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The Medical Bulletin of Haseki

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Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

The aim of the Medical Bulletin of Haseki is to publish original research papers of the highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

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The Medical Bulletin of Haseki

Instruction to Authors

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Ethical committee approval may be requested by the Editor or Associate Editors for clinical research studies. Authors are responsible for the contents of the manuscripts and for the accuracy of the references.

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The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can create at http://orcid.org.

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Articles sent to the editor for publication should be written single-sided on A4 pages, double-spaced in 12-point, arial/times, new roman font and with 2.5 cm margins. Abbreviations must be explained clearly in parentheses in their first instance within the text and custom abbreviations should not be used. Numbers 1 to 10 should be given as text (In the two treatment groups the second day) and numbers 11 or bigger given as numbers. However, numbers 1-10 with a descriptive suffix should be given with numbers (1 year) while numbers that start sentences (Fifteen-year-old female patient) should be given as text.

The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

The rules for the title page, references, figures and tables are valid for all types of articles published in this journal.

Patients have a right to privacy. When not essential, identifying information, patient names and photographs should not be published, unless the written informed consent of the patient (parent or guardian) has been given.

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"Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated.

Results should also be given in detail to allow the reproduction of the study.

The Discussion section should provide a correct and thorough interpretation of the results. The references should be directly related to the findings of the authors.

Study Limitation should be detailed in the section.

Conclusion section should provide highlighted and interpreted with the study's new and important findings.

Acknowledgements should be as brief as possible. Any support should be acknowledged in this section. (Acknowledgements should be only send with the "Cover Page".)

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

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The reference list should be typed on a separate page at the end of the manuscript. If there are more than 6 authors, abbreviation of "et al." should be used for the authors out of the first three. Journal titles should be abbreviated according to the style used in the Index Medicus. All the references should be written according to the Vancouver system as follows:

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Case Report

Original Article

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Validity and Reliability of the Turkish Version of the Physicians Spiritual Well-Being Scale

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Abstract

Aim: This study was undertaken to translate and adapt the Physician's Spiritual Well-Being Scale into the Turkish language and investigate its validity and reliability for Turkish physicians.

Methods: This methodological study was conducted on a sample of 162 physicians at different public and private institutes in Istanbul province, Turkey, between February and March 2022. Principal Component Analysis was applied to the data of the sample group to reveal the structural similarity between the original form and the Turkish version of the scale. The scale's reliability was confirmed by evaluating Cronbach's alpha's internal consistency.

Results: The factor analysis confirmed the four original factors of the PSpWBS: "self-esteem", "care for the patient", "interpersonal relationships", and "meaningful life". The total explainable variance was 54%. Factor analysis showed that the internal consistency Cronbach alpha value for the scale was between 0.645 and 0.889.

Conclusion: The Physician's Spiritual Well-Being Scale has satisfactory reliability and validity and could be used for the assessment of the spiritual well-being of a physician.

Keywords: Spiritual well-being, physician's spiritual well-being, cross-cultural adaptation, reliability, validity

Introduction

The concept of burnout, one of the most frequently used words today, was used in the 1970s in the USA to describe the emotional and physical exhaustion experienced by employees working in customer service. Burnout refers to the individual's perception of exhaustion, depersonalization, and a decrease in the will to succeed (1). Burnout is quite common in the health professions (2). Burnout, which is already relatively high in the health professions, is extremely high among physicians. It is probably inevitable for a physician to experience temporary burnout throughout his or her professional career (3).

We do not see a complete definition of physician health in the literature. To support physician health, there are efforts and publications aimed at increasing spirituality and self-reflection (4). In addition, workshops, conferences, and other multidimensional programs have been aimed at supporting this issue (5,6). However, well-being is a different concept, and if we do not know what this concept is, we will also not be able to tell if all these studies have worked. Many people who deal with physician health within the framework of burnout attribute being healthy to whether they have burnout. However, this understanding is as inadequate as defining health as the absence of disease. Applying this general definition of health to physicians is also insufficient due to the internal contradiction of balancing their personal lives with being a physician. The physician-patient relationship is significant to the provision of health services, and there are many studies showing the importance of this (7). From the receipt of the patient's medical history to the creation of a treatment plan, the physician's relationship with his patient is based on effective communication. In patient-physician encounters, both verbal and nonverbal forms of communication affect effective communication.

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Although most of the communication in these interactions involves sharing information about diagnosis and treatment options, most doctors agree that these encounters are related to the patient's psycho-social healing connection or treatment (8).

Physician-patient communication affects the behavior and attitudes of the patient regarding disease and increases compliance with treatment (9,10). Health services can be provided in public, private, and university healthcare institutions, and there are differences between work-related stressors in these institutions. These differences, in turn, can lead to differences in physicians' well-being. In addition, it is not well known how some work-related psychosocial factors, such as role ambiguity and patient or teamwork-related problems, affect physicians' spiritual well-being. However, studies have shown that patient-related stress and role ambiguity may be related to physicians' well-being (11). Little is known about the role of these specific psychosocial stressors in the well-being differences between physicians working in different health sectors, such as primary and secondary healthcare and the private sector. Even though there are reasonable efforts to enhance well-being, reduce psychosocial distress and health problems, and increase the ability to work, physicians must show the behavior of responding to the needs of patients that replaces their interests, and this is a professional rule (12). From this perspective, they receive training to learn self-sacrifice as a part of their professional identity. This situation accustoms physicians to the idea that thinking about their patients health is secondary (13). If well-being means balancing work and personal life, it may not be possible for physicians to achieve well-being (14).

Physicians' well-being affects their attitudes toward their patients, the quality of care, and patient-physician communication (15). For the communication between the doctor and the patient to be healthy, many conditions depend on the patient and the doctor. One of these conditions is that the physician is in a state of spiritual well-being.

There are many studies on spiritual well-being, but these studies generally focus on patients' spiritual well-being and the relationships between spiritual well-being and coping with diseases. Spiritual well-being effectively affects individuals' physical and mental health (16). However, physicians also play a critical role in a patient's ability to cope with the disease. To establish a healthy patient-physician relationship and communication, the patient and the physician must have spiritual well-being. Burnout, job satisfaction, and physicians' mental health have been examined in patient-physician communication, but the physician's well-being has not been adequately studied. The well-being of the physician also affects the well-being of the patient. Patients need a healthy physician with spiritual well-being. It should not be forgotten that physicians are only humans and cannot control the life or death of their patients. However, it is expected that physicians who care for terminally ill patients will be able to do this. Even under this pressure and expectation, physicians should pay attention to their spiritual well-being and burnout. In studies conducted in Turkey, concepts such as burnout, depression, and anxiety have been extensively studied by researchers. In studies conducted in Turkey, concepts such as burnout, depression, and anxiety among physicians have been intensively investigated by researchers. However, the concept of spiritual well-being, that is, looking at their health from a holistic perspective, has been neglected. This study was undertaken to translate and adapt the Physician's Spiritual Well-Being Scale (PSpWBS) developed by Fang et al. (17) into the Turkish language and investigate its validity and reliability for Turkish physicians.

Methods

Compliance with Ethical Standards

Ethical approval was obtained from the Ethical Committee of Istanbul Sabahattin Zaim University (date: 28.01.2022, decision no: 2022/01). Consent was obtained from the study participants before the interview. The research process was conducted in accordance with the principles of the Declaration of Helsinki.

Sample Group

This methodological study examined the reliability and validity of PSpWBS. This study was conducted at health institutions in the Istanbul province of Turkey. A total of 162 physicians working in family medicine, public training and research hospitals, public service hospitals, university hospitals, community health centers, and private hospitals participated in the research from February to March 2022. Eligible participants were physicians who graduated from medical school. Physicians working in Istanbul province who agreed to participate in the study were included in the sample. The study used a convenience sampling strategy to provide easier access to participants when selecting participants from different organizations (18). The physician chief and other physicians recognized by the researchers were contacted via WhatsApp and phone. We prepared online questionnaire forms using Google Forms and distributed them to the physician chief and physicians through WhatsApp and e-mail. On the first page of the online survey, physicians were informed about the research, given contact information for the research team, and presented with an informed consent form.

Many different approaches are put forward in the literature to determine the sample size. The general validation study approach involves collecting 5 to 10 subjects for each question on the scale (18-22). Physician's Spiritual Well-Being Scale has a total of 25 items. In determining the sample size, the recommended sample size for methodological research is 125 physicians, which is at least five times the number of scale items (25 items) (23). Until this number was reached, all physicians who met the criteria were included in the study. As a result, 162 physicians were included in the study. This sample size provided more than the minimum requirement of five participants per item needed for psychometric testing (20,22). Accordingly, the sample size was considered adequate. Data were obtained by the online survey method. The personal information and scale forms applied to physicians were sent to the participants via Google Forms. Informed consent was obtained on the first page of the online survey. After a sufficient sample size was reached in the study, the application was terminated. Each participant took approximately 10 minutes to answer the data collection form.

Data Tools

The questionnaire form to be used in this study consists of two parts. The first part used the "Personal Information Form" created by the researcher and asked for the participants' demographic information. The second part used PSpWBS developed by Fang et al. (17).

Personal Information Form: It was created by the researcher and consisted of questions questioning the characteristics of physicians (gender, professional working years, marital status, specialization, academic title, managerial position, institution type, etc.).

Physician's Spiritual Well-Being Scale: The PSpWBS is a measurement tool developed by Fang et al. (17) to determine a physician's spiritual well-being. In the study of adaptation to Turkish, the name of the scale was used as "Physician's Spiritual Well-Being Scale", which has the same meaning as the original name because it is thought that it will reflect the content of the scale well. In the original 25-question scale, five questions were removed as a result of the analysis. Physician's Spiritual Well-Being Scale consists of 20 questions and four factors: "self-esteem", "care of the patient", "a meaningful life", and "interpersonal relationship". The participants evaluated the scale items with the help of a five-degree Likert scale (1= never to 5= always). Cronbach's alpha internal consistency of the original scale for each factor was between 0.625 and 0.794; Cronbach's alpha reliability coefficient of the overall scale was 0.864 (17). Accordingly, the scale has satisfactory reliability and validity and is the basis for assessing a physician's spiritual well-being.

Procedures

There is no universal agreement about adapting an instrument for use in a different cultural setting (24). However, there is a consensus that it is not appropriate to translate a questionnaire and use it in another linguistic context (25). Studies may have an extensive linguistic translation process, but more is needed to ensure construct validity and reliability (26). Similar steps have been proposed for scale adaptation studies in this context (24,27). To adapt the PSpWBS into Turkish, diverse methods were used to ascertain content, semantic, and technical equivalence. The essence of semantic equivalence is that the meaning of each item remains the same after translation into the target language (28). Back translation is the most common and highly recommended procedure for establishing semantic equivalence (29,30). In this study, the translation-retranslation procedure suggested by Brislin (1986)was followed in adapting PSpWBS to Turkish (29).

Translation and Structure Validity

This stage was based on the method proposed by Brislin (29) for adapting tools developed in a language other than the target language. This method involves a process of initial translation into the target language, evaluation of the initial translation, back translation into the source language, re-evaluation of the back translation, and consultation with experts.

