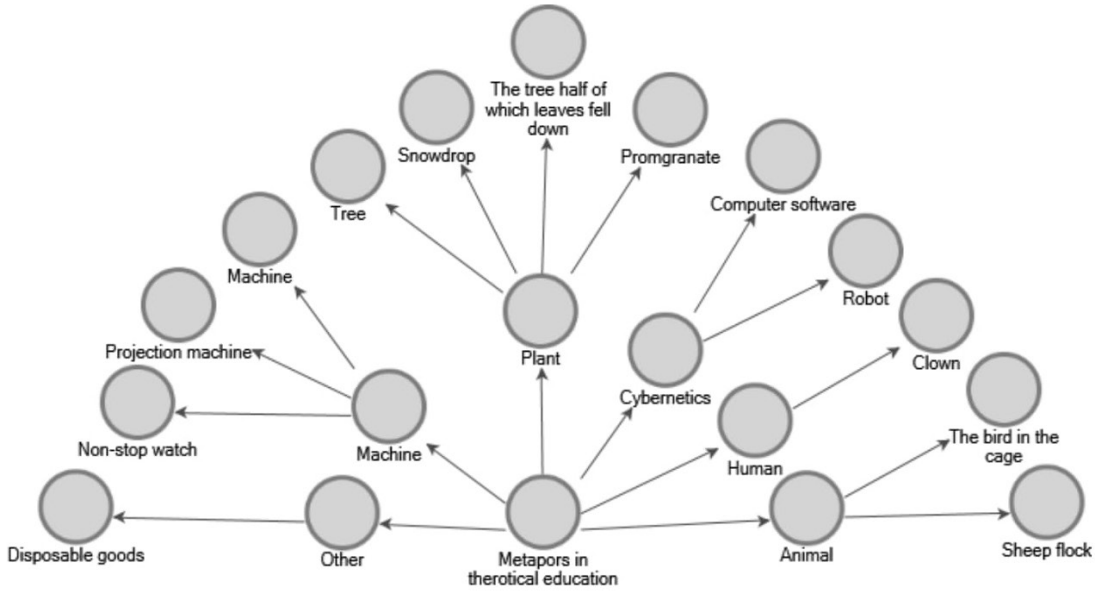

Figure 1. Thematic analysis of metaphors on theroretical education.

The study under the findings of the theoretical education problems revealed one of the sub-themes as instructors' insufficient effective class management. Kaya[13] stressed the problems related to lecturers in theoretical education and commented that active attendance and activities for students to question were not used sufficiently. Additionally, participants stated the problems with measurement and evaluation showed that they comprehensively thought about theoretical education. Themes, such as "nursing education's being far from making the students enjoy nursing profession" and "the insufficiency of nursing aspect in the subjects of courses," can present that nursing students thought about the insufficiency of autonomy in nursing. In the historical development of the nursing profession, autonomy has been a major problem in the studies.[14,15] Thus, it can be thought that nursing students were worried about the autonomy of nursing before working as a nurse.

When participants' views on factors that facilitate theoretical education are commented on, the sub-themes, such as theoretical education completion with laboratory practice and description of clinical experiences by lecturers in the course, are significant findings. Participants wanted to hear real sample cases in nursing applications and gave importance to seeing settings similar to real ones that could explain the importance of practical nursing. Accordingly, Dreyfus and Dreyfus[16], stressed the fact that practice knowledge based on real-life experiences has more didactic factors compared with theoretical knowledge in courses. The other themes, such as "classification of the curriculum according to the principle from simple to complex," "planning theoretical courses before clinical practice," "sufficiency of physical conditions and technical equipment," and "using of remarkable methods in teaching," were related to effective classroom management in terms of planning teaching methods used in course that supply suitable teaching materials and physical environment.

When participants' views on recommendations for theoretical education are generally analyzed, methods to enhance learning are the recommendation that is the most stated by participants. Findings on views by students also revealed that the sufficiency of lecturers affected the quality of theoretical education in nursing. The literature mentioned that nursing student expected the use of the right teaching strategies, methods, and techniques in theoretical courses.[7,8,17] The study by Atasoy and Sututemiz[8] revealed that lecturers' being active in courses was one of the most desired expectations of students, which are consistent with our study results.

It was also understood from participants' views that the sub-themes, such as giving up block-scheduling of courses and making laboratory practices more effective, were given priority. Similarly, in a qualitative study by Ewertsson et al.[18], practices in laboratories built a bridge between theory and practice as stated with the theme of "walking on the bridge."

One another recommendation for the theoretical aspect of nursing education was reducing the number of students in classrooms. Consistent with this finding in the report of the 2017 Nursing Undergraduate Education Workshop, the number of student quotas due to the difficulties experienced related to the over-numbered students both in theoretical and laboratory courses should be reduced as suggested.[9]

Additionally, participants also recommended that positive feedback to students should be given in the courses, and course topics should be taught through case reports. For instance, participant K8 mentioned teaching course topics through case reports as "In my opinion, course topics should be taught through case reports. There should be a case report at the end of each course. We learn much better with a case report." In some studies, students stated that they expected the lecturers to encourage themselves by using case reports in courses.[8,19,20]

As for metaphors, participants produced metaphors for theoretical courses, such as a tree half of that leaves fell, pomegranate, snowdrop, tree, robot, computer software, projection machine, machine, a clock that never stop working, flock of sheep, a bird in a cage, clown, and a thing used once. As it can be understood, most participants used metaphors with negative meanings. Only one of the metaphors with a positive meaning shows that students could not autonomously behave. For instance, K5 stated as "I think it is like a bird in a cage. We are in a cage and want to go out. Probably, we want to develop ourselves but we are limited. Anyway, we have wings and we can do something." Additionally, K12 stated "Being a student in this school is like a robot. The system of the school is monotonous. Get up early in the morning, go to school, again return home, go to bed, sleep, get up and go to school, and so on. You are as if you were turning the same wheel." In a study by Karagozoglu et al.[21], it was similarly revealed that the autonomy level of nursing students was lower than required.

CONCLUSION

Our study results revealed the problems in the theoretical aspect of nursing education and their recommendations to solve those problems through views of students based on their perspectives. Students' views can contribute to the studies to improve and develop nursing education.

Implications for Nursing Education

Our study results can put forward suggestions related to the theoretical aspect of nursing education to lecturers working in different fields of nursing education. Additionally, those results enable nursing education lecturers to notice their satisfaction, the difficulties they experienced, and their equivalent solutions.

Nursing students' views on theoretical education can widen the perspectives of lecturers inmanagement and training positions. Participants' negative point of view on block-scheduling of theoretical education is considerable. Students' stating about the difficulties of attending courses, which were 8 h long a day, and how those negatively affected them are evidence for a solution. Students stated that the system of timing in teaching was too difficult for them, they had difficulty in starting courses early in the morning and stopping in the evening, they felt burned outin the evening and they had no spare time for themselves for other activities. Lecturers should notice how difficult for students to attend the courses thought by the same lecturer all day-long, courses became monotonous in this way, students could not understand the course after a while, and the courses taught would become useless. Students themselves should assess the efficiency of the courses they attended to evaluate whether the nursing education has reached its goals. In literature, intensive and day-long course hours were stated as the source of stressors by students.[7,12] Theoretical education is the basis of practical education and training. Students' views on the problems related to the way courses were taught should be taken care of by lecturers and administrative staff. Since the number of students per class was overcrowded, students stated that lecturers could not effectively manage classes and they taught courses by using expository instruction method, thus they could not attract students' attention.

Additionally, more than half of nursing education consisted of practical education and training, students stated that lecturers did not teach courses with real-life cases or the nursing aspect in the content of the courses they taught was insufficient.

The study by Atasoy and Sututemiz[8] revealed that nursing students experienced problems related to the way lecturers taught courses and originating from lecturers themselves. The feedback from students will help to plan and carry out improvement in activities for nursing education as the students mention the quality of the education they attended.[22] Many quantitative studies are done on theoretical education in the literature; however, studies to reveal students' views on theoretical education in-depth are limited. Therefore, the findings of this study can lead to improved lecturers in nursing education. Participants also mentioned their views reflecting their satisfaction related to theoretical education. Students stated that lecturers' explaining about sample cases in courses and telling narratives from real-life events improved their learning, which enabled students to imagine the case. They also stated that supporting theoretical education with skill trainingin laboratories was very useful. Studies in the literature concluded that practices are done in clinical skill laboratories supported theory and practice and established a bridge between two aspectsof nursing education.[18] Taking those views into consideration, planning and sustaining nursing education is extremely important. Thus, to support nursing students' levels of professional autonomy and creativity, education and training methods conducted in education faculties should be re-examined and improved. These findings can positively contribute to long-term outcomes, such as enhanced nursing education quality, improved theoretical nursing education aspect, qualified care applications, more economical health care systems,and patients care.

Main Points

- Theoretical education is the basis of practical education and training.
- It can contribute to the development of the nursing education curriculum.
- The improvement and development of the theoretical aspect of nursing education positively affect the practice.

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ETHICS

Ethics Committee Approval: This study was initiated with the permission of the Faculty of Nursing and the approval of the Clinical Researches Ethics Committee of Akdeniz University (date: 01.03.2017; approval number: 137).

Informed Consent: A consent form was signed between the researcher and each participant on the use of data for analysis to be reported and disseminated.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: L.M., S.S., İ.G.; Design: L.M., S.S., İ.G.; Data collection; L.M., S.S.; Analysis and/or Interpretations; L.M., İ.G.; Writing: L.M., S.S.

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RESEARCH ARTICLE

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The Effects of Extracellular Magnesium on Gastrointestinal Contractility

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Abstract

BACKGROUND/AIMS: Magnesium (Mg^{2+}) is the second most abundant anion in the human body. It plays important roles including as a cofactor in many critical enzyme systems like energy transfer, storage and utilization. Changes in the concentration of extracellular Mg^{2+} may cause many pathological conditions such as neuromuscular hyperactivity, psychiatric disturbances, calcium/potassium abnormalities, and overactivity of cardiac muscle. Many investigations have been conducted on the effects of Mg^{2+} on cardiac, skeletal and vascular muscle contraction; however, much less is known about the effect of extracellular Mg^{2+} on gastrointestinal smooth muscle systems and gastrointestinal contractility. In the current study, we aimed to study the effects of extracellular Mg^{2+} on the isolated ileal responses induced by angiotensin II(ANG) contraction and in response to calcium and sodium channel blockers.

MATERIALS and METHODS: Healthy adult Wistar rats were used in this work. The ileal segments were isolated and suspended in isolated organ tissue-bath. The contractile responses induced with ANG were recorded. To study the effects of extracellular magnesium, the perfusion medium was changed to without magnesium, 2xMg and 4xMg. In these standard and modified perfusion mediums, the ileal segments were incubated with the calcium channel blocker diltiazem (Benz(othi)azepines) and sodium channel blocker prilocaine (2-(Propylamino)-o-propionotoluidide) and then ANG-induced contraction was recorded.

RESULTS: The results showed that in the Mg-free perfusion medium the ANG-induced contractions were increased and when extracellular magnesium was increased 2x-fold and 4x-fold in the perfusion medium, the ANG-induced responses were significantly decreased. Also, in the standard and modified Mg perfusion medium, the calcium and sodium channel blockers significantly decreased the ANG-induced contractions in isolated ileal segments.

CONCLUSION: Changes in the extracellular magnesium concentration in the perfusion medium significantly affect the gastrointestinal contractility. Without Mg, the contractility was increased, but with 2x-fold and 4x-fold increases in Mg, the contractility was significantly decreased. Mg had a dose-dependent inhibitory effect on ANG-induced contractions in the isolated ileal segments.

Keywords: Extracellular magnesium concentration, calcium and sodium channel blocker, isolated ileal contractility

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INTRODUCTION

Magnesium (Mg^{2+}) is one of the most important and prominent ions in the human organism, such as calcium (Ca^{2+}), sodium (Na), and potassium, and is the major cation that is necessary for the function of hundreds of enzyme systems. Mg^{2+} plays a role in the pathogenesis of hypertension, and a correlation is determined between serum Mg^{2+} and the incidence of cardiovascular diseases.[1] Oral Mg^{2+} intake was shown to act as a natural Ca^{2+} channel blocker.[2] Additionally, many drugs, such as diuretics and proton-pomp inhibitors, can cause Mg^{2+} deficiency[3] since both Mg^{2+} and these drugs use the same transport mechanisms in the organism, such as absorption, metabolism, and excretion. Therefore, when a person is taking these drugs, there is a risk of interaction with Mg^{2+} status.[4] Additionally, Mg^{2+} depletion is frequently observed in patients who are hospitalized. Generally, it is secondary to renal or intestinal Mg^{2+} loss and is particularly seen in patients with diabetes mellitus who have neuromuscular symptoms, hypokalemia, and cardiovascular complications.[5] Mg^{2+} treatment is becoming an important adjunct in some conditions, such as eclampsia, cardiovascular diseases, diabetes mellitus, asthma, and others.[6] The rapid onset of Mg^{2+}'s effects suggests an extracellular action on Ca^{2+} entry.[7]

L-type Ca^{2+} channel blockers are usually used to treat several clinical situations, mainly cardiovascular disease, and specifically, hypertension. L-type Ca^{2+} channel blockers have been used for many years for cardiovascular disease, thus their side effect profile has been well studied. However, their effects on the contractility of the gastrointestinal tract are less known.

Voltage-gated Na channels are dynamic membrane proteins and are responsible for starting the action potential in all excitable membranes.[8] Tappenbeck et al.[9] observed that the contractility-enhancing effects of local anesthetic are based on interaction with smooth muscle membranes, modulated by its molecular structure and lipophilicity.[10] The ion channels and ion transport systems are located in the cell membranes of the smooth muscle[11] as in all other excitable membranes. Na fluxes play a small role in smooth muscle contraction of the feline colon;[12] however, they contribute to the production of slow waves in human interstitial cells of Cajal (ICC).[13] The ICC cells present in the human intestine have a mechanosensitive Na channel current and play a role in the control of intestinal motor function.[13]

This study investigated the effects of extracellular Mg^{2+} concentration on the angiotensin II (ANG)-induced contraction on isolated ileal segments. Additionally, in different extracellular Mg^{2+} perfusion mediums, the effects of the Ca^{2+} channel blocker, diltiazem, and Na channel blocker, prilocaine, were investigated on the amplitude of angiotensin-induced contractions on the isolated rat ileum. As the Na and Ca^{2+} channel blockers are widely used, this study aimed to determine their possible effects in different extracellular Mg^{2+} concentrations on gastrointestinal system motility.

MATERIALS AND METHODS

In these experiments, Healthy adult Wistar rats (n=20) weighing 150–250 g were used. This study received the approval of the Local Ethics Committee of Near East University (date: 02/20/2020, reference number: 2020/105). The animals were lightly anesthetized with pentobarbital (35 mg/kg i.p) and were killed by decapitation and exsanguination. The ileum strips were mounted in an isolated organ bath containing standard Tyrode solution (mM: NaCl of 137, KCl of 2.68, $MgCl_2$ of 1.05, $CaCl_2$ of 1.8, NaH_2PO_4 of 0.42, $NaHCO_3$ of 11.9, and glucose of 5.5) and were bubbled with 95% O_2 and 5% CO_2 mixture at 370 C at pH 7.4. Four types of Tyrode solutions were used in these experiments: (i) standard, (ii) Mg-free, (iii) 2-fold Mg^{2+}, and (iv) 4-fold Mg^{2+}. In separate experiments, the bath medium was changed to either Mg^{2+} -free (omitting $MgCl_2$ and adding equimolar NaCl), or 2-fold Mg^{2+} and 4-fold Mg^{2+} (Omitting NaCl adding equimolar 2-fold, 4-fold $MgCl_2$) solutions. The control group used standard Tyrode as the perfusion medium. The ileum pieces contracted with ANG in doses of 1.2 × 10–8 M, which was accepted as the maximal ANG-induced contractions in the control group. Local anesthetic prilocaine was used in doses of 2.3 × 10–5 M. After the addition of the prilocaine doses, ANG was added after a few minutes into the medium and the results were recorded. The Ca^{2+} channel blocker diltiazem was used in doses of 5.5 × 10–6 M. The ileal segments were washed several times and left for 60 min before each agent was added into the bath solution. The Ca^{2+} channel blocker was added first then followed by the addition of prilocaine and ANG into the medium and the results were recorded. These processes were performed in standard Tyrode solution as the control group, Mg^{2+}-free, 2-fold Mg^{2+}, and 4-fold Mg^{2+} groups.

RESULTS

The effects of extracellular Mg^{2+} concentrations on the ANG-induced contractions on the isolated ileal strip were examined in these experiments. Additionally, the effects of Ca^{2+} channel blocker diltiazem and Na channel blocker prilocaine on ANG-induced contractions in percentage were examined. The ANG-induced percentage contractions in standard Tyrode, Mg^{2+}-free, 2-fold Mg^{2+}, and 4-fold Mg^{2+} are shown in Figure 1.

In the standard Tyrode solution (control group), when the Ca^{2+} and Na channel blockers were separately used, the responses to ANG were significantly reduced. Additionally, when the channel blockers were used together, the ANG-induced contraction significantly decreased. As shown in Figure 1, an increased response to ANG in the Mg^{2+}-free medium was not statistically significant compared to the control group. Further, in the Mg^{2+}-free perfusion medium, when Ca^{2+} and Na channel blockers were used either separately or together, the ANG-induced contractions

were higher than the control group although the difference was not statistically significant.

When 2-fold and 4-fold Mg^{2+} medium were used, the contractile responses to ANG were significantly decreased in all high Mg^{2+} perfusion mediums compared to the responses obtained in the standard Tyrode and Mg^{2+}-free perfusion mediums. If the 2-fold and 4-fold Mg^{2+} perfusion mediums are compared with each other, the ANG-induced contraction decreased but without any significance.

As shown in Figure 1, diltiazem significantly decreased the ANG-induced contractions in all perfusion mediums used. Additionally, prilocaine decreased the ANG-induced contractions in all perfusion mediums.

Statistical analyses were performed with unpaired t-test. Significance values different from the control were accepted as $*p < 0.05$, $**p < 0.01$ $***p < 0.001$ vs. values were presented as mean ± SEM (standard error of mean).

DISCUSSION

The present study showed that when Mg^{2+} was omitted from the perfusion medium, the ANG-induced ileal contractions increased, but the responses significantly decreased when Mg was added 2-fold and 4-fold into the perfusion medium. Additionally, when Ca^{2+} and Na channel blockers were added to the perfusion medium, the responses significantly decreased in all used mediums.

Our results showed that in the Mg^{2+}-free perfusion medium,

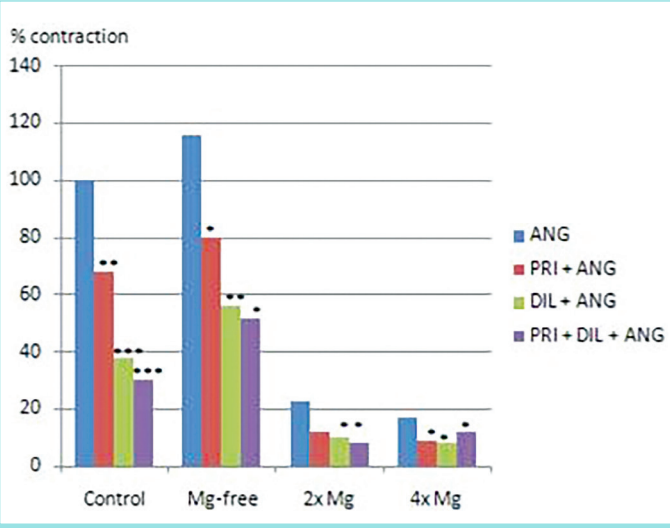

Figure 1. The ANG-induced percentage contraction in standard, Mg^{2+}-free, 2-fold Mg^{2+}, and 4-fold Mg^{2+} tyrode solutions. The diltiazem and prilocaine effects on ANG-induced percentage contraction.

ANG, Angiotensin; DIL, Diltiazem; PRI, Prilocain; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

the responses to ANG increased. Reducing the concentration of Mg^{2+} (When Mg^{2+} is removed) from the normal Tyrode solution enhanced the spontaneous basal activity, whereas the addition of Mg^{2+} gradually abolished this spontaneous activity. Muscle contraction induced by FS or carbachol was enhanced in Mg^{2+}-free Tyrode solution. The addition of Mg^{2+} inhibited the response to both forms of stimulation in a dose-dependent manner.[14]

Lin et al.[15] showed that Mg^{2+} isoglycyrrhizinate inhibits L-type Ca^{2+} channels and Ca^{2+} transient. The effect of Mg^{2+} is in a dose-dependent manner in myocyte. Also, it was shown that increased internal free Mg^{2+} concentration partly inhibits the activity of Na/Ca exchange, or might limit its ability to trigger Ca release.[16] Our results showed that as the concentration of Mg^{2+} in the extracellular fluid increased, the ANG-induced contraction percentage decreased. Additionally, the presence of Ca^{2+} and Na channel blockers in the perfusion medium further reduced the responses. Our results showed that the contractile responses significantly decreased with the Ca^{2+} channel blocker. The inhibitory effects of Mg^{2+} were potentiated when the Ca^{2+} concentration in the Tyrode solution was reduced to 0.6 mM, whereas increasing the extracellular concentration of Ca^{2+} (5.4 mM) reduced the inhibitory effects of Mg^{2+}. Yu et al.[14] demonstrated that the contractile alterations at different concentrations of extracellular Mg^{2+} correlated with similar changes in intracellular free Ca^{2+}.[14] Heron[17] postulated that Mg^{2+} and Ca^{2+} are dependent on each other as the disrupted balance of one has an impact on the other.

Ca^{2+} is the most important signaling molecule in all cells and is involved in numerous essential functions including cell life and death. Intracellular Ca^{2+} should be increased for the contraction of smooth muscle cells like all other muscle cells. Cytosolic Ca^{2+} increases by opening the Ca^{2+} channels either in the surface cell membrane or organelles membrane. The smooth muscle cell needs much more Ca^{2+} from the extracellular medium.