Phase I: First Translation: First, a total of three people, including two native Turkish-speaking faculty members who are fluent in English and have conducted scientific research in the field of spiritual well-being and one native Turkish-speaking person from the field of English linguistics, translated the scale items from English, the source language, into Turkish, the target language.

Phase II: Synthesis of Translations: In the second stage, similar and different translations of the three different translations were combined to form a single form. This form with similar and different Turkish translations was sent to three faculty members who conducted research in the spiritual well-being field, experienced scale adaptation, and had a good command of English and were asked to select the Turkish translations that best represented the English original. The translations were reviewed for consistency, comprehensibility, word and sentence structures, and cultural appropriateness. After some changes were made as a result of the first evaluation, a consensus was reached.

Phase III: Back Translation: At this stage, all items agreed upon in the previous stage were sent to two foreign language experts different from the ones who did the first translation for back translation from Turkish to English, whose native languages were Turkish and English.

Neither the re-translator was familiar with the concepts under investigation nor had a medical background. This would increase the possibility of avoiding information bias and revealing different meanings of the items in the translated scale (26). This process validated the tool's content and identified inconsistencies or conceptual mistakes.

Phase IV: Synthesis of Back Translations: At this stage of the translation process, two experts who are native Turkish speakers fluent in English and experienced in adapting measurement tools examined all items in the first three stages in detail. These two experts determined the Turkish translations that best expressed the items in the original language, discussed all items until consensus was reached, and finalized the scale items. As a result of this process, it was decided to use the final version of the scale in the current study.

Phase V: Testing of the Pre-Final Version: To test the comprehensibility of the scale items for which language and content validity were ensured, the instrument was administered as a pre-test to twenty physicians with characteristics similar to those of the sample group in this study. In the pre-test, the participants were asked to explain each item, and notes were taken by the researchers on whether the participants understood the item referred to. In the preliminary study, the researchers made final semantic edits to the compiled version in line with the responses. The Turkish scale was finalized after discussion with three physicians regarding the physician's spiritual well-being.

Statistical Analysis

This study used IBM SPSS Statistics for Windows Version 24.0 for data analysis. Expert opinions were taken for content validity. In the current study, principal component analysis (PCA) was used, and the criteria for selecting factors included the eigenvalue (>1), at least 5% of the explainable variance. For the reliability analysis of the scale, internal consistency measurements (Cronbach's alpha coefficient) and item-total correlation measurements were performed. The significance level was set at = 0.05. Before PCA, the Kaiser-Meyer-Oklin (KMO) sampling adequacy test and Bartlett's test of sphericity were used to test the factorability of the item correlation matrix. Items with factor loadings greater than 0.40 were included in the evaluation (31).

Results

Characteristics of Participants

After the translation phase, the validity and reliability study of the scale was carried out with a total of 162 physicians, 97 (59.9%) male and 65 (40.1%) female. The mean age of the physicians was 43.82 years (standard deviation=10.22) ranging from 24 to 66 years. Characteristics of participants are shown in Table 1.

Construct Validity

The final version of the scale adapted into Turkish was tested on a main sample of 162 physicians. Expert opinions were obtained to adapt PSpWBS to Turkish culture and to ensure that Turkish physicians could easily understand it. No changes were made to the items by expert opinions.

Table 1. Distribution of physicians according to characteristics (n=162)

	$\bar{x}$	SD
Age	43.82	10.224
Professional working years	18.63	10.447
	N	**%**
Gender		
Female	65	40.1
Male	97	59.9
Marital Status		
Married	135	83.3
Single	27	16.7
Academic title		
General practitioner	43	26.5
Assistant physician	13	8
Specialist physician	78	48.1
Faculty member	28	17.3
Specialization		
Basic medical sciences	9	5.6
Internal medicine sciences	64	39.5
Surgical medical sciences	45	27.8
No response	44	27.1
Managerial position		
Yes	44	27.2
No	118	72.8
Institution type		
Family health centers	18	11.1
Public service hospitals	50	30.9
Public education and research hospital	43	26.5
University hospitals	22	13.6
Class A private hospital	21	13
Non-class A private hospital	8	4.9
Have you been physically or verbally assaulted by patients?		
Yes	116	71.6
No	46	28.4
Has anyone died around you recently?		
Yes	66	40.7
No	96	59.3

$\bar{x}$: Mean, SD: Standard deviation

First, confirmatory factor analysis (CFA) was conducted on the scale adapted into the Turkish. According to the CFA results, acceptable fit values could not be reached, and it was seen that the factor loadings of many items were low and not significant. For this reason, the factor structure of the Turkish form was analyzed using PCA (32) as in the original source. The analysis, one of the oblique rotation techniques, the "direct oblimin technique," was preferred as a factor rotation technique.

Before PCA, KMO sampling adequacy was used to test the factorability of the item correlation matrix. In the current study, the KMO coefficient was found to be 0.84, and the calculated value shows that the sampling adequacy is "very good" (KMO=0.80-0.89) (28). The observed KMO value of 0.84 is within the recommended KMO value range. Therefore, the sample size in the study is sufficient. Bartlett's Test of Sphericity was conducted to examine whether the correlation matrix was different from the unit matrix. Bartlett's Test of Sphericity was found significant (χ^2=1305.231, p<0.001). Bartlett's Test of Sphericity is used to test whether the correlation matrix is a unit matrix with all diagonal terms equal to 1 and off-diagonal terms equal to 0 (33). These values indicate that the data set is suitable for PCA. Principal component analysis was applied to the data belonging to the sample group to reveal the structural similarity between the original form and the Turkish version of the scale. After PCA, items with factor loadings below 0.40 and items with high factor loadings in more than one factor were removed from the scale. Factor analysis using PCA revealed four factors with eigenvalues >1.0. Factors with eigenvalues higher than 1 were considered in determining the factors. In this context, five items (items 11, 17, 20, 21, 23) were removed from the scale, and the distribution of the remaining 20 items to the factors is shown in Table 2.

The current study examined the four-factor structure in the original research with the PCA, and the four-factor structure of the scale was confirmed; "care for patients", "a meaningful life", "interpersonal relationships" and

Table 2. Factor loadings, eigenvalues, and explained variance values after PCA

		Corrected item-total correlation	Factor 1	Factor 2	Factor 3	Factor 4
Q3	I think my existence has meaning.	0.549	0.828			
Q4	I feel that I am in optimal conditions to help my patients.	0.587	0.772			
Q1	I believe that I am capable of promoting growth in others.	0.643	0.763			
Q10	I consider that I am in a state of spiritual well-being.	0.650	0.762			
Q5	I believe comprehensive life experiences enrich my life.	0.618	0.745			
Q14	I can stabilize myself through my beliefs or religion.	0.632	0.589			
Q15	I see challenges as an opportunity to improve myself.	0.613	0.554			
Q18	Eventually everyone will die one day, so I want to appreciate every day I live.	0.585	0.524			
Q25	Taking care of patients enables me to develop self-esteem and value.	0.669	0.486			
Q6	I am not sure about the significance of taking care of terminally ill patients.	0.155		0.715		
Q19	I find it difficult to take care of my patients' spiritual needs.	0.493		0.682		
Q2	I find doctor-patient communication difficult.	0.396		0.543		
Q13	I find it difficult to take care of my patients' spiritual needs.	0.523		0.455		
Q12	When I am in a dilemma. I can share it with others.	0.271			0.685	
Q9	I find it difficult to manage my patients' physical problems.	0.318			0.660	
Q24	I can put myself in others' shoes and think for them.	0.213			0.570	
Q7	I want to explore issues that are related to myself.	0.205			0.427	
Q8	I can handle death easily.	0.256				0.798
Q16	When I think of my own death. I feel confused and uncomfortable.	0.308				0.705
Q22	I know how to deal with the sense of loss when my patient dies.	0.210				0.525
Eigenvalue			6.002	1.784	1.598	1.35
Explained variance			0.30	0.09	0.08	0.07

Factors: (1) self-esteem; (2) Care for patients; (3) interpersonal relationship; (4) a meaningful life

"self-esteem." The factor loadings of the scale items are between 0.427 and 0.828. The first factor includes nine items and the factor loadings are between 0.486 and 0.828. The explainable variance for the first factor was 30%, which included questions 1, 3, 4, 5, 10, 14, 15, 18, and 25. The content of the questions had to do with belief in oneself and self-esteem. Therefore, the first factor was named "self-esteem" as in the original scale. The second factor included four items, and the factor loadings were between 0.455 and 0.715. The explainable variance for the second factor was 9%, which included questions 2, 6, 13, and 19. These were related to "care for patients," therefore, the second factor was named 'care for patients' as in the original scale. The third factor included four items and the factor loadings were between 0.427 and 0.685. The explainable variance for the third factor was 8%, which included questions 7, 9, 12, and 24. These concerns interpersonal interaction and sharing. Therefore, the third factor was named "interpersonal relationship," as in the original scale. The fourth factor included three items, and the factor loadings were between 0.525 and 0.798. The explainable variance for the fourth factor was 7%, which included questions 8, 16, and 22. The content of the questions had to do with life philosophy, meaning of life, and life and death studies. Therefore, the fourth factor was named "a meaningful life," as in the original scale. The total variance explained for the four factors of PSpWBS was 54%. Factor loadings above 0.40 of items for the scale are presented in Table 2.

Item Analysis

Table 2 shows the corrected item total correlation and factor loadings. In the current study, the corrected item-total correlation was between 0.205 and 0.669, except for one item. The corrected item total correlation for one item is 0.155 (Q6). Since the factor loading of this item was 0.715 and the correlation coefficient was not negative, it was deemed appropriate not to remove it from the scale. The factor loadings of the scale items are between 0.427 and 0.828 (Table 2).

Table 3 shows the t-test results of physician's spiritual well-being according to upper and lower 27% groups. There was a significant difference between the scores of physicians in the lower and upper 27% percentiles of the four factors and the general scale [t(43)= -17.914, -15.860, -13.811, -18.992 and -14.485, p<0.001]. The score differences were in favor of those in the upper 27% (Table 3).