Smooth muscle cells have many Ca^{2+} channels, such as voltage-gated Ca^{2+} channels and RyRs for increased intracellular Ca^{2+} concentration. Depolarization causes L-type Ca^{2+} channels to open enabling Ca^{2+} to enter down its concentration gradient into cells. The stimulatory signal results in increased cytosolic Ca^{2+} levels, which activates muscle contraction.[18] In smooth muscle, Ca^{2+} enters the cell through many ways, particularly two different types of Ca^{2+} channels, then activates contractile filaments and induces contraction. These Ca^{2+} channels are inhibited by Ca^{2+} channel blockers and/or nitro compounds. Ca^{2+} inhibits both of these Ca^{2+} channels and relaxes the muscle. A portion of the smooth muscle contraction is due to the release of Ca^{2+} from the cellular storage site. Caffeine and norepinephrine release Ca^{2+} from this store to induce a transient contraction. The contraction induced by caffeine is greatly augmented in the absence of Mg^{2+}. The other effect of Mg^{2+} deficiency is to

inhibit the effects of various vasodilators. Vascular endothelium releases a substance that relaxes vascular smooth muscle and this relaxation is also inhibited by Mg^{2+} deficiency. Thus, Mg^{2+} has multiple sites, and the mechanisms of action in smooth muscle are still controversial.[19]

In gastrointestinal smooth muscle, like all in smooth muscles, the upstroke action potential is principally mediated by Ca^{2+} influx through voltage-dependent L-type Ca^{2+} channels and is responsible for the initiation of contraction. Ca^{2+} channel blockers or Ca^{2+} antagonists reduce smooth muscle contraction by inhibiting Ca^{2+} ions fluxes.[20] In this study, diltiazem was used as a Ca^{2+} channel blocker and results indicated that the ANG-induced contraction was reduced in all the used perfusion mediums. Diltiazem blocked the L-type Ca^{2+} channels.[20]

Our study results showed that when Na ions were blocked by prilocaine Na channel blocker, the ANG-induced contractions significantly reduced. Several investigations have reported the effects of local anesthetic on Na channels in particular.[21-23] The role of Na fluxes in smooth muscle contraction is controversial; however, it has been shown to play a role in the generation of slow-wave in human ICC cells.[13]

CONCLUSION

Changing the extracellular Mg^{2+} concentration affects the ANG-induced contraction in isolated ileal segments. In the Mg^{2+}-free perfusion medium, the ANG-induced contraction increased. The addition of 2-fold Mg^{2+} and 4-fold Mg^{2+} into the perfusion medium significantly decreased the responses. The Ca^{2+} channel blocker diltiazem and Na channel blocker prilocaine decreased the isolated rat ileal contractility. Diltiazem decreased Ca^{2+} entry into the gastrointestinal smooth muscle as with any other smooth muscle. Prilocaine decreased Na and probably Ca^{2+} entry into the cells. This study showed that changing the concentration of extracellular Mg^{2+} ions affects gastrointestinal contractility. However, further studies are needed to better clarify the role of extracellular Mg^{2+} and it should be further confirmed by human investigations.

Main Points

- Mg^{2+} ions play an important role in many enzyme systems in the organism.
- The angiotensin-induced contractions in the Mg^{2+}-free perfusion medium increased in the isolated gastrointestinal segments.
- When Mg^{2+} ions increased in the perfusion medium either 2-fold or 4-fold, the responses to ANG significantly decreased
- Mg^{2+} ions play an important role in gastrointestinal contractility.

ETHICS

Ethics Committee Approval: This study received the approval of the Local Ethics Committee of Near East University (date: 02/20/2020, reference number: 2020/105).

Informed Consent: Animal experiment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., A.Ö.; Design: E.K.; Supervision: E.K., A.Ö.; Resource: E.K., A.Ö.; Materials: E.K., A.Ö.; Data Collection: E.K.; Analysis: E.K.; Literature Search: E.K., A.Ö.; Writing: E.K., A.Ö; Critical Reviews: E.K.

DISCLOSURES

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RESEARCH ARTICLE

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The Correlation of Calculated Testosterone Indices with Metabolic Markers in Polycystic Ovarian Syndrome

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Abstract

BACKGROUND/AIMS: Polycystic ovarian syndrome (PCOS) is mainly considered a reproductive disease with chronic anovulation and infertility. Metabolic syndrome risk in patients with PCOS is shown in many studies, and mainly hyperandrogenemia component has a strong predictor of metabolic disorders. This study aimed to compare the value of bioavailable testosterone (BioT) and free androgen index (FAI) levels to determine the correlation with metabolic parameters in patients with PCOS.

MATERIALS and METHODS: This study included 83 females with PCOS of reproductive age, according to Rotterdam criteria from outpatient clinics of the Department of İstanbul Training and Research Hospital from January 2020 to October 2020 for our retrospective cohort analysis. FAI was calculated as FAI = (testosterone/SHBG) × 100. Calculations of BioT were conducted using the formula from total testosterone (TT), SHBG, and albumin values.

RESULTS: FAI and BioT levels were 5.60±5.73 ng/dL and 21.11±15.44 ng/dL respectively. A positive, moderate, and statistically significant correlation was found between body mass index (BMI) and FAI (r=0.402, p=0.009), whereas a positive, moderate, and statistically significant correlation between BMI and BioT (r=0.491, p=0.002). A positive, moderate, and statistically significant correlation was found between low-density lipoprotein and FAI (r=0.377, p=0.040).

CONCLUSION: Our study is one of the few studies that investigated and compared the concentrations of BioT and FAI with the metabolic markers in PCOS and indicated the corresponding suitability of both androgen indices in detecting metabolic syndrome risk in PCOS. These indices give more valuable insight into metabolic disturbances than commonly analyzed TT levels.

Keywords: Polycystic ovary syndrome, metabolic syndrome, hyperandrogenism

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common disease of females, associated with chronic anovulation. Hyperandrogenism is the key feature of PCOS as defined by all criteria.[1-3]

Patients with PCOS have a most commonly determined hyperandrogenism by calculating the total testosterone (TT) levels, but low concentrations in women typically lead to poor diagnostic performance; however, its measurement is questionable.[4] PCOS has mainly been considered a reproductive disorder; however, previous study results have shown that PCOS also has an association with metabolic and cardiovascular risk.[5,6]

Albumin and sex hormone-binding globulin (SHBG) are two of the four proteins that bind to circulated plasma testosterone

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in the bloodstream. Only 0.5%–3% of TT is not protein-bound and free, referred to as free testosterone (FT). The testosterone bound by albumin, also known as "weakly bound" testosterone, immediately detaches, and becomes bioavailable when the FT levels are decreased. Thus, the sum of FT and albumin-bound are collectively referred to as the "bioavailable" testosterone (BioT), this is the percentage of testosterone that readily enters the cells and can be used for signaling.[7,8]

Moreover, gene expression and cell function regulation, and intracellular androgen receptor interaction are mainly coordinated by BioT.[9] Consequently, testosterone that is not bound to SHBG is commonly treated as biologically accessible to tissues; therefore, BioT may be a more accurate predictor of androgen bioactivity than TT.[10,11]

The sex hormone-bound fraction of testosterone is defined as the free androgen index (FAI) and is presumed to be intrinsically superior in hyperandrogenemia estimation, compared with TT measurement alone.

However, the definite contribution and aspect of BioT and FAI compared to TT or dehydroepiandrosterone sulfate (DHEA-SO4) in females with PCOS was not yet studied. Most current scientific reports on the clinical consequences of hyperandrogenism in patients with PCOS have focused on TT, whereas knowledge about the relationship of BioT and FAI levels with associated adverse outcomes is limited.

This study aimed to compare the values of different androgen markers with metabolic parameters in patients with PCOS.

MATERIALS and METHODS

This study included 83 females of reproductive age with PCOS for the retrospective cohort analysis from the outpatient clinic of the Department of İstanbul Training and Research Hospital from January to October 2020. The Revised Rotterdam criteria were used in the diagnosis of patients with PCOS, requiring at least two of the three clinical and/or biochemical manifestations: (1) oligo- or anovulation; (2) hyperandrogenism (clinical and/or biochemical); and (3) polycystic ovaries.[3]

Patients who took medicines that affect the metabolic and hormonal parameters (androgen, anti-androgen, lipid, and glucose) six months before the study were excluded. The exclusion criteria included hypothyroidism, hyperprolactinemia, nonclassical 21-hydroxylase deficiency, Cushing's syndrome, and androgen-secreting tumors, as well as individuals with chronic diseases (including cardiovascular-renal diseases), malignancies, active infection, and regular drug/alcohol/cigarette usage.

Laboratory Analysis

Hormone levels and lipid markers were analyzed in a biochemical laboratory. The serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), TT, prolactin (PRL), DHEA-SO4, and thyroid-stimulating hormone (TSH) serum levels were assessed using a UniCel DxI800 analyzer (Beckman Coulter, Brea, CA). Anti-Mullerian hormone (AMH) levels were measured using the electrochemiluminescence immunoassay method (Roche Cobas E411, Roche Diagnostics, Mannheim, Germany). Metabolic and lipid profiles, fasting glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and triglyceride were determined using a spectrophotometer (Beckman Coulter AU 5800 analyzer Beckman Coulter, Brea, CA, USA). The homeostasis model assessment for insulin resistance (HOMA-IR) was HOMA-IR = fasting blood glucose (mmol/L) × fasting blood plasma insulin (mU/mL)/22.5. SHBG concentrations were measured using an immunoassay (ARCHITECT®, Abbott Diagnostics).

The FAI was calculated as FAI = (testosterone/SHBG) × 100. Formula from the International Society for the Study of the Aging Male website was used for the BioT measurement (http:/www.issam.ch/freetesto.htm) from TT, albumin, and SHBG values that are calculated in the same manner described by Vermeulen et al.[12]

The study protocol was approved by the Ethics Committee of İstanbul Training and Research Hospital (date: 24/09/2020, issue number: 2054) and was conducted following the Declaration of Helsinki.

Statistical Analysis

Mean ± standard deviation was used in the expression of continuous variables, whereas categorical data was given as numbers and percentages. In the intergroup analysis for continuous variables, the Kolmogorov-Smirnov test for univariate data was used to assess the normal distribution data. The one-way analysis of variance test was used for three groups when the data were suitable for normal distribution; a t test was used for two groups, whereas the Mann-Whitney U test was used for two groups when the former was not suitable. The linear relationship between the variables was evaluated using Pearson's correlation test. Analyses were performed with International Business Machines Statistical Package for the Social Sciences Package Program (version 22.0; IBM Corporation, Armonk, NY, USA). Cases in which a type 1 error level of <5% was considered statistically significant.

RESULTS

The mean age of patients with PCOS was 23.19±5.41 years, and their mean body mass index (BMI) value was 25.91±6.23. AMH, LDL, HDL, total cholesterol, LH, FSH, PRL, TSH, fasting glucose, triglyceride, FT, hemoglobin A1c (HbA1c), HOMA-IR, estradiol (E2), SHBG, and insulin levels, and their mean and median values are presented in Table 1. TT, DHEA-SO4, FAI, and BioT levels were

65.26±25.41 ng/dL, 268.50±108.43 µg/dL, 5.60±5.73 ng/dL, and 21.11±15.44 ng/dL, respectively.

A negative, moderate, and statistically significant correlation was found between SHGB and FAI (r=−0.522, p <0.001), whereas a positive, moderate, and statistically significant correlation between TT and FAI (r=0.443, p=0.005).

A strong, negative, and statistically significant correlation was determined between SHGB and BioT (r=−0.625, p <0.001). A positive, moderate, and statistically significant correlation was determined between TT and BioT (r=−0.625, p <0.001). 0.434, p=0.006). A positive and statistically significant correlation (r=0.877, p <0.001) was also found between FAI and BioT.

A negative, moderate, and statistically significant correlation was found between SHGB and DHEA SO4 (r=−0.401, p=0.015), whereas a positive, moderate, and statistically significant correlation between TT and DHEA SO4 (r=−0.401, p=0.015). 0.461, p=0.001). Furthermore, a positive, moderate, and statistically significant correlation was found between FAI and DHEA-SO4 (r=0.531, p=0.001), whereas a positive and moderate correlation was found between BioT and DHEA SO4 (r=0.529, p=0.002). A positive, moderate, and statistically significant correlation was found between BMI and FAI (r=0.402, p=0.009), whereas a positive, moderate, and statistically significant correlation between BMI and BioT (r=0.491, p=0.002) (Table 2). A positive, moderate, and statistically significant correlation was found between LDL and FAI (r=0.377, p=0.040).

The total cholesterol and HOMA-IR values for FAI was ≥8.4 ng/dL in patients with PCOS, which was higher than the FAI of <8.4 ng/dL cut-off value; differences were not significant (p=0.305 and p=0.088). The total cholesterol and HOMA-IR values for TT was ≥75 ng/dL, which was higher than the TT of <75 ng/dL cut-off value; differences were significant only for HOMA-IR (p=0.326 and p=0.040, respectively). The total cholesterol and HOMA-IR values for DHEA-SO4 was ≥391 µg/dL, which was higher than the cut-off value for DHEA SO4 of <391 µg/dL; differences were not significant (p=0.051 and p=0.260, respectively). The total cholesterol and HOMA-IR values for BioT was ≥10 ng/dL, which was higher than the BioT of <10 ng/dL cut-off value; differences were not significant (p=0.638 and p=0.267, respectively) (Table 3).

DISCUSSION

A correlation was found between the LDL and BioT, BMI with BioT and FAI, and HOMA-IR with TT levels of patients with PCOS. Our study revealed the relationship between FAI and BioT values and TT, DHEA-SO4, and SHBG levels. Our results indicate the measurements of FT indices that provide new information on metabolic disturbances in PCOS.

The studies that investigate the relationship of metabolic syndrome (MetS) with TT and SHBG levels have been inconsistent. The clinical findings associated with MetS include abdominal obesity, dyslipoproteinemia, impaired glucose tolerance, and hypertension. A recent cross-sectional study in men reported that a lower TT level is correlated with low HDL, abdominal obesity, and hypertension. FT levels are found to be correlated with hypertension, whereas SHBG shows no correlation.[13] Another cross-sectional study also found a correlation between abdominal obesity and low TT levels.[14]

A limited number of reports are available on FAI levels in patients with PCOS and their associated consequences. Li et al.[15] found that high serum FAI levels were found in patients with a higher BMI and total cholesterol, HOMA-IR, and DHEA-SO4 levels. The 2005 SWAN study included 3,302 females and revealed low SHBG and high FAI levels associated with a higher BMI, triglycerides,

Table 1. Metabolic and Hormonal Parameters in Patients with PCOS

	PCOS (n=83)
Age (year) (Mean ± SD)	23.19±5.41
BMI (kg/m²) (Mean ± SD)	25.91±6.23
AMH (ng/ml) (Mean ± SD)	7.82±5.17
FSH (U/L) (Mean ± SD)	6.18±2.07
LH (U/L) [Medyan (min-max)]	6.7 (0.4–27.8)
Total testosterone (ng/dL) (Mean ± SD)	65.26±25.41
DHEA-SO4 (µg/dL) (Mean ± SD)	268.50±108.43
PRL (µg/L) (Mean ± SD)	15.25±10.53
TSH (ng/ml) (Mean ± SD)	1.82±0.81
Fasting glucose (mg/dL) (Mean ± SD)	89.99±14.63
Trigliceride (mg/dL) (Mean ± SD)	88.16±45.19
LDL (mg/dL) (Mean ± SD)	112.20±32.59
HDL (mIU/mL) (Mean ± SD)	54.47±17.12
Total cholesterol (mIU/mL) (Mean ± SD)	177.02±36.44
Free Androgen Index (FAI) (ng/dL) (Mean ± SD)	5.60±5.73
Bioavailable Testosterone (ng/dL) (Mean ± SD)	21.11±15.44
Free Testosterone (ng/dL) (Mean ± SD)	0.91±0.71
Hba1c (Mean ± SD)	5.48±0.44
HOMA-IR Median (min–max)	1.8 (0.7–9.90)
E2 (ng/L) Median (min–max)	34 (14–445)
SHGB (nmol/L) Median (min–max)	48.3 (9.6–418)
Fasting insulin (mU/L) Median (min–max)	8.75 (4–105)

Values are described as mean ± standard deviation, median (minimum–maximum).

BMI, Body mass index; PCOS, Polycystic ovarian syndrome; AMH, Anti-mullerian hormone; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; PRL, Prolactin; DHEA-SO4, Dehydroepiandrosterone sulfate; TSH, Thyroid-stimulating hormone; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; E2, Estradiol; SHBG, Sex hormone-binding globulin; n, Number.

Table 2. Correlation of Hormonal and Metabolic Parameters with Testosterone Indices in PCOS

		SHGB (nmol/L)	Total testosterone (ng/dL)	Free Androgen Index (FAI) (ng/dL)	Bioavailable testosterone (ng/dL)	DHEA SO4 (µg/dL)
Total Testosterone (ng/dL)	**r**	0.108				
	p	0.507				
	N	40				
Free Androgen Index (FAI) (ng/dL)	**r**	−0.522(**)	0.443(**)			
	p	**<0.001**	**0.005**			
	N	41	39			
Bioavailable Testosterone (ng/dL)	**r**	−0.625(**)	0.434(**)	0.877(**)		
	p	**<0.001**	**0.006**	**<0.001**		
	N	39	38	39		
DHEA-SO4 (µg/dL)	**r**	−0.401(*)	0.461(**)	0.531(**)	0.529(**)	
	p	**0.015**	**0.001**	**0.001**	**0.002**	
	N	36	53	35	33	
LDL (mg/dL)	**r**	−0.134	0.138	0.377(*)	0.340	0.220
	p	0.450	0.346	**0.040**	0.076	0.132
	N	34	49	30	28	48
HDL (mIU/mL)	**r**	0.161	0.023	−0.291	−0.338	−0.031
	p	0.320	0.870	0.090	0.059	0.823
	N	40	55	35	32	53
Triglyceride (mg/dL)	**r**	−0.020	0.095	0.178	0.147	0.008
	p	0.900	0.489	0.299	0.415	0.955
	N	41	55	36	33	53
Fasting glucose (mg/dL)	**r**	−0.037	0.014	0.035	0.050	0.156
	p	0.811	0.921	0.834	0.768	0.264
	N	45	56	39	37	53
Fasting insulin (mU/L)	**r**	0.005	0.032	0.014	−0.033	−0.162
	p	0.973	0.814	0.935	0.849	0.242
	N	43	56	38	36	54
HOMA-IR	**r**	−0.086	0.165	0.232	0.196	0.039
	p	0.576	0.211	0.145	0.233	0.777
	N	45	59	41	39	56
BMI (kg/m²)	**r**	−0.199	0.150	0.402(**)	0.491(**)	−0.029
	p	0.200	0.253	**0.009**	**0.002**	0.829
	N	43	60	41	38	57

Pearson correlation analysis; r, Correlation coefficient; **Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed); significant values are shown in bold.

BMI, Body mass index; DHEA-SO4, Dehydroepiandrosterone sulfate; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; SHBG, Sex hormone-binding globulin.

fasting plasma glucose, and low HDL levels in premenopausal females.[16] Similarly, our study revealed a positive correlation between BMI and LDL levels. These positive associations between FAI and LDL were also demonstrated in another report by Cai et al.[17], which found a positive association between FAI levels and LDL, BMI, waist circumference, and a negative association with HDL levels in females with PCOS. In line with our findings, non-SHBG-binding testosterone (BioT, FAI) levels were found to be correlated with obesity in patients with PCOS and healthy subjects.

Table 3. Evaluation of total cholesterol and HOMA-IR values at given cut-off values of testosterone indices

	Total Cholesterol (mIU/mL) (mean ± SD)	*p*-value	HOMA-IR Median (min–max)	*p*-value
Free Androgen Index (FAI)				
<8.4 ng/dL (n=53)	174.20±32.80	0.305*	1.70 (0.7–9.90)	0.088**
≥8.4 ng/dL (n=30)	187.71±18.73		2.25 (1.50–5.80)	
Total testosterone				
<75 ng/dL (n=59)	174.44±32.12	0.326*	1.60 (0.7–9.90)	**0.040****
≥75 ng/dL (n=24)	185.16±47.81		2.05 (1.10–7.10)	
DHEA-SO4				
<391 µg/dL (n=65)	172.22±30.01	0.051*	1.70 (0.7–9.90)	0.260**
≥391 µg/dL (n=18)	191.00±17.50		1.85 (1.50–5.90)	
Bioavailable testosterone				
<10 ng/dL (n=29)	182.30±24.18	0.638*	1.70 (0.7–9.90)	0.267**
≥10 ng/dL (n=54)	176.78±32.91		1.95 (1.20–7.10)	

*T-test; **Mann-Whitney U test; significant values are shown in bold; DHEA-SO4, Dehydroepiandrosterone sulfate; n, Number.

The positive correlation between LDL and FAI is assumed as an indicator of high levels of FAI and is a good prognostic marker for patients with PCOS since high LDL levels are strongly associated with coronary artery diseases and cardiovascular risk.

Hyperinsulinemia stimulates the production of adrenal androgens,[18] whereas SHBG levels decrease due to increased insulin levels through the inhibition of liver synthesis, which in turn, increases testosterone concentrations.[19] A recent study used the HOMA-IR cut-off value of two to separate patients with PCOS into two groups and two-fold higher FAI values were found in the >2 HOMA-IR group than in the <2 HOMA-IR group.[20] Insufficient correlation between fasting insulin, fasting glucose, and HOMA-IR levels with FAI and BioT in our study may be due to the relatively young age and low BMI of our study population. We assume that the FAI value in PCOS should be evaluated based on the different disease phenotypes.

Our study revealed a 5.6 mean FAI value in patients with PCOS. These results differed from those obtained in studies regarding PCOS in people of different ethnicities. In Malaysian females with PCOS, the mean FAI value was 9.2;[21] 6.1 among Chinese females;[22] and 4.97 in a study on the European population.[23] Standardized measurement methods and ethnicity-specific FAI cut-off levels should be investigated for the homogeneity of scientific findings through the establishment of an individual reference range and a validated assay.

This study had several limitations. First, this study was conducted using a relatively young and low BMI PCOS population; studies with wide phenotypic variation may provide more accurate and definitive results regarding the value of free androgen levels in these patients; however, measuring free androgen levels is still more definitive in determining the risk of MetS than using TT and DHEA-SO4 levels for them. A relatively small number of studies in females with PCOS were recognized that investigate high androgen parameters and long-term health risks.

Therefore, more reports are needed with large and more diverse subjects with different populations that are observed for a longer period are mandatory to validate and confirm our study results and interpret the effects of different testosterone measurements in the risk for MetS and MetS associated increased risk of type 2 diabetes mellitus and cardiovascular disease in patients with PCOS.

Main points

- High FAI and BioT is a stronger predictor of MetS risk than other common androgenic parameters in females with PCOS.
- Patients with PCOS with high FAI and BioT levels should be carefully monitored by physicians for future metabolic consequences even if they had normal androgen parameter levels.
- FAI and BioT could be used to monitor the responsiveness to therapy of patients with PCOS instead of measuring the declined TT levels.

ETHICS

Ethics Committee Approval: The research was approved by the clinical research Ethics Committee of İstanbul Training and Research Hospital (decision no: 2054, date: 24.09.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: N.A.; Design: N.A.; Materials: B.Ş.K.; Data Collection and/or Processing: N.A.; Analysis and/or Interpretation: N.A.; Statistical Analysis: B.Ş.K.; Writing: B.Ş.K.

DISCLOSURES

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Conflict of Interest: The authors declare no conflict of interest.

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RESEARCH ARTICLE

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Clinical Features of Ectopic Thyroid Gland in Children: Single Center Experience

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Abstract

BACKGROUND/AIMS: Ectopic thyroid gland is the most common cause of permanent congenital hypothyroidism. Thus, this study aimed to examine the clinical and laboratory findings of patients with ectopic thyroid glands.

MATERIALS and METHODS: Age of diagnosis, gender, presenting symptoms, anthropometric measurements, capillary thyroid-stimulating hormone (TSH) in neonatal screening, venous TSH and free thyroxine (FT4), thyroglobulin, IQ score, thyroid gland imaging results, and treatment doses were extracted from the patients' hospital files.

RESULTS: Thus study included 26 patients (Female: 20) with the diagnosis of ectopic thyroid. The mean age of the diagnosis in patients born before the neonatal screening program (68.22 ± 59.02 months) was higher than those born after neonatal screening (1.32 ± 1.41) ($p < 0.001$). All patients had overt or subclinical hypothyroidism. The most common localization was the sublingual thyroid gland, which was detected in 23 patients (88.4%). The molecular genetic analysis of 16 patients with persistently elevated TSH and FT4 did not detect thyroid hormone receptor beta (TRβ) gene mutation. The Cattel intelligence test scores were within normal ranges, except for one case that had been diagnosed at the age of 4 years. Patients who had been diagnosed at the neonatal screening program had a better final height standard deviation score ($p = 0.018$) but without differences in the Cattel intelligence test scores ($p = 0.373$). TSH was normal in the sample of neonatal screening in one patient (TSH = 1.2 µIU/mL).