Internal Consistency

Table 4 shows the Cronbach alpha internal consistency coefficients of the factors and the correlation coefficients between the factors. In scale development studies, Cronbach's alpha analysis is used to test the internal consistency of items using Likert scale (34). For research scales, a Cronbach's alpha value below 0.60 is considered as "unacceptable"; between 0.60 to 0.65 "undesirable"; between 0.65 to 0.70 "minimally acceptable"; between 0.70 to 0.80 "noteworthy"; between 0.80 to 0.90 "very good"; and above 0.90 "the researcher should consider shortening the scale" (35). This study revealed Cronbach's alpha value as the sub-factors between 0.645 and 0.889. The internal consistency coefficient for the overall scale was 0.857 (Table 4). This value signifies the high reliability of the scale items. Although reliability can set

Table 3. T-test results of physician's spiritual well-being sub-factors according to upper and lower 27% groups (n=44)

	Groups	Mean	SD	df	t
Self-esteem	Lower 27%	2.46	0.45	43	-17.914**
	Upper 27%	4.39	0.28		
Care for patients	Lower 27%	2.16	0.35	43	-15.860**
	Upper 27%	3.91	0.40		
Interpersonal relationship	Lower 27%	2.97	0.33	43	-13.811**
	Upper 27%	4.23	0.29		
A meaningful life	Lower 27%	2.40	0.45	43	-18.992**
	Upper 27%	4.44	0.28		
PSpWBS total	Lower 27%	2.75	0.30	43	-14.485**
	Upper 27%	4.04	0.30		

**p<0.001, df: Degree of freedom, SD: Standard deviation

Table 4. Cronbach's alpha internal consistency coefficients and Pearson correlation coefficients between factors

	n	Mean	SD	Cronbach's alpha	Factor 1	Factor 2	Factor 3	Factor 4
Factor 1	9	3.48	0.78	0.889	1			
Factor 2	4	3.05	0.72	0.662	0.480**	1		
Factor 3	4	3.59	0.53	0.652	0.344**	0.258**	1	
Factor 4	3	3.54	0,83	0.645	0.323**	0.081	0.151	1

**p<0.01, Factors: (1) self-esteem; (2) Care for patients; (3) interpersonal relationship; (4) a meaningful life

an upper limit for validity, it can never guarantee validity. For this reason, in our adaptation study, content validity was also checked by having the scale examined by experts on this subject (36). In addition, there is a significant positive relationship between the factors in general (r=0.480-0.258, p<0.01). Only factors four, factors two, and factor three were not significantly correlated.

Discussion

There are many studies in Turkey on spiritual well-being, but no studies have investigated spiritual well-being in physicians. To our knowledge, this is the first methodological study in Turkey to measure the spiritual well-being of a physician using physician data. Because there are no other credible scales available at the moment to measure the SpWB of a physician in Turkey, it was impossible to make any comparisons. In the current literature, there are many measurement tools that assess the spiritual well-being of patients (37-39) and nurses (40). However, there are limited measurement tools to assess the spiritual well-being of physicians. The study aimed to examine the reliability and validity of the Turkish version of PSpWBS, which was developed by Fang et al. (17) to determine the spiritual well-being of a physician. For this purpose, data were collected from a sample consisting of physicians, and analysis studies were carried out on these data. In this regard, our findings suggest that PSpWBS adapted into Turkish is a valid and reliable measure for evaluating the level of spiritual well-being of physicians.

There are many techniques used in factorization. Principal component analysis is the most commonly used factorization technique (31). In the current study, PCA was applied within the scope of the scale construct validity. As a result of PCA (KMO value, 0.84; Barlett sphericity, $\chi 2=1305.231$, p<0.001) it was concluded that the data would reveal appropriate factors. The result of the PCA, the four-factor structure of the scale, was confirmed. In scale development studies, various criteria are used to determine the scale factor structure. Some of these criteria are that the variance explanation percentage for each factor obtained should be at least 5%, and the total variance explained should be 40% or more (21,41). The current study analyzed the validity and reliability of PSpWBS, which manifested a four-factors construct. The factors' explainable variance was between 7% and 30%. PSpWBS explains 54% of the total variance. This result ensures a considerably high variance for a scale and is thus acceptable in terms of the literature.

Item-total Pearson correlation coefficients are expected to be at least 0.20 (35). In the current study, the item-total Pearson correlation coefficients are between 0.205 and 0.669, except for one item. The item-total Pearson correlation coefficient for the 6th item was 0.155. Since the factor loading of this item was 0.715 and the correlation coefficient was not negative, it was deemed appropriate not to remove it from the scale. The factor loadings of the scale items are between 0.427 and 0.828. In the literature, factor loadings were considered high if above 0.60 and moderate if between 0.30 and 0.59 (34).

In addition, there is a significant positive relationship between the factors in general. Only factors four, factors two, and factors three were not significantly correlated. Moderate correlations between different constructs in a measurement tool can be accepted as an indicator of the fit between constructs (42). It can be said that the correlation results support the emergence of appropriate constructs. The correlations between "care for patients", "a meaningful life", and "interpersonal relationships" were not significant and should be examined in detail in another study.

The ability to discriminate significantly between groups with high and low scores on the scale establishes another piece of evidence of the internal validity of the scale (22). To test the discriminant validity of the overall scale and sub-dimensions, t-test analysis was performed for the scores in the lower and upper 27%. The results indicate that the discriminant validity of the scale between the lower and upper groups was achieved (p<0.001).

The American Psychological Association (APA, 1974) defined reliability as the freedom of measurement results from error (43). The most commonly used method to calculate the reliability coefficient in scale development and cross-cultural adaptation studies is Cronbach's alpha (44). In the current study, Cronbach's alpha internal consistency coefficient was calculated for the reliability of the scale. The reliability value of a measurement tool is desired to be above 0.70 (26). However, a value of 0.70 or below should not be interpreted as low reliability (41). Factor analysis showed that the internal consistency Cronbach value for each factor was between 0.645 and 0.889. The Cronbach alpha value for the internal consistency of the total scale was 0.857, which signified that the items in the scale had high reliability and were aimed at measuring the same concept (41). According to these results, it can be concluded that PSpWBS is at an acceptable level. Fang et al. (17) found that the internal consistency Cronbach's alpha value for each factor was between 0.625 and 0.794, and the total scale was 0.864. The scale has four reverse-scored items (2, 6, 9, 13, 16, and 19). A higher score elevated levels of spiritual well-being in the subject.

Physician's Spiritual Well-Being Scale is a suitable tool for understanding the spiritual well-being of physicians in a Turkish cultural context. Spiritual well-being is a condition that can have negative consequences for physicians and

the patients they serve. The physician's spiritual health impacts patient care and is a part of medical ethics that should be emphasized (17). Professional associations, medical education, universities, accreditation organizations, health policymakers, and physicians should consider this situation a strategic priority and a moral imperative. Physicians should focus on the status of their spiritual well-being, and it is suggested that future studies should focus on the phenomena of the spiritual well-being of physicians with the goal of developing continuing education for the promotion of spiritual well-being in physicians. In addition, physicians should develop various conceptual models to identify the factors contributing to spiritual well-being and guide interventions to increase spiritual well-being.

Study Limitations

The study has some limitations. First, since PSpWBS is a new scale, no studies have discussed the results of the scale adapted to Turkish. Future studies will help to understand and discuss the various dimensions of PSpWBS more clearly. Secondly, Cronbach's alpha reliability coefficient was preferred to evaluate the scale's reliability because it was measured at a single point in time. The reason for this is the difficulty of reaching the same physician a second time. Future researchers can re-evaluate the reliability by making measurements more than once using the test-retest method. Third, CFA was first applied to the scale adapted into Turkish; however, according to the CFA results, acceptable fit values could not be reached, and it was seen that the factor loadings of many items were low and not significant. Therefore, the construct validity of the scale was analyzed with PCA as in the original study. It is recommended that researchers who will conduct studies with the scale test the construct validity of the scale with CFA. Finally, the fact that our study is the first measurement tool that can be used to assess the spiritual well-being of physicians in Turkiye is the strength of our study.

Conclusion

The PSpWBS Turkish form is a suitable tool for understanding the spiritual well-being of physicians in a Turkish cultural context. In the current health system, there is a lot of pressure on physicians, and they carry a heavy workload. This situation affects physicians' spiritual well-being and becomes a factor that prevents them from performing the desired performance while practicing their profession. Physician spiritual health impacts patient care and is a part of medical ethics that should be emphasized. Future studies on the spiritual well-being of physicians may provide more insight into their spirituality. In addition, continued research is recommended to refine and verify its psychometric properties among physicians.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethical Committee of Istanbul Sabahattin Zaim University (date: 28.01.2022, decision no: 2022/01).

Informed Consent: Consent was obtained from the study participants before the interview.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: H.S., Analysis or Interpretation: A.B., Literature Search: H.S., Writing: H.S.

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Original Article

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Effect of Online Learning During the COVID-19 Pandemic on Tension-Type Headache, and Anxiety Among Medical Students

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Abstract

Aim: Screen exposure can lead to numerous health problems, such as headaches, in students. This study aimed to investigate the impact of online learning on tension-type headache (TTH) and its association with anxiety among medical students who attended online classes during the novel coronavirus disease-2019 pandemic.

Methods: This cross-sectional study was conducted between June 1 and 15, 2021, among preclinical medical students at the Ataturk University Faculty of Medicine in Erzurum. The data were collected via an online survey. Sociodemographic features and characteristics of online classes and headaches were collected. Anxiety levels were measured using the generalized anxiety disorder test-7 (GAD-7) scale. Questions for the preliminary diagnosis of TTH were prepared based on the International Classification of Headache Disorder Diagnosis.

Results: The mean age of the participants was 20.6±3.0 years, and 52.2% (n=297) were women. Tension-type headaches affected 323 (56.8%) students, while 246 (43.2%) had no headaches. In addition, 41.3% (n=135) of the participants with TTH reported experiencing headaches after online classes, and 47.1% (n=154) of those with TTH stated that their headache intensity increased after online classes. The mean GAD-7 score was 11.2±5.2 among the participants with TTH, compared to 8.7±5.2 among those with no headache ($p<0.01$). Significant differences were observed between the groups in terms of daily screen time ($p=0.019$), GAD-7 score ($p<0.001$), and gender ($p<0.001$).

Conclusion: The study findings indicate that TTH is common in medical students during online learning. Efforts should be made to educate students on screen use, and stress reduction programs should be included in the curriculum.

Keywords: Online learning, tension-type headache, medical student, screen time, anxiety

Introduction

The novel coronavirus disease-2019 (COVID-19) caused a global pandemic in March 2020 (1). Millions were infected and died during the pandemic, and COVID-19 poses a serious worldwide threat to public health (2). The COVID-19 pandemic has also led to radical changes in global education systems. As educational institutions closed down, the severe acute respiratory syndrome Coronavirus-2 pandemic resulted in the imposition of e-learning in medical education. Many countries have resorted to online classes to reduce the rate of transmission of the virus (3).

Clinical rotations were canceled or replaced during the pandemic, and exams were temporarily suspended or conducted online. The epidemic quickly transformed traditional face-to-face teaching into an online classroom activity. While university courses were held online, educational activities, including meetings, continuous professional development activities, congresses, assignments, projects, presentations, and exams, were also moved to the online platform (4,5). This new training

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system resulted in additional time spent in front of a digital device. In our previous study, 94% of medical students reported that the time they spent in front of the screen increased during the pandemic (5).

Prolonged exposure to these devices can lead to numerous health problems in students, such as headaches, eye strain, anxiety, neck and back pain, and sleep disorders (6). Perez-Dominguez et al. (7) concluded that while screen time differed across the countries surveyed, students' mental and physical health was adversely impacted (backache, eye fatigue, etc.). One of the health-related consequences of online learning is headache. The most common type in the general population is tension-type headache (TTH), the second most common disease worldwide (8).

Stress and posture are known causal factors, while modern living conditions also impact headaches. The increased use of digital technologies has also recently been linked to headaches (9). Patients with TTH typically suffer from mild or moderate bilateral compression-type pain attacks with no worsening caused by physical activity, lasting from 30 minutes to seven days. No nausea or vomiting occurs, although autophobia or phonophobia may be present. According to the IHS, patients experiencing at least 10 headache episodes with these characteristics are diagnosed with TTH. Tension-type headaches occurring once or less per month are classified as sparse episodic, and TTH occurring on more than one but fewer than 15 days a month are classified as frequent episodic. Chronic TTH is defined as headaches on 15 or more days a month (10).

Tension-type headaches adversely affect mental skills such as memory, attention, concentration, and reading (11). Factors affecting TTH development include mental stress, sleep problems, hormonal fluctuation, postural tension, and forward head posture (12). Headache-related absenteeism from the workplace on several occasions a year is reported in 10% of individuals with TTH (13).

During the COVID-19 pandemic, lockdowns, restrictions, and quarantine aimed at preventing the spread of the disease, the closure of university campuses and public areas such as cinemas, gymnasiums, and cafes, the transition from face-to-face education to distance education, and students continuing their education from home prevented them from socializing and resulted in stress and anxiety. Both the use of distance courses and students' quest for self-learning, knowledge, and socialization on social media and online platforms have led to an unprecedented use of technological devices and an inevitable increase in screen time (4). Spending extended periods in front of screens due to online learning, which became mandatory in medical schools with the COVID-19 pandemic, can contribute to the development of TTH by causing postural abnormalities, sleep problems, and stress. Understanding the relationship between medical students' online education experiences and headaches will allow the development of preventive strategies. To the best of our knowledge, no previous studies in Turkey have investigated the frequency of TTH in online learning among medical students.

This study investigated the impact of online learning on TTH and the association with anxiety among medical students who attended online classes during the COVID-19 pandemic.

Methods

Ethics Approval and Consent to Participate

Ethical permission for the study was obtained from the Ataturk University Faculty of Medicine Ethical Committee (IRB number B.30.2.ATA.0.01.00/250-03/26 dated 15.04.2021). The study was conducted following the principles of the Declaration of Helsinki. All participants in this study signed an informed consent form.

Study Design

This cross-sectional study was conducted between June 1 and 15, 2021, among preclinical medical students at the Ataturk University Faculty of Medicine in Erzurum, Turkey. The study population consisted of 930 preclinical students at the Ataturk University Faculty of Medicine.

Medical training in Turkey lasted six years, the first three of which are known as the preclinical period. As of June 2021, preclinical semester student education was provided solely online. No face-to-face educational activities were held, such as theoretical courses, laboratory and practical applications, exams, assignments and projects, student congresses, meetings, or elective courses. Only preclinical semester students who took all relevant courses online were included in the study. Students in the clinical period who attended face-to-face courses were excluded.

Participants and Data Collection

The students were informed about the aim of the study and were then invited to participate. One hundred twenty-eight students did not respond. Thus, data were collected from 802 students, with a survey response rate of 86.2%. Of these, 54 forms were excluded from the analysis because they were incomplete or left unfinished. One hundred seventy-nine participants with migraine symptoms and other types of headaches were also excluded. All the excluded students with migraines and other types of headaches were referred to a neurologist. The final analysis thus involved complete data from 569 students (Figure 1).

The data was collected via a web-based survey created using Google Forms. The survey questions were prepared by the researchers based on previous literature.

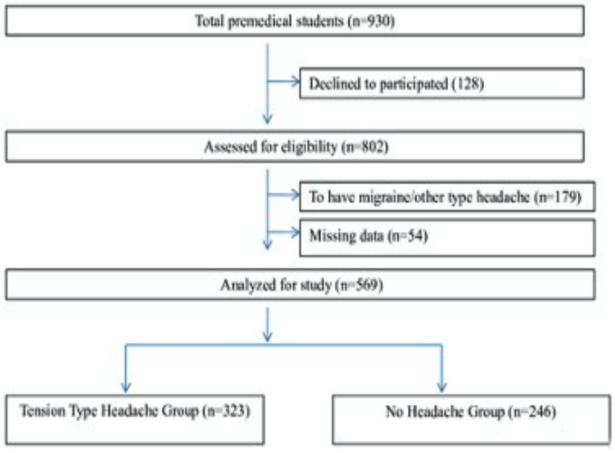

Figure 1. Flow chart of the participants

The survey was piloted with 20 students before being finalized. The students were invited to participate in the study through WhatsApp® groups. The survey link was shared with the students via WhatsApp® groups specific to preclinical students. Participation was entirely based on voluntary consent. The students were allowed two weeks to respond to the survey. Two reminder messages were sent during that time on a weekly basis. No questions required any personal information to be given. The first item in the survey was "I voluntarily consent to participate in the study", and students could not move on to the questions without responding. Online consent was thus obtained. The data collection was terminated after two weeks.

The data collection tool consisted of four parts: (1) socio-demographic features; (2) questions about online classes; (3) questions about headaches; and (4) the generalized anxiety disorder test-7 (GAD-7).

The sociodemographic questions consist of concerning age, gender, class, the online class linking tool employed, the device screen size, and daily screen time.

To establish a preliminary diagnosis of TTH, students were asked whether they experienced headaches and, if so, when these headaches started, their frequency, character, and duration, the severity of the pain, and accompanying findings. Questions for the preliminary diagnosis of TTH were based on the International Classification of Headache Disorder Diagnosis (10).

The GAD-7 measured the participants' anxiety levels. This valid and reliable tool for scaling generalized anxiety disorder was developed in 2006 by Spitzer et al. (14). It was subsequently adapted to Turkish by Konkan et al. (15). Generalized anxiety disorder test-7 investigates participants' symptoms related to anxiety over the past two weeks. It is answered and scored on a 4-point Likert-type scale (0=almost nothing, 3=almost every day). Possible scores ranged between 0 and 21. At a cut-off score ≥10, the GAD-7 has 89% sensitivity and 82% specificity in determining generalized anxiety disorder (14). The Cronbach's alpha value in this study was 0.86.

Each student was allowed to complete the questionnaire only once. No questions required the students to identify themselves. The data were checked by two researchers following online collection.

Statistical Analysis

Statistical Package for the Social Sciences version 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Numerical variables are expressed as the mean and standard deviation, and categorical variables are expressed as numbers and percentages. Numerical data were analyzed for the normal distribution using skewness. The independent sample t-test and chi-square test were used to analyze the differences between the two groups in terms of outcome measurements. P-values <0.05 were regarded as statistically significant.

Results

Five hundred and sixty-nine preclinical medical students were included in the study. The participants' mean age

Table 1. Descriptive characteristics of the study group

Characteristics	n (%)
Gender	
Female	297 (52.2%)
Male	272 (47.8%)
Electronic device used for online classes	
Laptop computer	341 (59.9%)
Desktop computer	52 (9.1%)
Smartphone	144 (25.3%)
Tablet	32 (5.6%)
Daily screen time	
1-3 hours	115 (20.2%)
4-7 hours	161 (28.3%)
8-10 hours	180 (31.6%)
>10 hours	113 (19.9%)
Headache type	
TTH	323 (56.8%)
No headache	246 (43.2%)
GAD-7 Score	
Anxiety	296 (52%)
No anxiety	273 (48%)
	Mean ± SD
Age (years)	20.6±3.0
GAD-7 Score	10.1±5.3

GAD-7: General anxiety disorder-7, TTH: Tension-type headache

was 20.6±3.0 years, and 52.2% (n=297) were female. Additionally, 52.4% (n=298) were in year 1, 3.5% (n=20) were in year 2, and 44.1% (n=251) were in year 3.

Tension-type headaches were reported in 323 (56.8%) students, while 246 (43.2%) reported no headaches. In addition, 41.3% (n=135) of the participants with TTH reported headaches after online classes. A further 47.1% (n=154) of the participants with TTH reported worsening the intensity of their headaches after online classes. Other descriptive characteristics, including headache symptoms and anxiety scores, are summarized in Table 1.

A comparison of the TTH group and the headache group is presented in Table 2. Statistically significant differences were observed between the groups in terms of daily total screen time, GAD-7 scores, and gender ($p<0.05$). The mean GAD-7 score was 11.2±5.2 in the participants with TTH and 8.7±5.2 among those with no headache ($p<0.01$).

The relationship between daily screen time and TTH is shown in Table 3. When the groups were compared in themselves, TTH was significantly higher in students with daily screen times of 8-10 hours or over 10 h (p=0.001 and p=0.006, respectively).

Discussion

Long-term screen use is a known trigger factor in the emergence of headaches (16). More than half

Table 2. Comparison of the TTH and non-TTH groups in terms of different variables

Characteristics	TTH (n=323) n (%)	No headache (n=246) n (%)	p (χ^2)
Academic year			
1	180 (60.4%)	118 (39.6%)	0.96
2	13 (65%)	7 (35%)	
3	130 (51.8%)	121 (48.2%)	
Electronic device used for online classes			0.116
Laptop	205 (60.1%)	136 (39.9%)	
Desktop	23 (44.2%)	29 (55.8%)	
Smartphone	76 (52.8%)	68 (47.2%)	
Tablet	19 (59.4%)	13 (40.6%)	
Screen size			0.188
4-7 inches	75 (54.4%)	62 (45.6%)	
8-11 inches	25 (51%)	24 (49%)	
12-14 inches	90 (63.8%)	51 (36.2%)	
15-18 inches	114 (57.3%)	85 (42.7%)	
>18 inch	20 (45.5%)	24 (54.5%)	
GAD-7 Score			
Anxiety	193 (65.2%)	103 (34.8%)	<0.001*
No anxiety	130 (47.6%)	143 (52.4%)	
Gender			
Female	201 (67.7%)	96 (32.3%)	<0.001*
Male	122 (44.9%)	150 (55.1%)	

GAD-7: General anxiety disorder-7, TTH: Tension-type headache, *p<0.05

Table 3. Relationships between students' daily screen times and TTH

Characteristics	TTH (n=323) n (%)	No headache (n=246) n (%)	p-value (one sample χ^2)	p-value (χ^2)
Daily total screen time				0.019*
1-3 hours	64 (55.7%)	51 (44.3%)	0.225	
4-7 hours	76 (47.2%)	85 (52.8%)	0.478	
8-10 hours	112 (62.2%)	68 (37.8%)	0.001**	
>10 hours	71 (62.8%)	42 (37.2%)	0.006**	

TTH: Tension type headache, **One sample χ^2 test (<0.05); *χ^2 (<0.05)

(60%) of the students in this study had TTH. Symptoms commenced after online education in 41% of students, and the intensity of existing TTH also worsened after online learning in 47%. Anxiety was also high among preclinical medical students. This percentage is quite high and indicates that TTH and anxiety are prevalent among students. Our findings are consistent with the results of studies focusing on the relationship between screen time and headaches (17-19).

The global use of computers and the internet is increasing rapidly. However, excessive screen use has been shown to cause different types of headaches, fatigue, sleep problems, dizziness, neck and back pain, memory and learning difficulties, social isolation, depression, anxiety, and internet addiction (20).