CONCLUSION: The majority of our patients with ectopic thyroid gland was female and had sublingual thyroid gland. Delayed diagnosis of overt and subclinical hypothyroidism due to neonatal screening unavailability, did not affect the psychomotor development but caused poor growth outcome. Neonatal screening cannot always detect the ectopic thyroid gland.

Keywords: Ectopic thyroid gland, neonatal screening, neurodevelopmental outcome, growth retardation, TRβ gene mutation

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INTRODUCTION

Dysgenetic thyroid gland accounts for 80%–85% of patients with permanent congenital hypothyroidism (CH). The ectopic thyroid gland constitutes 60% of dysgenesis[1] and can be detected at any age, with an average age of 40.5 years for all age groups[2]. Age upon diagnosis in childhood peaks in two periods: 1–2 years and 4–5 years[3]. Children with a missing diagnosis at the neonatal period are presented later in life with the symptoms of hypothyroidism or compression depending on the thyroid gland localization. Growth retardation is the most common presenting feature in childhood. Additionally, lingual, sublingual, and laryngeal ectopic thyroid can cause bleeding, difficult intubation, and perioperative bleeding due to foreign body and upper airway obstruction, dyspnea, dysphagia, and superficial vein ulceration in the ectopic thyroid tissue[2,4-7]. The therapy of choice is L-Thyroxin, which is essential not only for hypothyroidism treatment but also for compressive symptom prevention by reducing gland size. Surgical treatment or I-131 ablation are recommended in patients with ectopic thyroid in severe compression/obstruction or bleeding despite appropriate L-Thyroxin therapy[8].

During the organogenesis, disorders that result in a defective migration of the thyroid gland to its normal anatomical position account for the etiology of the ectopic thyroid gland. However, the etiopathogenesis has not been fully elucidated. Maternal anti-thyroid antibodies are suggested to cause a migration defect by agonistic effects on thyroid antigens. Additionally, some involved gene mutations (Nkx 21, Nkx 25, PAX8, FOXE1, and HHEX) in thyroid development and differentiation have been reported to cause an ectopic thyroid gland[2]. Furthermore, thyroid dysgenesis is suggested as a polygenic disease, which can be affected by various epigenetic factors[9-11].

The most common locations of the ectopic thyroid gland include the lingual, sublingual, thyroglossal, pretracheal, laryngotracheal, laterocervical, submandibular, and retroperitoneal region, and rarely in esophagus, mediastinum, heart, aorta, adrenal glands, pancreas, gall bladder, and skin. Dual ectopia is extremely rare. Often one of the tissues is located in the lingual or sublingual region and the other in the subhyoid (usually) or suprahyoid region[9,12]. Persistent hyperthyrotropinemia (PH) in treated thyroid dysgenesis children is a well-known situation[13]. It has been attributed to suboptimal therapy or abnormal setting of the thyroid hormones' negative feedback control of pituitary thyroid-stimulating hormone (TSH) secretion. Therefore, some case reports in the literature with PH were attributed to thyroid hormone receptor beta (*TRβ*) gene mutation in the ectopic thyroid gland[14]. Thyroid hormone resistance (THR) is characterized by the unresponsiveness of the target organ to thyroid hormone. Loss of function mutations in the *TRβ* gene accounts for the underlying genetic etiology. Markedly elevated free thyroid hormone level and normal or slightly elevated TSH are the main hormonal features of THR. THR can rarely accompany to ectopic thyroid gland with an estimated frequency of 1: 140,000,000 [14]. This study aimed to evaluate the clinical and laboratory findings of 26 patients who were diagnosed before and after neonatal screening program with the ectopic thyroid gland and investigate the presence of THR in patients with persistently elevated TSH and free thyroxine (FT4) under L-Thyroxin treatment.

MATERIALS and METHODS

Data of 26 patients with ectopic thyroid gland diagnosis between 2009 and 2019 in the Pediatric Endocrinology Department of a tertiary center hospital were retrospectively analyzed. The ethical approval was obtained from the local ethics committee (document no: 19.12.2019/398). An informed consent form was obtained from the parents of all children following the Declaration of Helsinki. Age upon diagnosis, gender, presenting symptoms, anthropometric measurements, capillary TSH value in neonatal screening, venous TSH and FT4, thyroglobulin value, thyroid gland imaging (ultrasound (USG)/scintigraphy) results, and treatment doses were extracted from the patients' hospital files. *TRβ* gene mutation analysis was performed in patients with persistently elevated TSH and FT4 despite appropriately adjusted L-Thyroxin dose. The Cattel intelligence test was performed in patients older than 6 years to evaluate the IQ score. TSH and FT4 levels were analyzed on the Abbott Architect i8000 device using the Electrochemiluminescence Immunoassay method. Normal ranges were 0.35–4.94 μIU/mL for TSH and 0.70–1.48 ng/dL for FT4. Thyroid scintigraphy was performed using 2–4 mCi Tc^{99} pertechnetate. Ectopic thyroid gland was defined as abnormal thyroid localization in scintigraphy, which was confirmed using a correlative USG once applicable.

Statistical Analysis

Statistical analyses were performed using International Business Machines Statistical Package for the Social Sciences Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Continuous variables were presented as mean ± standard deviation (SD), whereas categorical variables were presented as number and percentage (%). The Shapiro-Wilk test was used for the normality data distribution. The comparison of patients who were born before and after the neonatal screening program was made using the Student's *t*-test for normally distributed values and the Mann–Whitney *U* test for non-normally distributed data. A *p*-value of <0.05 was considered statistically significant.

Molecular Genetic Analysis

Genomic DNA of patients was extracted from the peripheral blood using a MagPurix Blood DNA Extraction Kit by MagPurix 12 (Zinexts Life Science Corp., Taiwan) following the manufacturer protocol. All coding exons of the *TRβ* gene and their flanking

splice site junctions were amplified by polymerase chain reaction using custom-designed primers. The libraries were prepared with the Nextera V2 kits (Illumina Inc.) following the manufacturer's instructions. Next-gene sequencing was carried on the MiSeq platform (Illumina, San Diego, CA, USA). Results were analyzed according to alignments of *TRβ* gene transcript (NM_000461.4) via Geneticist Assistant software.

RESULTS

A total of 26 patients with ectopic thyroid gland (20 females) diagnoses were recruited. The mean age of patients was 39.32 ± 55.5 months (0.1–192). The clinical and laboratory features of patients are shown in the table. Since 2006, our country has had a national neonatal screening program based on capillary TSH measurement in blood spots. Eleven patients were admitted due to elevated TSH levels in neonatal screening. Of 12 patients who were born after the screening program had launched, 11 have high TSH in blood spots obtained for neonatal screening. The average capillary TSH was 82.23 ± 33.24 μIU/mL (1.2–105). TSH was normal in the sample of neonatal screening in one patient (TSH = 1.2 μIU/mL). Of whom, the diagnosis of CH and sublingual thyroid gland was considered during an outpatient clinical visit at the age of 2 months, where an elevated TSH was detected in venous TSH measurement.

Of 26 patients, 23 have first venous TSH above the upper detectable limit of 100 μIU/mL, whereas <30 μIU/mL in the remaining three patients. Patients who were born before the neonatal screening program had lower venous TSH values compared to those diagnosed during neonatal screening (p = 0.03). Mean FT4 was 0.47 ± 0.23 ng/dL (ranges 0.1–0.9) and the mean thyroglobulin level was 117.62 ± 147.63 ng/mL (ranges 5.1–482). Scintigraphy detected the sublingual thyroid gland in 23 out of 26 (88.4%) patients, lingual in 1 (3.8%), and submental thyroid in 1 (3.8%), whereas thyroid scintigraphy could not be performed in 1 patient who was on L-Thyroxin therapy at admission. Thyroid USG did not observe the thyroid gland in normal localization but the upper line of the trachea. Psychomotor development was normal in all patients, except for one patient who was diagnosed at 4 years old. This patient had a mild learning disability and IQ score at the lower normal limit in the Cattel intelligence test.In 16 patients with a persistently elevated TSH and FT4 during follow-up, mutation analysis for the *TRβ* gene was performed, and no mutation was detected. TSH and FT4 levels of 16 children were shown in Figure 1.

The mean age upon diagnosis for patients born before the neonatal screening program was 68.22 ± 59.02 months. Of whom, 10 patients were admitted to the clinic due to growth retardation, 1 with prolonged jaundice, 1 with speech delay, and 2 with elevated TSH level in a routine laboratory examination (Figure 2). Patients who were born before the neonatal screening program, thereby with diagnosis delay, had lower final height and weight SD scores compared to those diagnosed during neonatal screening (p = 0.018, p = 0.016, respectively). However, no statistically significant difference was found in the Cattel intelligence test scores, FT4 and thyroglobulin levels at the diagnosis, and final L-Thyroxin doses (p = 0.373) (Table 1).

DISCUSSION

This study evaluated the clinical characteristics, diagnostic methods, neurodevelopmental outcome, and molecular genetics analysis of 26 patients (age range: 3 days–16 years old) with ectopic thyroid gland diagnosis and revealed a female predominance, with the majority of patients having sublingual thyroid gland. One of the 12 (8.3%) patients who underwent neonatal screening had missing diagnoses. Our study, to the best

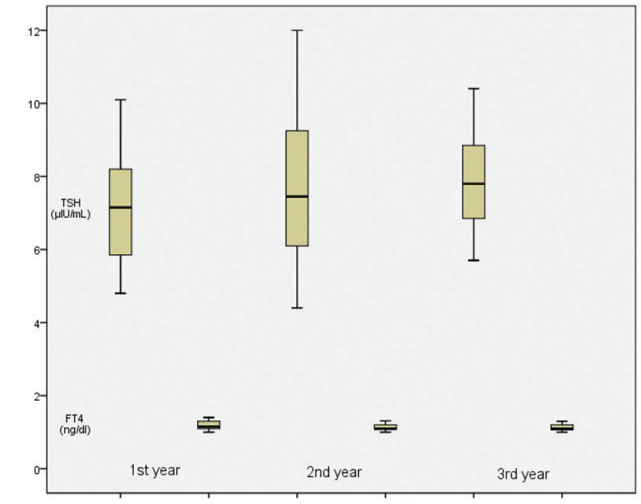

Figure 1. TSH and FT4 levels of 16 children with persistently elevated TSH and FT4.TSH, Thyroid-stimulating hormone; FT4, Free T4.