Previous studies in the pediatric age group have reported that computer use (gaming, social media use, and internet use) is one of the primary triggers of recurrent headaches in children (21). On the other hand, a recent study has shown that online education may be more effective and has numerous advantages for medical students. In recent years, there have been an increasing number of recommendations for online education in undergraduate medical programs (22). However, it is important to note that these recommendations also imply that health problems associated with excessive computer use may become significant in the coming years. Therefore, while online education offers several benefits, it is crucial to address potential health concerns and implement strategies to mitigate the negative effects of prolonged computer use on medical students' well-being.

Smartphone use exceeding three hours has increased headaches by causing secondary insomnia and fatigue at night. Playing on computers for more than four hours a day was associated with headaches in a study of adolescents in Brazil. The results of this study showed that more than 80% of students reported any type of primary headache that is related to excessive use of electronic devices and video games (23).

A study from China found that computer use exceeding 8 hours per day was associated with headaches. This cross-sectional study revealed a high prevalence of TTH among information technology staff, and the prevalence of TTH was higher than in the general Chinese population. In conclusion, excessive computer use was identified as a significant risk factor for TTH (24). These findings highlight the importance of addressing the impact of computer use on a person's health and implementing measures to mitigate the risk of TTH in this population.

No significant relationship was determined between the type of electronic device used for connecting to online learning, the size of the screen, and TTH in the present study. However, an important relationship was found between screen time and TTH. Tension-type headaches were significantly higher in students with daily screen times of 8-10 hours or over 10 hours. Similar results were obtained in previous studies evaluating the relationship between screen time and headaches. A study from Iceland found a significant correlation between screen time and headaches in a large pediatric age group sample. In this study, the risk of headaches increased in students with a screen time exceeding two hours, and the risk increased 1.6-2 times when the screen time exceeded four hours (25). A study of 2276 students in nine countries found that students spent 8.7 hours a day in front of screens. Physical health symptoms such as back pain, irritability, and emotional imbalance also occurred or increased in these students (7). In the study by Abou Hashish et al. (19) with 353 students from the Saudi University medical, nursing, and health college, it was determined that there was a positive and significant relationship between the duration of screen exposure and headache. In the same study, it was also shown that more than half of the participants had a high screen exposure time, and students who were not satisfied with the online learning environment had more headaches (19).

A quarter of the students in this study used smartphones to connect to online learning. Due to their multifunctional features, smartphones are currently used for internet access, participation in social networks, and digital gaming rather than simply making phone calls. Smartphones can lead to problems such as headaches, neck and shoulder pain, posture and musculoskeletal problems, eye problems, and anxiety. A clinical study among adolescents reported that greater smartphone use was associated with more sleep problems and higher levels of depressive symptoms (26).

Tension-type headaches are a common neurological condition found to be associated with sleep dysfunction. Numerous studies have provided evidence for the connection between TTH and various sleep disturbances (27). In our previous study, symptoms of insomnia were found to be present in 24% of medical students during the pandemic (28). Although we did not evaluate sleep problems, phone use was also high in the current study.

In a study involving 549 students from 31 public medical schools in Germany, Michaeli et al. (29) reported headaches in 33% of students who studied online during the pandemic, with a prevalence of anxiety of 48%. The prevalence of anxiety in their research was similar to that in this study. However, the frequency of headaches was much higher than that in this study. They reported a significant relationship between daily screen time and headache and that each additional hour spent in front of the screen increases the likelihood of headaches by

1.09 times. Preclinical students also experienced more headaches than clinical training students (29).

Our study involved only preclinical students, and no difference was observed between the three academic years in terms of TTH. Rafi et al. (30), in their study with 2352 university students, showed that high screen time and anxiety were risk factors for headache.

It has been shown that reasons such as internet connection problems, distraction due to the learning environment, sleep problems, and a lack of communication in online learning cause stress in students (17,31,32).

More than half of the students in this study had anxiety symptoms. In our previous studies conducted in the early stages of the pandemic, we found the frequency of anxiety to be 70% in medical students and 40% in the general population (5,33).

In the current study, GAD-7 scores were significantly higher in students with TTH than in non-headache groups. Studies have reported significantly higher anxiety scores in individuals with TTH than in control groups (34). Anxiety increases the perception of pain, while pain causes anxiety (35). While social distancing and restrictions have increased anxiety in the COVID-19 pandemic, increased screen time has also been identified as a factor exacerbating the risk of anxiety (36). Approximately 80% of the students in this study spent more than four hours a day in front of their screens. Long screen times and restrictions imposed due to the pandemic may have also had an impact on our students' anxiety scores.

Study Limitations

There are some limitations to this study. First, it was conducted with preclinical students at a single medical school. The results cannot generalized to all medical school students. Face-to-face interviews with the students were impossible because of the pandemic, and the data were therefore collected via a web-based survey. However, the online sampling technique can cause under- or over-reporting compared to self-selection and other methods. The GAD-7 scale, which evaluates anxiety, is also a self-assessment tool, and the results are based on the students' self-reports. Finally, since there was no control group in our study, the causality between online learning and TTH cannot be interpreted definitively. Nonetheless, this study demonstrates a relationship between TTH and online education among medical students, a subject that has not been previously studied.

Conclusion

The results of this study suggest that online education during the COVID-19 pandemic may cause TTH in medical students and that there is a potential association between online learning and the exacerbation of TTH symptoms. Considering the relationship between headaches and screen time, keeping online lesson times short, interrupting classes at appropriate intervals, and resting the eyes regularly may be beneficial. Taken together, these findings underscore the need for targeted interventions and support mechanisms to mitigate the negative impact of online learning on the well-being of medical students. The results of this study may guide remedial interventions in the prevention and reduction of headaches due to screen exposure in online learning environments. Future research should explore the underlying mechanisms linking online classes, TTH, and anxiety to inform the development of effective strategies for promoting student health and academic success in the context of remote education.

Ethics

Ethics Committee Approval: Ethical permission for the study was obtained from the Ataturk University Faculty of Medicine Ethical Committee (IRB number B.30.2.ATA.0.01.00/250-03/26 dated 15.04.2021).

Informed Consent: All participants in this study signed an informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.C.T., N.B., Y.C., Design: E.C.T., N.B., Y.C., Data Collection or Processing: E.C.T., Y.C., Analysis or Interpretation: Y.C., Literature Search: E.C.T., N.B., Y.C., Writing: E.C.T., N.B., Y.C.

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

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Original Article

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The Diagnostic Rate and Clinical Implications of Neuron-Specific Enolase in Neuroendocrine Tumors and Small Cell Lung Cancer: Data from the Ministry of Health of the Republic of Turkey

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Abstract

Aim: Neuron-specific enolase (NSE) is a widely used tumor marker for the diagnosis of neuroendocrine tumors and small cell lung cancer (SCLC). This study aimed to evaluate the utilization, diagnostic rate, distribution by gender and age groups, and variation in test requests across different healthcare institutions for NSE.

Methods: A cross-sectional analysis based on Data from the Ministry of Health of the Republic of Turkey data from 2017 to 2021 was conducted. Neuron-specific enolase tests were requested from a total of 24,763 individuals, and the results of 110,401 tests were evaluated.

Results: Neuron-specific enolase has emerged as the most commonly requested tumor marker in pediatric hematology and oncology clinics. Compared to other tumor markers (cancer antigen 19-9, carcinoembryonic antigen, cancer antigen 15-3 etc.), NSE testing demonstrated the highest diagnostic rate. The test was predominantly requested prior to or simultaneously with the diagnosis and less frequently after the diagnosis. NSE testing showed a higher positivity rate in individuals with confirmed neuroendocrine tumors and SCLC than in others. Moreover, public, training, research, and university hospitals requested NSE tests more than other institutions.

Conclusion: Neuron-specific enolase plays a significant role as a valuable tumor marker in the diagnosis of neuroendocrine tumors and SCLC. This study highlights the diagnostic rate, utilization in pediatric hematology and oncology clinics, and variations across healthcare institutions.. The findings of this study can guide clinicians and researchers in the management of these malignancies.

Keywords: Neuron-specific enolase, biomarkers, tumor

Introduction

Neuron-specific enolase (NSE) is an isoform of the enzyme enolase that is specifically expressed in neurons within the nervous system. This isoform is closely associated with the development, function, and diseases of the nervous system. The primary function of NSE is to participate in the conversion of glucose to energy through the glycolysis pathway. Neuron-specific enolase is particularly regarded as a key enzyme in neuronal energy production, and due to this characteristic, it serves as an important biomarker in the investigation of nervous system disorders. Neuron-specific enolase is highly expressed, particularly in neuroendocrine tumors. These tumors are non-neuronal in origin but possess neuronal features. The NSE is employed as an indicator to assess the neuronal differentiation and the degree of malignancy in such tumors. Elevated NSE levels serve as a significant clinical tool in the diagnosis, prognosis evaluation, and monitoring of treatment response in neuroendocrine tumors. In cases of neuronal damage, NSE levels increase in the blood because of neuronal degradation. In addition, elevated NSE levels are observed in conditions such as brain injury, traumatic brain injury, ischemic stroke, and neurodegenerative diseases. Therefore, NSE is a valuable

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biomarker for the early detection of neurological damage and monitoring the treatment response (1).

Neuron-specific enolase is a tumor marker used in the diagnosis of neuroendocrine tumors and small cell lung cancer (SCLC). Small cell lung cancer, which accounts for 10-20% of lung cancers, is the most malignant type and is also the most responsive to chemotherapy and radiation therapy (2). However, it carries a high risk of recurrence and distant metastasis, with a 5-year survival rate of less than 5% (3). Neuron-specific enolase serum concentration has been found to be positively associated with tumor size, advanced tumor stage, and distant metastasis. Additionally, it is believed to have a promising role in predicting the response to chemotherapy and radiation therapy (4).

The aim of this article is to analyze on the clinical significance of NSE as a tumor marker in the diagnosis and prognosis evaluation of neuroendocrine tumors and SCLC, as well as to increase awareness on the subject, identify clinician trends, and guide the correct use of tumor markers in this way.

Methods

Compliance with Ethical Standards

Ethical approval for the study was obtained from the Ministry of Health of Turkey General Directorate of Health Information Systems (approval no: 95741342-020, date: 27.11.2019), and all data were anonymized to ensure privacy. This study adhered to ethical guidelines and protected the privacy and confidentiality of the individuals included in the data.

Study Design

This cross-sectional study utilized data from the Ministry of Health, covering a five-year period from 2017 to 2021, including 110,401 tests from 24,763 individuals. The data included information on NSE tests requested from individuals across different regions and healthcare institutions in the country. The test counts were evaluated in detail. Neuron-specific enolase levels represent the results obtained through the immunoassay method and were derived using the E-Nabiz system of the Turkish Ministry of Health. The ministry's database is referred to as e-Nabiz. This database encompasses the health records of patients who have sought medical services from all healthcare institutions in Turkey, including demographic characteristics, laboratory data, medication usage, comorbidities, and other health-related records.

Study Population

The study population comprised individuals who underwent NSE testing during the study period. Both men and women were included in the analysis.

Data Collection

Data were collected from medical records and laboratory databases. The information included demographics (gender, age), test requests, test results, neuroendocrine tumors and SCLC diagnoses, and healthcare institution types.

Database and e-Pulse

e-Pulse is a platform developed by the Ministry of Health in Turkey that allows individuals to store and manage their health information digitally. For this study, patient information and health records were collected using the e-Pulse system. During the data collection process, personal information was protected and the principle of privacy was fully respected.

Health Coding Reference Server and International Classification of Diseases Codes

Health Coding Reference Server (SKRS) is a data recording and reporting system used by the Ministry of Health in Turkey. This system aids in the more effective management of health services. In this study, data pulled from the SKRS and International Classification of Diseases codes were used to analyze disease diagnoses, treatment plans, and the overall state of health services. International Classification of Diseases codes are a standard disease and health problem classification system created by the World Health Organization and used worldwide. These codes are important tools for identifying, monitoring, and treating diseases.

Statistical Analysis

Descriptive statistics were used to analyze the data. The test counts, test rates per population, rates of exceeding the reference range, and cancer diagnosis rates were calculated and compared across different variables, including gender, age groups, geographic regions, and healthcare institution types.

When comparing the number of NSE tests by year, it was observed that the test count and tests per 100,000 population increased between 2017 and 2019, but showed a significant decrease in 2020 and 2021 (Figure 1).

In terms of test requests by gender, similar to the general population, the number of test requests for females increased as the years progressed between 2017 and 2019, but exhibited a significant decrease in 2020 and 2021. Neuron-specific enolase ranked sixth among the tumor markers tested in females across all years.

Similarly, for males, the number of test requests increased as the years progressed between 2017 and 2019, but showed a notable decrease in 2020 and 2021.

When the number of test requests for females and males was compared by year, the ratio was 1/1.16 in 2017,

1/1.07 in 2018, 1/1.09 in 2019, 1.19 in 2020, and 1/14 in 2021. Except for NSE and PSA, all other tumor markers were more frequently requested for female patients in all years (Table 1).

In terms of test consumption per 100,000 population, NSE had the lowest rate in the 18-64 age range, followed by the 0-17 age range, and the highest rate was observed in the 65 and older age group. Among the other tumor markers, the lowest rate was observed in the 0-17 age group, the second lowest in the 18-64 age group, and the highest rate was observed in the 65 and older age group (Table 2).

	NUMBER OF TESTS	NUMBER OF APPLICATIONS	NUMBER OF PEOPLE	NUMBER OF TESTS PER PERSON	NUMBER OF TESTS PER 100,000 POPULATION
AFP	15.618.083	4.274.378	3.213.258	4,86	18.899
CA 125	22.680.568	5.120.380	3.917.240	5,79	27.445
CA 15.3	21.579.044	4.077.373	2.981.142	7,24	26.112
CA 19.9	25.808.137	5.251.969	4.018.913	6,42	31.230
CA 72.4	911.834	160.519	141.974	6,42	1.103
CEA	27.394.778	5.533.959	4.016.178	6,82	33.150
NSE	**110.401**	**29.969**	**24.763**	**4,46**	**134**
PSA FREE	12.876.151	4.336.930	3.020.756	4,26	15.581
PSA TOTAL	21.547.232	9.608.915	5.812.043	3,71	26.074

Figure 1. Total consumption of tumor markers between 2017-2021

When comparing the rates of receiving a cancer diagnosis at any time for individuals who underwent NSE testing, in 2017, 63% of individuals received a cancer diagnosis, whereas in 2018, 71% did, 56% in 2019, 57% in 2020, and 52% in 2021. Among individuals who had tumor markers requested, NSE had the highest diagnostic percentage in all years (Table 3).

When analyzing the test request timing in relation to the diagnosis of patients, except for 2017, in other years, the tests were requested more frequently before the diagnosis, followed by simultaneous requests with the diagnosis, and the least requests were made after the diagnosis (in 2017, most requests were made at the time of diagnosis) (Table 4).

Neuron-specific enolase tests were most frequently requested in the Marmara region. The second most frequent region was the Mediterranean region in 2017, the Eastern Anatolia region between 2018 and 2019, and the Central Anatolia region between 2020 and 2021. The region with the lowest test requests was consistently the Black Sea region. When comparing the Marmara region, which ranked first in 2021, with the last-ranked Black Sea region, the ratio was 85.

When analyzing the test requests per 100,000 population by geographic region, in 2017, the highest rate was observed in the Mediterranean region, while between 2018 and 2019, it was the Eastern Anatolia region, and between 2020 and 2021, it was the Marmara region. The lowest region was consistently the Black Sea region. When comparing the Marmara region with the second-ranked Central Anatolia region in 2021, the ratio was

Table 1. Number of test requests by year in age groups

	2017			2018			2019			2020			2021		
	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
NSE	5.767	7.095	3.272	7.003	11.555	5.819	9.445	10.933	5.734	8.085	8.702	4.687	7.145	9.529	5.630

NSE: Neuron-specific enolase

Table 2. Test consumption per 100,000 people by years and age groups

	2017			2018			2019			2020			2021		
	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
NSE	25	14	47	31	22	81	41	21	76	36	16	59	31	18	71

NSE: Neuron-specific enolase

Table 3. Percentage distribution of patients who required tumor markers and were diagnosed with cancer at any time

	2017		2018		2019		2020		2021	
	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer
NSE	37%	63%	29%	71%	44%	56%	43%	57%	48%	52%

NSE: Neuron-specific enolase

1.07, and when compared with the lowest-ranking Black Sea region, the ratio was 21 (Table 5).

When comparing the test requests by clinics, medical oncology had the highest number of test requests in all years. Pediatric hematology and oncology ranked second. Dermatology and venereal diseases, pediatrics, and internal medicine clinics ranked third. The internal medicine clinic ranked seventh in 2017 and fifth in 2019. Family medicine did not appear in the top 10 clinics. The emergency medicine clinic ranked 10th in 2017 and 2020 and ninth in 2018 (Figure 2).

When the diagnoses entered in the test request applications were examined, in 2017, the most common diagnoses were malignant neoplasms of the skin, while in 2018 and 2020, it was an unspecified malignant neoplasm, and in 2019 and 2021, it was vitamin D deficiency and unspecified diagnoses. Overall, the most common diagnoses over the five years were malignant neoplasms in an unspecified region, followed by vitamin D deficiency and unspecified diagnoses, and pain not classified elsewhere.

When comparing the rates of exceeding the reference range of the test, the highest rate was observed in 2017 at 74.30%, while the lowest rate was 52.15% in 2021, showing a decrease as the years progressed. Neuron-specific enolase had the highest rate of exceeding the reference range among all tumor markers.

When the rates of exceeding the reference range were compared based on the healthcare level, the highest rate of 64.32% was observed in the tertiary level, followed by 55.11% in the secondary level and 51.01% in the primary level institutions.

Based on the institution type, when the rates of exceeding the reference range were examined, the overall rate was 63.00%, with the highest rate being 73.78% in public and training and research hospitals, followed by 58.13% in university hospitals, and 53.44% in private healthcare institutions. Neuron-specific enolase had the highest rate in public, training and research hospitals, whereas other tumor markers had the lowest rate in public, training, and research hospitals.

When analyzing the rates of exceeding the reference range by geographic regions, the highest rate of 91.8% was observed in the Eastern Anatolia region in 2018 and 2019, which had the highest test requests and tests per 100,000 population. The second-highest rate of 82.2% was observed in the Southeast Anatolia region, which had the lowest number of tests per 100,000 people. The lowest

Table 4. Distribution of cancer diagnoses related to NSE

Year	Related cancer diagnosis		Non-related cancer diagnosis		Total number of people tested
2017	1,812	40.61%	3,960	88.75%	4,462
2018	2,363	38.97%	5,345	88.16%	6,063
2019	2,763	38.20%	5,953	82.30%	7,233
2020	2,744	45.71%	5,918	98.58%	6,003
2021	2,757	44.41%	5,929	95.51%	6,208

NSE: Neuron-specific enolase

Table 5. Geographical distribution by NSE years and number of test requests

2017		2018		2019		2020		2021	
Region	Number of tests	Region	Number of tests	Region	Number of tests	Region	Number of tests	Region	Number of tests
Marmara Region	7,450	Marmara Region	8,121	Marmara Region	9,761	Marmara Region	9,468	Marmara Region	10,883
Mediterranean Region	3,120	Eastern Anatolia Region	7,464	Eastern Anatolia Region	6,048	Central Anatolia Region	4,629	Central Anatolia Region	5,203
Central Anatolia Region	2,427	Central Anatolia Region	3,687	Central Anatolia Region	4,244	Mediterranean Region	3,360	Aegean Region	2,797
Eastern Anatolia Region	1,628	Mediterranean Region	3,185	Mediterranean Region	3,592	Egaegean Region	2,589	Mediterranean Region	1,996
Aegean Region	1,339	Aegean Region	1,641	Aegean Region	1,957	Eastern Anatolia Region	1,081	Eastern Anatolia Region	1,004
Southeast Anatolia Region	115	Southeast Anatolia Region	187	Southeast Anatolia Region	398	Southeast Anatolia Region	270	Southeast Anatolia Region	293
Black Sea Region	55	Black Sea Region	92	Black Sea Region	112	Black Sea Region	77	Black Sea Region	128

NSE: Neuron-specific enolase

2017		2018		2019		2020		2021	
MEDICAL ONCOLOGY	3.368	MEDICAL ONCOLOGY	10.200	MEDICAL ONCOLOGY	8.347	MEDICAL ONCOLOGY	5.575	MEDICAL ONCOLOGY	4.630
CHILDREN'S HEMATOLOGY AND ONCOLOGY	3.056	CHILDREN'S HEMATOLOGY AND ONCOLOGY	3.886	CHILDREN'S HEMATOLOGY AND ONCOLOGY	5.080	CHILDREN'S HEMATOLOGY AND ONCOLOGY	4.465	CHILDREN'S HEMATOLOGY AND ONCOLOGY	3.901
DERMATOLOGY	1.804	DERMATOLOGY	2.014	CHILD HEALTH AND DISEASES	1.894	CHILD HEALTH AND DISEASES	1.573	DERMATOLOGY	2.535
CHILD HEALTH AND DISEASES	1.125	CHILD HEALTH AND DISEASES	1.363	NEUROLOGY	1.790	NEUROLOGY	1.504	NEUROLOGY	1.538
RADIATION ONCOLOGY	880	NEUROLOGY	1.097	INTERNAL MEDICINE	1.038	DERMATOLOGY	1.159	CHILD HEALTH AND DISEASES	1.449
NEUROLOGY	869	INTERNAL MEDICINE	795	CHEST MEDICINE	901	CHILD SURGERY	754	INTERNAL MEDICINE	1.042
INTERNAL MEDICINE	685	CHILD SURGERY	477	CHILD NEUROLOGY	723	INTERNAL MEDICINE	741	GENERAL SURGERY	698
MEDICAL BIOCHEMISTRY	472	MEDICAL BIOCHEMISTRY	460	DERMATOLOGY	599	CHEST MEDICINE	692	CHEST MEDICINE	652
GASTROENTEROLOGY	432	EMERGENCY MEDICINE	428	ENDOCRINOLOGY AND METABOLISM DISEASES	584	GENERAL SURGERY	612	CHILD SURGERY	643
EMERGENCY MEDICINE	419	CHEST MEDICINE	323	CHILD SURGERY	555	EMERGENCY MEDICINE	592	GASTROENTEROLOGY	642

Figure 2. NSE top 10 clinics according to the years and the number of tests requests

rate of 51.3% was observed in the Black Sea region.