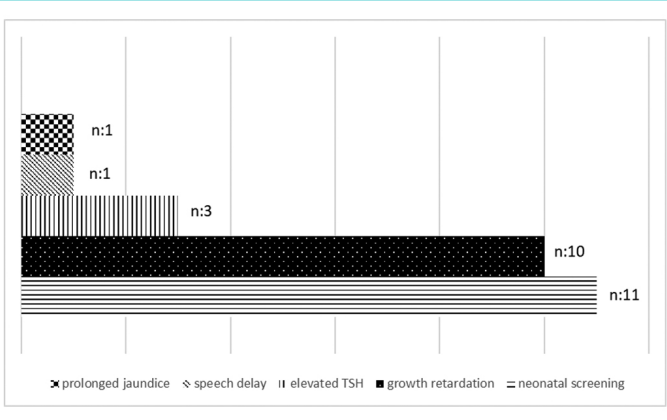

Figure 2. Manifestations of children with the ectopic thyroid gland.

n: Number

Table 1. Comparison of patients with and without neonatal screening

	Neonatal screeningavailable (mean ± SD)	Neonatal screening not available (mean ± SD)	p-value	Total (mean ± SD)
Capillary TSH (µIU/mL)	82.18±33.25	-	-	82.18±33.25
Age of diagnosis (month)	1.32±1.41	68.22±59.02	<0.001**	39.92±55.56
Venous FT4 (ng/dL)	0.44±0.21	0.45±0.23	0.36*	0.44±0.22
Venous TSH (µIU/mL)	108.33±20.41	88±28.02	0.03*	95.17±29.25
Thyroglobulin (ng/mL)	181.83±187.56	57.18±62.39	0.135*	110.60±142.15
Current age(year)	6.12±3.48	12.3±3.91	<0.001**	9.69±4.81
Current height SD	−0.45±1.14	-1.99±1.84	0.018**	−1.34±1.74
Current weight SD	−0.2±1.16	−1.18±2.2	0.016**	−0.76±1.87
Current L-thyroxine dose (µg/kg/day)	3.08±1.18	3.48±1.61	0.571**	3.31±1.43
IQ score	101.28±18.77	98.93±14.88	0.373**	99.68±15.8

*: Independent sample t-test, **: Mann-Whitney U test, TSH, Thyroid-stimulating hormone; FT4, Free T4; SD, Standard deviation.

of our knowledge, is the first study that evaluated the clinical features and long-term outcome of patients with the ectopic thyroid gland and compared patients born before and after the neonatal screening program.

All large series that evaluated patients with ectopic thyroid reported a female predominance with ratios ranging between 61% and 88%[4-7]. Our series revealed a similar rate of female predominance (76%). The exact mechanism for female predominance in patients with ectopic thyroid glands has not been fully elucidated.

Lingual thyroid is the most common form among ectopic thyroids[8]. The frequency of the sublingual thyroid gland has been reported as 47% [4], 34.6% [5], 17%[6], and 53%[7]. Our patient group, unlike other studies, reported 88.3% sublingually and 3.8% lingually located ectopic thyroids. The discrepancy between the lingual and sublingual thyroid ratios could be related to the underlying genetic and epigenetic etiologies that cause migration abnormalities during organogenesis.

The mean age upon diagnosis of patients born before the neonatal screening program (68.22 ± 59.02 months) was higher than those born after the program. No difference was found in Cattel intelligence test scores, FT4, thyroglobulin, and final L-Thyroxin dose among those who are born before and after the screening program (Table 1). Growth retardation was more prominent in patients who were born before the screening program. Despite achieving euthyroidism, after an average of 7-year follow-up, patients who were diagnosed earlier in neonatal screening had a better growth outcome compared to those without neonatal screening. However, no difference was found in psychomotor development, which suggested that a small thyroid gland might produce well-enough thyroid hormone and achieve a thyroid hormone value that can prevent neurodevelopmental delay but does not appear to achieve appropriate growth.

Compression symptoms in the lingual thyroid are more common than sublingual thyroid[4]. None of our patients had any signs of compression due to ectopic thyroid, which was attributed to the higher frequency of sublingual thyroid and the lower mean age upon diagnosis compared to the cases reported in the literature.

Patients with ectopic thyroid gland usually have an elevated TSH upon diagnosis in the neonatal period. Neonatal screening programs reported a broad range from 15 to 144 mIU/L of average TSH of patients with the ectopic thyroid gland[15,16]. Therefore, in TSH-based neonatal screening programs, there is a risk of missing the diagnosis of the ectopic thyroid gland, which has been reported as 1.6% in lingual thyroid[3]. A study that evaluated the French neonatal screening program results in

9 years revealed that 50 patients missed the diagnosis. Of those patients, 23 (4 with agenesis and 11 with ectopic thyroid) have TSH below the cut-off value assigned in the screening program[17]. Capillary TSH, which was examined twice in our patients in the national neonatal screening program, was normal in 1 (8.3%) of 12 patients (first sample TSH of 1.2, second sample TSH of 0.01). This patient was diagnosed with sublingual thyroid at the age of 2 months after the measurement of high TSH in an outpatient clinical visit. The mean TSH level was 82.23 ± 33.24 mIU/L in the remaining 11 patients. Similar to the literature, our patients have a high mean capillary TSH level, except for the case with a missing diagnosis. However, despite the low cut-off TSH value assigned in our neonatal screening program (4.5 mIU/L) compared to many screening programs, the rate of missed diagnosis of ectopic thyroid in the screening program was 8.3% (1/12) that was higher than those reported in the literature. Furthermore, an autopsy study involving 200 cases reported a 10% frequency of ectopic thyroid[3]. This high rate of ectopic thyroid gland suggests much more cases with missing diagnosis and a higher exact frequency of ectopic thyroid gland than those reported in the literature.

Scintigraphy, which requires high TSH levels during scanning, is the gold standard in ectopic thyroid diagnosis. Many centers performed scintigraphy at a later age when treatment is ceased. Those centers claim that ectopic thyroid diagnosis or agenesis does not change the treatment approach. Contrarily, USG is suggested as a non-invasive method, which is easily accessible, distinguishes between structural anomaly and normal gland, and gives information about thyroid size. Additionally, detection of vascularization in ectopic thyroid tissue in cervical USG increases the diagnostic sensitivity[2]. However, we do not entirely agree with this approach. Elevated TSH does not affect individuals with thyroid agenesis but stimulates the thyroid gland, which causes enlargement, thereby increasing the risk of compression. Therefore, scintigraphy and correlative ultrasound or vice versa are recommended as an adjunctive tool in case the first test does not provide adequate information about the localization as well as the size of the thyroid gland.

Hypothyroidism is detected in 33%-62% of patients with ectopic thyroid[8]. Hyperthyroidism and thyrotoxicosis have also been reported very rarely[4]. All our patients had overt or subclinical hypothyroidism at diagnosis. The rate of hypothyroidism was higher than that reported in the literature. Patients with euthyroid at birth may progress to overt or subclinical hypothyroidism in case of increased thyroid hormone requirement and accelerated growth such as puberty, pregnancy, trauma, and infection[1].

PH is a common problem during CH treatment. Factors, which might contribute to PH, include an inadequate dose of L-Thyroxin, patient's noncompliance, and incomplete maturation of feedback mechanism that regulates TSH secretion. TSH levels usually stabilize after the first year of treatment. PH has been shown in 20%–40% of infants with CH. However, it persists in 10% of these patients to childhood[18]. THR and ectopic thyroid can rarely coexist with PH. The etiopathogenesis of the co-existence of these two rare entities is unknown. Retinoid X receptor (RXRs), a heterodimer of the thyroid hormone receptor, plays a key role in embryonic development and organogenesis. Therefore, the relationship between mutant *TRβ* and RXRs during thyroid organogenesis has been speculated to create a dominant-negative effect, thereby causing dysgenetic thyroid gland[19].

There are four patients with the ectopic thyroid gland and THR in the literature[14,19-21], of whom three showed *TRβ* mutation. *TRβ* mutation analysis was performed in 16 patients with persistently elevated TSH and FT4 during follow-up, and mutation was not detected in any of those patients. Therefore, the persistent high TSH and FT4 are attributed to treatment noncompliance.

This study has some limitations. It was a retrospective study. Previously, when the TSH value was >100 mIU/L, the quantitative value could not be measured. Thus, the initial serum TSH value of some patients was unknown.

Therefore, in our series of 26 patients, the majority with ectopic thyroid glands were female with a predominance of sublingual thyroid. Some patients cannot be detected in the newborn screening program since capillary TSH in the neonatal screening can be below the cut-off value. In patients with ectopic thyroid who are born before the start of the neonatal screening program, overt or subclinical hypothyroidism did not affect the neurodevelopmental outcome but led to a poor growth prognosis. Patients with biochemical THR did not genetically confirm this situation, which made this association controversial and suggested to be co-incidental in previously reported cases.

Main Points

- The ectopic thyroid gland is the most common cause of permanent congenital hypothyroidism.
- Neonatal screening cannot always detect the ectopic thyroid gland.
- Subclinical hypothyroidism due to the ectopic thyroid gland may not affect the neurodevelopmental outcome but lead to poor growth prognosis in children.

ETHICS

Ethics Committee Approval: The ethical approval was obtained from the Gazi Yaşargil Training and Research Hospital Ethics Committee (document no: 19.12.2019/398).

Informed Consent: An informed consent form was obtained

from the parents of all children following the Declaration of Helsinki.

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Authorship Contributions

Conception: M.D., E.Ü., M.A., H.D., M.N.Ö.; Design: M.D., E.Ü., M.A., H.D., M.N.Ö.; Supervision: M.D., E.Ü., M.A., H.D., M.N.Ö.; Materials: M.D., E.Ü., M.A.; Data Collection and/or Processing: M.D., E.Ü., M.A.; Analysis and/or Interpretation: M.D., H.D., M.N.Ö.; Literature Search: M.D., H.D., M.N.Ö.; Writing: M.D., H.D., M.N.Ö.; Critical Review: M.D., H.D., M.N.Ö.

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REVIEW

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Current Approaches to the Concept of Occlusion in Implantology

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Abstract

Successful dental implant applications can be achieved with an appropriate indication, correctly applied surgical intervention, careful prosthetic planning, and high oral hygiene. As is known, occlusion is a very important and critical factor. The implant bone interface is not a structure that can resist the incoming forces, such as natural teeth, thus more care should be taken in the arrangement of occlusion in implant-supported prostheses. Studies showed that occlusion applied in implant-supported prostheses is the most important factor that affects long-term success. However, scientific data regarding occlusion and implementation principles are still insufficient. Therefore, this study aimed to determine the types of occlusion that are used in implant-supported prostheses following the edentulous cases and increase awareness regarding the occlusion in implant-supported prostheses.

Keywords: Implant; prosthetic restoration; occlusion; all-on-4

INTRODUCTION

Implant-supported fixed prostheses have recently become a desired treatment option in the rehabilitation of patients with lacking teeth due to their success rates.[1] Occlusion plays a functional and biologically important role in the success and longevity of prosthetic restorations.[1-3] The concept of occlusion in implant-supported prostheses has been proposed based on natural dentition and the occlusion concept in full dentures.[4]

In an ideal occlusal relationship, the loads on the teeth should be evenly distributed. Horizontal forces that can affect the teeth should be avoided or at least minimized. Therefore, the loads come parallel to the long axis of the teeth. According to Okeson[5], the muscular and skeletal stable position of the joints can only be maintained under stable and ideal occlusal conditions that are achieved by equal and simultaneous contacts of all teeth and by directing the occlusal forces parallel to the long axis of the tooth. The following are 3 acceptable occlusal schemes: (1) Balanced occlusion, (1-i) bilaterally balanced occlusion, and (1-ii) lingualized occlusion; (2) Group functional occlusion (with unilateral balance); and (3) Mutual protective occlusion, (3-i) Canine guidance, and (3-ii) Anterior group guidance.