In terms of gender, when examining the rates of exceeding the reference range, it was generally 62.48%, with 65.11% in males and 59.40% in females. The NSE had the highest rate of exceeding the reference range among all tests.

When analyzing the rates of exceeding the reference range by age groups, the highest rate of 74.90% was observed in the 0-17 age group, followed by 49.19% in the 65 and older age group, and 10.44% in the 18-64 age group. When comparing the age groups (0-17/18-64/65 and older) in terms of rates, the ratios were calculated as 1.62/1/1.06.

When analyzing the rates of exceeding the reference range by admission status, it was observed that the highest rate of 66.11% was for inpatients, followed by 62.46% for outpatients, and 57.85% for day patients. When compared in order (inpatient/outpatient/day patient), the ratios were calculated as 1.14/1.07/1. Neuron-specific enolase had the highest rate of exceeding the reference range among all tumor markers for all groups.

When analyzing the rates of exceeding the reference range in the presence of a cancer diagnosis, a total of 62.93% of individuals tested positive. Among them, 63.36% had a cancer diagnosis, whereas 62.22% did not. The NSE had the highest rate of exceeding the reference range among all tests, regardless of the presence of a cancer diagnosis.

In terms of the clinics that requested NSE tests, when examining the rates of tests exceeding the reference range, the highest rate of 75.43% was observed in the Pediatric Hematology and Oncology clinic, followed by 74.61% in the Pediatric Surgery clinic, and 72.83% in the Pediatric Neurology clinic. Among all clinics, tumor marker tests were most frequently requested by the medical oncology clinic, with a rate of 55.90%. The Pediatric Hematology and Oncology clinic ranked second, with a rate of 75.43% (top-ranked). The Dermatology and Venereal Diseases Clinic, which ranked third in all years, had a rate of 17.76%, which was the lowest among the top 10 clinics. Family medicine and emergency medicine clinics did not appear among the top 10 clinics.

Discussion

The findings of our study revealed several important aspects regarding the clinical utility of NSE as a tumor marker. Pediatric hematology and oncology clinics have emerged as the primary settings where NSE testing is most commonly requested, indicating its significance in the evaluation of pediatric malignancies. Moreover, our results demonstrated that NSE exhibited the highest diagnostic rate compared to other tumor markers, underscoring its effectiveness in the diagnosis of neuroendocrine tumors and SCLC. Interestingly, NSE test requests predominantly occurred before or simultaneously with the diagnosis, suggesting its role as an initial screening tool in the diagnostic workup. In contrast, NSE testing was less frequently performed after the confirmation of the diagnosis. Notably, our study showed a higher positivity rate for NSE among individuals with a confirmed cancer diagnosis, further supporting its clinical relevance in detecting cancer-related abnormalities. Additionally, the higher frequency of NSE test requests observed in public, training and research hospitals and university hospitals suggests widespread recognition and utilization of NSE in these healthcare settings. Remarkably, NSE test results frequently exceeded the reference range, setting it apart from other tumor markers and highlighting its potential as a reliable indicator for the presence of underlying malignancies.

SCLC, which accounts for 10-20% of lung cancers, is the most malignant type and the most responsive to chemotherapy and radiotherapy. Although SCLC is generally more common in males, there has been an increase in the number of cases in females worldwide over the past 50 years (5).

A study by Lee et al. (6) included 262,826 patients diagnosed with SCLC. The patients were grouped based on age distribution, with 8,792 (5.1%) between 18 and 50 years, 96,721 (56.1%) between 50 and 70 years, and 66,940 (38.8%) aged 70 years. The median age of the study population was 66 (6). In our study, when comparing the number of test requests by age groups, NSE was most frequently requested in the 18-64 age group, followed by the 0-17 age group, and the least frequently requested in the age group of 65 and above.

A study by Lu et al. (7) demonstrated that NSE supports the stem-cell-like properties of SCLC through the neuroblastoma suppressor of tumorigenicity 1 (NBL1) pathway and activates the BMP2/Smad/ID1 pathway (1). In our study, it was not possible to distinguish between the "NSE supports the stem-cell-like properties of SCLC through the NBL1 pathway and activates the BMP2/Smad/ID1 pathway" based on retrospective data analysis. The evolution of diagnostic technologies has potentially enhanced the accuracy and reach of NSE testing, making it a more sought-after method.

As medical professionals become more aware of the intricacies of pediatric malignancies, there seems to be a gravitation towards early and effective diagnostic methods, such as the NSE test (8). Continuous research and findings related to NSE could have bolstered its reputation and applicability in pediatric conditions. The structure and emphasis of the pediatric healthcare system in Turkey might deviate from global norms, leading to distinct diagnostic approaches.The extent of knowledge and training among Turkish clinicians about NSE's efficacy might differ from their international counterparts, leading to discrepancies in testing rates. While certain countries might focus their research efforts on specific diagnostic methods or cancers, Turkey's emphasis on NSE might be a result of unique research trajectories. The presence or lack of other diagnostic tools in various countries can sway medical professionals' dependence on NSE tests.

Our research underscores the pivotal role of NSE within the sphere of tumor markers, particularly among pediatric populations. The fact that pediatric hematology and oncology clinics frequently employ NSE testing speaks volumes about its diagnostic value in children's malignancies.

The prevalence of NSE testing in pediatric domains within Turkey reveals significant insights about the nation's healthcare priorities. It's crucial to delve into the causes of this trend and juxtapose it with global practices to optimize diagnostic tactics and elevate patient care standards (9). Moreover, these findings can serve as a guidepost for other countries, facilitating mutual learning and fostering a cohesive approach towards leveraging NSE's potential.

Study Limitations

Several limitations should be considered when interpreting the findings of this study. First, the retrospective nature of the study and the use of retrospective data may introduce inherent limitations in terms of accuracy and precision. Second, the study's limited time frame restricts the generalizability of the results to a specific period. Third, the data were obtained from a specific region or institution, which may limit the generalizability of the findings to other geographic locations or healthcare settings. Fourth, the study did not fully analyze the relationship between the evaluated parameters and other clinical or laboratory findings, highlighting the need for further studies to determine the independent effect of NSE and its correlation with other variables. Fifth, the study focused solely on the use and effectiveness of NSE as a tumor marker, and comparative analyses with other tumor markers were not conducted. Finally, the study primarily evaluated test requests and results without considering other important clinical parameters such as treatment response or disease prognosis.

Conclusion

Our study highlights the prominent role of NSE as a valuable tumor marker in the diagnosis and assessment of neuroendocrine tumors and SCLC. The high diagnostic rate, frequent use in pediatric hematology and oncology clinics, and ability to detect cancer-related abnormalities distinguish NSE from other tumor markers. The findings of this study contribute to the existing body of knowledge and provide insights for clinicians and researchers in optimizing the clinical use of NSE in the management of these malignancies. Prospective studies in the future could provide further insights into the prognostic evaluation, treatment monitoring, and comparative effectiveness of NSE with other biomarkers.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ministry of Health of Turkey General Directorate of Health Information Systems (approval no: 95741342-020, date: 27.11.2019).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed

Authorship Contributions

Concept: S.B., Design: S.B., Data Collection or Processing: S.B., M.M.U., Analysis or Interpretation: S.B., M.M.U., Literature Search: S.B., M.M.U., Writing: S.B., M.M.U.

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Turkish Primary Care Patients' Overviews and Attitudes About Traditional and Complementary Medicine: A Cross-Sectional Study

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Abstract

Aim: Primary care physicians need to be aware of the types of traditional and complementary medicine (TCM) used by patients to be able to guide patients away from harmful approaches and to aim them toward useful or at least seeming benign approaches. This study aimed to determine the prevalence of the usage of TCM methods in Turkey and the level of knowledge and attitudes of applicants about these methods.

Methods: The universe of this cross-sectional study consisted of individuals aged 18 and over who applied to the Family Health Centers and agreed to participate in the study in 12 provinces in different regions of Turkey between July and December 2016. The questionnaires were applied to the volunteer participants by the researchers using face-to-face interview techniques. The questionnaire had 25 questions.

Results: 80.6% of the participants benefited from TCM, and 86.4% stated they believed in the effectiveness of TCM. Women, university graduates of college who had private insurance used TCM (respectively; p=0.031; p=0.004; p=0.000), and women (83.3%) found TCM more useful than men (p=0.005). The most frequent reason for using TCM was "heard that it was useful".

Conclusion: The results of our study indicated that a large portion of Turkish primary care patients use TCM and recommend it to their relatives. Therefore, health policies and academic knowledge should be developed in this sense.

Keywords: Complementary alternative medicine, family health center, attitude, knowledge

*This study has taken place in the 7th International Participation of Congress on Family Medicine as a poster presentation and the paper was awarded the third prize.

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Introduction

When individuals encounter health issues, they actively seek solutions. These quests often lead individuals to explore traditional and complementary medicine (TCM) either in conjunction with or as an alternative to modern medical treatments (1). While significant strides in technology and scientific advancements have revolutionized the diagnosis and treatment of numerous diseases, the use of TCM alongside modern medicine has been on the rise since the twentieth century, with the aim of promoting overall health and treating illnesses (2).

According to the World Health Organization (WHO), traditional medicine encompasses a vast body of knowledge, skills, and practices rooted in the beliefs and experiences of diverse cultures. These practices are employed not only to maintain one's current state of health under improved conditions but also to prevent physical and mental illnesses and enhance treatment outcomes (3). Within the framework of existing healthcare services, these therapeutic approaches are referred to as "traditional and complementary", regardless of whether they align with societal traditions. Furthermore, "traditional and complementary" encompasses all treatment modalities employed outside the realm of modern medicine (4-8).

The prevalence of TCM usage has steadily increased in our country since the twentieth century. In a study conducted by Tulunay among individuals with chronic illnesses, it was observed that women use herbal therapies more frequently than men, with television programs being the most frequently cited source of information (9).

The primary responsibility of family physicians lies in preventive medicine (4). However, TCM is not typically incorporated into the medical curriculum, potentially leaving physicians with knowledge gaps and biases regarding TCM (10). This circumstance often leads patients to withhold information about their TCM practices from their physicians, even though the use of such therapies is widespread globally. Primary care physicians need to be informed about the types of TCM utilized by their patients, enabling them to guide patients away from potentially harmful approaches and toward those that are beneficial or at the very least seemingly benign. In all cases, it is crucial for physicians to establish an open dialog with patients regarding complementary therapies, ensuring that patients are under the care of a comprehensively trained medical professional (11).