Occlusion in Implantology

For the last 25 years, the implant application in partial or fully edentulous patients has caused changes in the prosthetic treatment options, and prostheses have been placed on the

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implant substructures. The major drawback encountered in implant rehabilitation includes implant loss. Implant loss can be grouped into two large groups. The first is the early losses that occur during the surgical protocol, and the second is the late losses after osseointegration. Late losses after osseointegration may be due to several reasons, including bone resistance, plaque formation, and excessive occlusal loading.[6] Many pieces of literature say that excessive occlusal loading can cause bone loss around the implant,[7-9] as well as mechanical complications in implants and prostheses, such as screw fractures, prosthesis, and implant fractures.[10]

Proper prosthetic knowledge and practice are required for good implant therapy. Appropriate occlusion is a critical factor in the long-term use of the implant after a successful implant application.[6] Regardless of how successful the surgical technique is, the stresses that exceed physiological limits are the main reason for bone resorption around the implant.[11] One of the important etiological factors in implant loss is trauma due to occlusion. Radiological stratification or groove observation is also associated with excessive occlusal loading.[12]

Natural dentition may show a physiological adaptation to traumatic occlusion.[12] In the function of the jaws with natural teeth, the implant bone substructure does not have forces against the forces coming to the jaws that carry the implant-retained prosthesis, whereas the periodontal ligaments have the opportunity to absorb incoming forces or allow the movement of the tooth at physiological limits. The compressibility and deformability of the periodontal ligament in natural teeth lead to differences in force adaptations compared to implants.[13] The natural tooth moves quickly between 56–108 µm and rotates in the 1/3 apical of the root during lateral loading in force application, thereby reducing the lateral forces in the tooth. Contrarily, the implant gradually moves. Under the same lateral force, implants can reach 10–50 µm.[14]

When the implant with an incorrect occlusion is not corrected for occlusion and exposed to excessive occlusal forces, the force will directly affect the implant bone interface.[12] If the formed occlusal force exceeds the capacity of the absorb tension interface, implantation will fail and the implant will be lost.[13] The implant site capacity to withstand occlusal forces depends on (i) zone difference (occlusal forces increase backward) and (ii) supporting bone quality (a stable bone without augmentation is a golden standard).

Another issue that increases the importance of occlusion in the implant-retained prosthesis is that while the natural teeth have neuromuscular mechanisms and a proprioceptive mechanism to protect them from the harmful forces upon them, no such specific mechanism for implant-retained prostheses is available. Therefore, individuals using implant-retained prostheses cannot fully control the forces during functional jaw movements, and it becomes difficult for them to notice any error in occlusion or a point where the force intensifies.[15] No periodontal ligament is determined in the basic structure of osseointegration, and the proprioceptive potential is less than the tooth. The implant is rigidly-placed, thus much less likely to be embedded or moved.[12]

With a force above physiological limits on the implants, the bone responds with resorption. The most important reason for cervical bone resorption that occurs after implantation is excessive forces due to incorrect occlusal arrangements. In addition to bone resorption, shear forces that may occur because of improper occlusion may cause cement separation in cement-retained prostheses and fracture of screws and other denture fasteners.[15] However, the structure of occlusal contacts and relationships may change due to the tooth or prosthesis, loss of tooth or implant, and mucous atrophy. Therefore, the occlusal relationships of implant-supported prostheses should be regularly checked (at short intervals of 3–6 months).[12]

Causes that Overloads Implants

Excessively long cantilevers (>15 mm in the lower jaw and 12 mm in the upper jaw): Long cantilevers applied to implant prostheses may cause overload in implants, peri-implant bone loss, and prosthetic failures.[16] When bite force is applied to the prosthesis with the distal wing, the highest axial and tipping forces are observed in distal implants. This situation was higher in those supported with three implants compared to prostheses supported with five or six implants.[16] In cases where the cantilever length is >15 mm, more implant prosthesis failure is observed than in cases of <15 mm.[17]

Para-functional movements: Para-functional movements and improper occlusal design were reported to be related to implant bone loss, implant fall, implant fracture, and prosthesis failures.[18]

Excessive premature contacts: Excessive premature contacts have been reported to cause loss of osseointegration and excessive marginal bone loss in premature contacts at 100 µm height.[18]

Wide occlusal plate: Generally, narrowing the occlusal plate by 30%–40% in the molar region is recommended. The narrowed occlusal tray will reduce the forces and the tipping moment that will come out of the long axis of the implant.[19]

Increased tubercular slopes: Studies reported that tubercular slopes are one of the most important factors in tipping moment formation. The flatness of the area around the centric contacts will transmit the occlusal forces in the apical direction.[19]

Low bone density and quality: Low-density bone will be more susceptible to occlusal forces and this will prolong the recovery time.[6]

The insufficient number of implants: Proper sharing of force between implants will increase the success rate.[6]

Ideal Occlusion in Implant-Supported Prostheses

The first study on which occlusion type is more appropriate in implant prosthesis was done by Leihom in 1983,[15] wherein Leihom suggested bilaterally balanced occlusion due to bone resorption in cases where the forces are not evenly distributed.[15] However, bilaterally balanced occlusion type has been reported to create an extremely destructive effect on the implant-supported fixed prosthesis of individuals whose bone in the posterior region is much weaker compared to other regions due to the principle of evenly distributed forces.[6]

In 1986, Jemt stated that occlusion should be in full contact in all tooth groups and tubercle-fossa relationship in maximum intercuspal position in implant-supported prostheses, and the lateral loads should be distributed in the anterior region in all eccentric movements and create a disclusion occlusion in the posterior segment.[6] This view is especially valid in full mouth fixed restorations where the lateral and posterior segments are extremely sensitive to lateral forces.[20] Therefore, the meaning of ideal occlusion in implant-supported restorations is not different from the meaning in natural dentition.

Geometry, number, length, diameter, angulation, and location of implants, type, and geometry of prosthesis, prosthetic material, fit of the superstructure, direction and severity of prosthetic loads, opposing arch status, mandible deformation, bone density, patient age, and gender can influence occlusion. Thus, determining the ideal occlusion type for implant-on-implant prostheses following a single factor is misleading. Therefore, each case should be evaluated within itself, and the appropriate occlusion type should be determined by considering all the above-mentioned factors.[21] Mericke-Stern et al.[22] listed the basic principles of occlusion in prosthesis as follows:

- Bilateral stabilization should be provided in centric occlusion.
- Occlusal contacts and forces should be equally distributed.
- There should be no conflict between the centric occlusion in the back position.
- There should be wide freedom in centric occlusion.
- Anterior guidance should be provided.
- The working and balancing sides should have lateral wandering movements without conflicts.

Occlusion in Implant-Supported Prostheses Applied Without a Single-Tooth

The most important point in single dental implants is to make prosthetic restorations that do not allow rotation. Additionally, in these restorations, the tooth form with less tubercle height inclination should be modeled and full protection should be provided in lateral and protrusive movements.[11]

The success rate of single dental implants prepared in the posterior region is relatively lower than implants that are placed in the anterior region because the height of the bone where the implant will be placed in this region is low due to restrictive anatomical factors, such as maxillary sinus and mandibular nerve. In this region, bone quantity is generally minimal and occlusal forces are higher.[23]

The largest implant that can be placed should be preferred to eliminate offset contacts. Complications such as screw and implant fracture and screw loosening can be seen due to occlusal forces. A three-point contact (tripodal centric occlusal contacts) should be provided in single-tooth restorations, the occlusal plate should be narrowed, and the occlusal plate should be shaped to direct the forces to the long axis of the implant to eliminate these complications and at least reduce their damage.[24]

In centric occlusion, the implant-supported crown should have a gap of 30 μm.[25] This distance is particularly important as the implant-supported prostheses cannot move while natural teeth can move in their periodontal sockets under heavy loads. If this occlusal space is not sufficiently provided, implant-supported prostheses are exposed to heavy loads. Additionally, patients cannot understand whether their implant-supported crowns are high because no periodontal membrane is found around their implant, with a limited proprioceptive mechanism. Faint contacts should be provided in the eccentric relationship to eliminate lateral forces. The implant is protected from excessive mechanical loads if the implant can be concealed within the natural occlusion using infra-occlusion.[25]

The patient's current occlusion will be used in single-tooth restorations. However, a single implant placed in the canine area will be under a great load while providing the disclusion of the teeth in the mouth. Group function occlusion should be preferred in these patients to distribute the incoming occlusal forces to the anterior and posterior teeth.

In restorations made, occlusion should be rechecked before and after cementation with 40-micron thick articulating paper. Bilateral and simultaneous occlusal contacts should be provided, and early contact points should be eliminated.[26]

In single dental implants, the occlusal forces on the implant should be minimized, whereas the force transmission to the adjacent teeth should be maximized.[6]

Anterior and lateral guidance should be provided on the natural tooth. Working and balancing side contacts on single-tooth restoration should be prevented.[6] Mild or moderate non-contact, hard light contact is a reasonable approach to distribute occlusal forces between the implant and the teeth in the maximum intercuspal position.[27]

Reducing the inclination of the tubercle is necessary for posterior single dental implants to create contact areas with a 1-1.5 mm flat surface oriented to the center and apply a narrowed occlusal table.[28] Wennerberg and Jemt[29] stated that in single molar implants, occlusal contact located in the center reduces bending moments, as well as mechanical problems, and implant fractures.

Occlusion in Implant-Supported Prostheses Applied in the Partially Edentulous Cases

The restoration of edentulous crests with distal extensions has been a controversial issue. There are two types of treatment approaches in Kennedy class I and II cases: 1) Planning an implant-supported prosthesis separately made from the natural dentition by placing two implants on the crest in the distal extension area, which can be screw-retained or cement-retained, and 2) dental implant supported fixed prosthesis planning using natural teeth adjacent to the toothless area with a distal implant.[11]

Canine preservative occlusion should be used with anterior teeth in the application of fixed bridges for the posterior region on the implant, implant supports in Class I or II partial edentulous cases. Thus, the forces that can come to both the alveolar bone and the support are ensured to reduce and relieve the stresses.[30]

Natural physiological dentitions often have canine preservative and group function occlusion. If these are not damaged by tooth extraction, they should not be randomly damaged with prosthetic applications. With anterior teeth, occlusion with canine guidance should be used. Thus, in lateral and forward movements of the lower jaw, the posterior teeth are separated from each other under the guidance of the canine and lose their contact.[23]

If the patient has lost canine teeth or has periodontal damage, group function is preferred. Thus, the incoming forces are distributed between the teeth and implants without concentrating on the implant. With small molars in the mouth, group function is also preferred.[11]

In Kennedy's class III cases, the distance between the implants and the occlusal surfaces of opposing teeth should be 30 µm during light or medium contact of natural teeth located in the anterior or posterior toothless area, as in single-tooth implants. Loading should be as axial as possible and contact should be avoided during protrusive and lateral movements.[27] In Class III and IV partial edentulism cases, group functional occlusion or canine guidance occlusion type should be used.[31]

In the group function, all buccal tubercles of the working teeth side are in contact, whereas no contact should be made with any teeth on the balance side. The group function closure type is used to distribute the incoming loads to all implant supports without concentrating on a single implant and prevent excessive lateral forces on the implant.[11]

Group function or unilateral balanced occlusion establishment is necessary in cases where canines are extracted or periodontally damaged. Fully adjustable articulators should be used to ensure occlusion.[30]

In Kennedy class IV cases, in maximum intercuspal position, contact with the anterior teeth should be avoided and loads should be covered by the posterior natural teeth. If an implant is located in the canine area, the clinician has to decide whether to include this implant in lateral movements.[27]

The following factors should be considered in Class IV Anterior restorations:[30]

- If fixed restorations are to be made, no contact should be created between the teeth in the anterior region.
- In patients with anterior removable restoration, the anterior artificial teeth should not have contact or should be passive, occlusal contact should be in protrusive or lateral movements.
- If a flat (monoplane) occlusion is chosen, anterior tooth contacts should be preferred during the function.
- The distal tipping moment at the anterior bridges should not exceed the anteroposterior length of the implant.

Occlusion in Implant-Supported Prostheses Applied in the Fully Edentulous Cases

Occlusion in Implant-Supported Overdenture Prostheses

Balancing the forces is extremely important in both jaws. If the opposite jaw is toothless, an implant-supported fixed prosthesis should not be the first choice. A mandibular overdentures supported by two implants would be more appropriate for planning when using a flexible attachment that provides mobility. The occlusal loads are equally distributed to two implants by placing the implant in the canine areas in the anterior region and connecting these implants with a bar. In mucosa-implant-supported prostheses, 4 implants are placed in the anterior region of the mandible and combined with a bar.[31]

With sensitive and easily irritated mucosa, alveolar nerve pressure due to mandibular bone resorption, a gag reflex, and a knife-ridge crest or sharp mylohyoid edge, only implant-

supported overdentures should be preferred. The support of 4–6 implants between the mental foramina is used. Function in the posterior region is provided by the bilateral extensions of the prosthesis. If the opposite arch contains natural teeth, this type of overdenture prosthesis is preferred to ensure correct stress distribution.[31]

Under normal conditions in overdentures, bilaterally balanced lingualized occlusion is recommended in a patient with a normal crest. Monoplane occlusion should be used in excessively resorbed crests.[22] A consensus that bilaterally balanced occlusion is advantageous in terms of the stability of overdenture is made; however, not many clinical studies compared it with other occlusions.[6]

Peroz et al. compared balanced occlusion with canine-guided occlusion in 22 patients using traditional complete dentures in their clinical study. Using an analog scale, canine guidance was shown comparable to balanced occlusion in prosthetic retention, aesthetic appearance, and function.[6] Çalıkkocaoğlu[20] stated that lingualized occlusion should be used instead of a balanced occlusion in implant-supported overdenture prostheses.

In conclusion, when adjusting occlusion in implant-supported overdenture prostheses applied to a fully edentulous patient, a lingualized or balanced occlusion type should be preferred since the posterior area is supported by the mucosa, whereas the anterior region is supported with prosthetic attachments. Additionally, the tubercles in the teeth used in the removable dentures should be at a slope that will not interfere with horizontal movements. The occlusal plate width should also be narrower than normal prostheses.

Occlusion in Implant-Supported Fixed Full-Arch Prostheses

Bilateral balanced occlusion is recommended in cases with complete dentures in the opposing arch for full-arch fixed prostheses. Canine-guided occlusion is recommended in cases with the natural tooth in the opposing arch or cases with the upper and lower fixed implant-supported prosthesis. Some studies suggested providing mild anterior guidance in situations opposing to the natural tooth.[6] Group function occlusion is recommended in cases where the implant cannot be placed in the canine area due to anatomical conditions.[12] Recently, the literature suggests lingualized occlusion as the ideal occlusion in implant-supported fixed or removable prostheses.[12]

Bilateral and anteroposterior simultaneous contacts are reported to be obtained at the centric relationship and maximum intercuspal position to distribute occlusal forces during navigational movements.[6] Contact should be removed in lateral movements in the areas where cantilevers are applied. Providing 1–1.5 mm of freedom in the centric relation in occlusal contacts will prevent premature contacts that will occur during function.[32] Working side contacts that are anteriorly placed are recommended to prevent posterior overload.[33] If there is a cantilever extension in full-arch fixed restorations, providing a small (100 µm) infra-occlusion to the cantilever area will reduce the load on the prosthesis.[6] Higher success has been reported in prostheses with a cantilever length of <15 mm in the lower jaw. Cantilevers <12 mm should be applied in force direction and bone quality in the upper jaw. Today, the optimal amount of distal cantilever is recommended as only 7 mm.[12]

Two occlusal planes are defined and recommended for full-arch implant-supported fixed prostheses: (a) canine-guided occlusion and (b) lingualized occlusion. Only the posterior teeth are in contact with the centric relationship in the canine-guided occlusion concept. The upper palatal tubercles and lower buccal tubercles are closed by the fossa of the opposing teeth. The posterior teeth are in disclusion and the incisal edges guide the lower jaw in the protrusive movement. In lateral movements, it guides along the lingual surface of the upper canine, the distal slope of the lower canine, and the mesial slope of the buccal tubercle of the first premolars.[15] Thus, the anterior teeth protect the posterior teeth or implants against destructive lateral forces during eccentric movements. This occlusion is defined as the most effective occlusion type in terms of chewing, and at the same time, is highly preferred for optimum aesthetic appearance.[12] However, the creation, alignment, and regulation of such an occlusion require significant laboratory and technical experience and a good clinical experience. Canine-guided occlusion requires multiple and simultaneous posterior contacts. These contact points should be in the form of a tripodal tubercle-fossa relationship. Lateral forces should be avoided as much as possible.[34] The creation and arrangement of such complex contacts is a very difficult procedure for full-arch implant-supported prostheses. Chairside occlusal arrangements are usually required.[12]

Alternative occlusal planes were proposed after it was realized that the preparation and maintenance of the canine-guided occlusion were difficult and time-consuming. Lingualized occlusion is generally recommended for full-arch implant-supported restorations. Their purpose is similar, but the major benefit of this occlusal plane is its ease of application and adaptation. It directly transmits the incoming forces to the long axis of the implants. No contact was made between the lower buccal tubercles and the upper palatal tubercles. Preparation time in the laboratory is reduced and this occlusal plane defines posterior occlusion, which is more easily observed in the laboratory and clinical environment and therefore unwanted occlusal contacts can be identified and corrected more easily.[12] A minor disadvantage of the lingualized occlusion type is the slight gap between the buccal tubercles of the lower teeth and the upper teeth. This gap does not create aesthetic problems as it occurs in the posterior region of the arch.[34] Especially in full-

arch implant-supported fixed restorations, the occlusion should be well evaluated, and the incoming forces should be equally distributed. Therefore, help can be obtained from computer-aided occlusal analysis methods (T-scan system).[18]

Both quantitative and qualitative methods are used to evaluate occlusal relationships. Using qualitative methods, only the occlusal contact point localization can be determined. Among the quantitative methods used in the occlusal relationship evaluation, T-scan and photo-occlusion systems are used to align the contacts and determine their density. Especially in full-arch fixed implant-supported restorations, occlusion should be well evaluated and incoming forces should be equally distributed.[12]

The T-scan system consists of a sensor, handle, processing unit, and an installed printer. When the patient correctly bites the sensor, it turns into data on the closing screen. This occlusion analysis method shows the pressure of occlusal contacts and the changes in this pressure within the time until maximum contact occurs, as the patient begins to bite the sensor.[3] It gives information on the early contacts after the onset of occlusion. Since the occlusion paper marks all contacts, information about which contact occurs first is not provided.[12] The T-scan occlusal analysis method is used for the following purposes:

- Compensating occlusion during dentin rehearsal of full-arch restorations
- Balancing after trial and finishing of complete dentures
- Balancing the splint in patients with temporomandibular joint problems
- Elimination of early contact of implant-supported prostheses
- Adjusting the pressure on the implants as desired in implant studies
- Balancing occlusion after all orthodontic work
- Determining the location of occlusion-induced pain that cannot be localized by the patient.[12]

Occlusion in Natural Teeth Implant-Supported Fixed Prostheses

Skalak[35] and Sullivan[36] reported that connecting implants to natural dentition is a potential danger for implants and teeth. Various studies[37-39] suggested the use of non-rigid connections between natural teeth and implants. Additionally, some implant systems have tried to imitate the periodontal membrane using resilient elements between the implant and the superstructure.

If the number, axis, and position of the implant are in doubt, the attachment of the natural tooth to the implant with rigid attachments is thought to provide additional support to the implants.[40] Gunne et al.[41] reported that tooth implant-supported prostheses have no negative effects on the success rate and can be recommended as a safe treatment alternative.

The idea of connecting natural teeth with implants has been discussed for a long time. Connecting the implants placed rigidly in the bone and teeth that have certain mobility is less preferred. Providing an ideal occlusion in fixed prostheses that receive support from these two structures that are connected with the bone in completely two different ways is quite difficult.[34]

Distributing the force equally in restorations where implants that can move 10–50 microns in the bone are attached with natural teeth with the elasticity and adaptation capacity of the periodontal ligament is difficult. Occlusion is much more difficult to adjust in tooth implant-supported prosthetic restorations as it is unstable due to minor dentition changes.[23]

A detailed study about the occlusion in this type of prosthesis with one or more implants in the posterior region and natural teeth in the anterior region is unavailable, thus a gap of 30–50 µm is recommended between the opposite arc to reduce the moment of force on the implant. The loads from light and moderate contacts are transmitted to the alveolar bone employing natural teeth. The load at higher contact is distributed between the natural tooth, the implant, and the prosthesis.[27]

Occlusion in All-On-4 Prostheses

All-on-four treatment concept has been developed to maximize the use of existing bone in atrophic jaws, achieve immediate function, and avoid both regenerative procedures that increase the cost of treatment and disease duration and the complications inherent in these procedures.[42] The protocol developed by Malo et al.[43] immediately loaded a temporary fixed prosthesis using four implants in fully edentulous jaws. While the foremost two implants are placed axially, the posterior implants are placed distally at an angle of up to 45° to minimize the cantilever length and allow the application of prostheses including up to 12-unit teeth.[43,44] High survival rates have been observed in implants in this concept.[45,46] However, some mechanical and biological complications associated with this concept were reported.[46-48] Occlusal overload is associated with the load after mechanical treatment, thus success becomes difficult when occlusal compliance is not optimized.[6,49]

Kim et al.[6] conducted a literature review to determine the preferred types of occlusion in implant prostheses. Accordingly, based on the condition of the prosthesis in fixed prostheses on implants, bilateral balanced, group function, or canine-guided occlusion may be preferred. However, Kim et al.[6] reported that this information was not supported by sufficient evidence. Scientific evidence on the type of occlusion to be preferred in the All-on-Four concept, which is a relatively new treatment concept,

is limited, and consensus statements have been formulated but remain controversial.[50,51]

Many studies treated interferences in excursive dynamic movements through the establishment of centric and lateral contacts within the inter-canine zone in attempting to secure mutually protected occlusion.[52-54] Tallarico et al.[47] used mutually protected occlusion with anterior guidance or balanced occlusion in cases of opposing natural dentition, fixed prosthesis, or complete denture. Ayna et al.[55] described the use of pressure-sensitive film in occlusion control of All-on-Four prostheses using a software application called Appendant.

Türker et al.[56] used different types of occlusion (bilateral balanced, group function, canine-guided, lingualized, and monoplane occlusion) in acrylic prostheses prepared according to the All-on-Four concept in the maxilla and mandible, and occlusal relation that occurs during chewing. He evaluated the stress distribution on the implants and alveolar bone based on the load using the finite element analysis method. He stated that the lowest stress values on alveolar bone and implants were observed in canine-guided occlusion.

Türker et al.[57] examined the stress values created by different types of occlusion (group function, canine-guided, and lingualized occlusions) on abutments, screws, and prostheses using the 3-dimensional finite element analysis method in the All-on-Four concept. Within the limits of the study, group function occlusion can be recommended to reduce stress on screws, abutments, and prostheses in the All-on-Four concept.

CONCLUSION

The prosthesis type and occlusion to be arranged should be determined by considering the patient's current occlusion and biomechanical parameters, such as implant orientation, bone density, and functional surface area dimension. No single special form of occlusion is determined in oral implantology. With a short-span fixed partial prosthesis or a single implant-supported crown constructed, the centric relationship and maximum tubercle contact should be provided, but the tubercles should not interfere in the eccentric position. When conventional prostheses are applied in class I and class II restorations, posterior disclusion should be applied. In class III and class IV restorations, the patient's current occlusion or group function occlusion should be applied, just as in individuals with natural teeth. The occlusion type of prosthesis on multiple implants made in a fully edentulous patient should be preferred as canine-guided in the presence of natural teeth in the opposite jaw, and bilaterally balanced occlusion in the presence of a full prosthesis in the opposite jaw. Çalıkkocaoğlu[20] stated that lingualized occlusion should be used in overdenture prostheses.

Main Points

• The establishment of correct occlusion has clinical significance for the long-term success of the implant-supported prosthesis.

• Excessive occlusal loads may cause bone loss, as well as mechanical complications, in implants and prostheses, such as screws, prostheses, and implant fractures.

• No single special form of occlusion is determined in oral implantology. The occlusion type has to be separately selected for each case.

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Authorship Contributions

Conception: S.O.; Design: S.O.; Supervision: S.O.; Data Collection and/or Processing: B.G.A.; Analysis and/or Interpretation: B.G.A.; Literature Review: Ö.Ö.; Writing: Ö.Ö.; Critical Review: Ö.Ö.

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