In this study, our primary objective is to assess the knowledge and attitudes of individuals concerning TCM, with the secondary aim of raising awareness about the most commonly employed TCM methods in Turkey.

Methods

Compliance with Ethical Standards

Our research is in thorough compliance with the Declaration of Helsinki. Ethics approval was obtained from the ethics committee of the Akdeniz University Faculty of Medicine Clinical Research for the study (approval number: 309, date: 01.06.2016). After the Ethics Committee's approval, the required authorization from the Turkish Public Health Institute was obtained.

Study Design

The design of the study is cross-sectional. The reporting of the study was conducted in accordance with the STROBE criteria. As a result of the literature screening, a 25-question survey was developed by the researchers. A pilot study was conducted with 20 people to evaluate the comprehensibility, readability, and applicability of the survey. As a result of the criticisms and suggestions received after the pilot study, the questionnaire was finalized. The questionnaires were administered to the volunteer participants using the face-to-face interview technique by the researcher and family physicians. The questionnaire includes questions about sociodemographic information, chronic diseases and drug use, knowledge levels, attitudes, and experiences about TCM.

Data Collection

The universe of this descriptive study consists of individuals aged 18 and over who apply to the Family Health Centers (FHC) and who agree to participate in the study in Antalya, Denizli, Nevsehir, Sakarya, Gaziantep, Sanliurfa, Bursa, Istanbul, Malatya, Balikesir, Ankara, and Canakkale. Assuming that the population over the age of 18, whose sample size is connected to a family physician, is 3400; taking $p<0.01$; calculated using random selection criteria at 1% margin of error and 99% confidence interval. In similar studies, the percentage of individuals using TCM was found to be 33%. While calculating the sample size, the 33% rate was used. The sample size was calculated at 1060. All participants who applied to the FHCs determined for the research for any reason and were over the age of 18 agreed to participate in the study and filled out the consent form.

Statistical Analysis

In the evaluation of the data, the relationship between categorical variables was examined using the chi-square test and the exact test. Statistical parameters are expressed as ratios (%) and frequencies (n). Statistical significance was set as $p<0.05$. The data were analyzed using the IBM SPSS version 22 package program (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States).

Results

One thousand seventy people participated in the study. 61.1% of the participants were women, and 45.7% were in the 30-50 age group. 67.1% were married, and 69.4% had children. 29.8% of the participants were primary school graduates, and 48.5% were working. 66.4% of employees did not work; 54.5% of those were housewives. The social security of 90.8% of individuals was social security insurance (SSI) (Table 1).

35.4% of individuals had chronic diseases. The two most common chronic diseases were diabetes (21.1%) and hypertension (17.6%).

While 80.6% (n=863) of the participants had a TCM method that they had previously benefited from, 86.4% (n=925) stated that they believed in the effectiveness of TCM methods. The most common reasons for application of TCM were cough (58.1%) and immune system weakness (49.5%); the most frequently used TCM method was herbal therapy (96.1%). The two most commonly used plants were lemon (80.4%) and linden (65.8%). The other grouped plants were green tea, turmeric, gojiberry, onion, thyme, and echinacea.

Table 1. Socio-demographic characteristics of the participants

Socio-demographic characteristics	Number (percent)
Region	
East	458 (43.6%)
West	593 (56.4%)
Age	
18-29	298 (27.8%)
30-50	486 (45.4%)
51-64	189 (17.6%)
65≤	97 (9%)
Gender	
Female	624 (59.8%)
Male	419 (40.2%)
Marital status	
Single	253 (24.2%)
Married	697 (66.7%)
Divorced	38 (3.6%)
Widow	57 (5.5%)
Child presence	
Yes	713 (71.2%)
No	288 (28.8%)
Level of education	
Literate	84 (8.2%)
Primary education	286 (27.8%)
High school	283 (27.6%)
College	98 (9.5%)
University	276 (26.9%)
Social security	
SSI	906 (90.2%)
Green card	26 (2.6%)
Special insurance	32 (3.2%)
No	40 (4%)

SSI: Social security insurance

The most common reason for using TCM was "having heard it was useful" (72.7%). In terms of education level, primary school graduates recommend TCM to other people more than other groups (30.5%) ($p<0.001$).

According to their socio-demographic characteristics, the most commonly known and used TCM methods and the most common reasons for their use are shown in Table 2.

The most commonly used TCM method in all age groups was herbal therapy. Herbal therapy was known mostly between the ages of 30 and 50 (97.5%) ($p<0.001$). The group that believed in the effectiveness of TCM was the 18-29 age group (90.3%) ($p=0.002$). Although not statistically significant, the group that found TCM most useful was 18-29 years old (82.6%) ($p>0.05$). The most common reason for using TCM among all age groups was to have heard that it was useful.

Compared with gender, the most well-known method of TCM was herbal therapy; women used herbal therapy more than men ($p=0.031$). Although the frequency of believing in the effectiveness of TCM was not statistically different, it was higher in women (87.8%) than men ($p>0.05$). Women (83.3%) found TCM more useful than men ($p=0.005$).

When the groups were compared according to marital status, it was observed that the most known and used method, herbal therapy, and divorced group were known and used it more than other groups ($p<0.001$).

When the groups were compared according to their educational status, it was seen that those who graduated from the university knew herbal therapy more ($p<0.001$) and that the graduates of the college used herbal therapy more (97.3%) ($p=0.004$). The most frequent reason for use was "having heard it is useful", and it was observed that it was statistically significantly more expressed by the literate (88.9%) ($p<0.001$).

When the groups were evaluated in terms of the presence of children, it was found that those who did not have children (96.3%) knew the herbal therapy much more ($p<0.001$).

When the people were grouped according to profession, it was seen that herbal therapy was significantly more known (96.9%) in the non-working group ($p<0.001$). It has been observed that the most frequent reason for using TCM is "to have heard that it is beneficial" ($p=0.003$).

The level of knowledge of the people about TCM with social security SSI was significantly higher than that of the others. Those who had private insurance also used TCM because they found it more useful and safer than the other groups ($p=0.007$).

The most common reason for using TCM was "heard that it was useful" for housewives (81%), and "difficulty

Table 2. TCM methods known and used according to their socio-demographic characteristics and reasons for their use			
	Known TCM method	**Used TCM method**	**Reason for using TCM**
Age			
18-29	Prayer (50.7%) Meditation (22.1%) Larva (8.7%)	Meditation (3.2%)	
30-50	Herbal therapy (97.5%) Hacamat (53.6%) Acupuncture (48%) Ozone therapy (26.8%)	Herbal therapy (96.2%) Manipulation (9.2%)	Worrying about drug side effects (30.9 %)
51-64	Thermals (77.2%) Leech (53.4%)		
65≤	Manipulation (30.9%)	Thermals (33.3%) Hacamat (14.5%) Acupuncture (13%) Leech (8.7%)	Having heard it is useful (81.4%) Finding TCM reliable (34.4%) Tired of using medication (32.9%) To think that TCM is cheaper (5.7%)
Gender			
Female	Herbal therapy (96.9%)	Herbal therapy (94.8%) Acupuncture (6.8%) Meditation (2.9%) Larva (2%) Mesotherapy (1.7%) Ozone therapy (1.5%)	Having heard it is useful (73%)
Male	Herbal therapy (95%)	Herbal therapy (93.4%)	Having heard it is useful (72.4%)
Marital status			
Married	Leech (51.5%)	Hacamat (11.6%)	
Single	Acupuncture (47.6%) Meditation (28.6%) Ozone therapy (24.6%) Larva (10.1%)	Meditation (4.9%)	
Divorced	Hacamat (57.1%) Manipulation (36.7%) Mesotherapy (22.4%)	Herbal therapy (97.6 %) Acupuncture (7.3%) Mesotherapy (4.9%) Ozone therapy (2.4%)	Finding TCM reliable (43.9%) Tired of using medication (41.5%) Avoiding drug side effects (36.6%) To think that TCM is cheap (7.3%)
Widow	Thermals (75.5%) Praying (54.7%)	Thermals (38.1%) Praying (35.7%) Leech (16.7%) Manipulation (11.9%)	Having heard it is useful (83.7%)
Level of education			
Literate			Having heard it is useful (88.9%)
Primary education			
High school			
College		Herbal therapy (97.3%)	
University	Herbal therapy (97.7%)		
Presence of chronic disease			
Yes	Herbal therapy (95.8%) Thermals (69.7%)	Thermals (29.6%) Hacamat (29.6%) Acupuncture (7.6%)	Having heard it is useful (76.7%)
No		Herbal therapy (95.3%) Prayer (26.6%) Meditation (2.9%)	Having heard it is useful (70.7%)

TCM: Traditional and complementary medicine

in applying to the health institution" was more common for students (11.9%).

According to the socio-demographic characteristics, the sources from which patients obtain information about TCM are shown in Table 3.

Discussion

The studies conducted in this regard in our country are generally at the regional level and/or conducted with few people. In addition, most studies focused on the use of TCMs for only one disease. Our study presents a comprehensive and overall assessment conducted in primary health care, which makes us superior to other studies.

80.6% of the participants stated that they use TCM, and this ratio is higher than the studies conducted abroad and the studies conducted in our country (8,10,11). The fact that our study was a primary care study and the large sample size may have contributed to this result.

According to the results of our study, the most commonly used TCM method was herbal therapy, in accordance with studies conducted by Oral et al. (12) and Uysal et al. (13). While herbal therapy was followed by nutritional medicine in the study of Thomson et al. (14),

Table 3. Comparison of socio-demographic characteristics and ways to learn about TCM

Socio-demographic features	The most common way of obtaining information	Significance
Age		
18-29	Internet (36.1%)	**p<0.001**
30-50	Others (58.4%)	
51-64	Radio/TV (20.3%)	
65≤	Radio/TV (11.8%)	
Gender		
Female	Others (70.8%)	p=0.673
Male	Herbalist (41.9%)	
Child presence		
Yes	Radio/TV (75.5%)	**p<0.001**
No	Others (44.2%)	
Marital status		
Single	Radio/TV (71.8%)	**p<0.001**
Married	Others (33.6%)	
Divorced	Herbalist (7.3%)	
Widow	Friends (6.1%)	
Level of education		
Literate	Radio/TV (12.4%)	**p<0.001**
Primary education	Family and relatives (32.1%)	
High school	Internet (27.3%)	
College	Others (17.7%)	
University	Others (56.6%)	
Job		
Still workers	Others (94.7%)	**p<0.001**
Workers	Friends (36.2%)	
Officials	Internet (18.8%)	
Self-employment	Herbalist (28%)	
Doctors	Others (18.7%)	
Midwives/Nurses	Others (65.4%)	
Assistant medical staff	Health workers (10.4%)	
Pharmacists	Others (6.5%)	
Dietitians	Others (0.9%)	
Unemployed	Family and relatives (43.1%)	
Housewives	Radio/TV (89.5%)	
Students	Others (66.7%)	
Retirees	Radio/TV (15.8%)	
Social security		
SSI	Others (99.1%)	**p=0.01**
Green card	Friends (1.6%)	
Special insurance	İnternet (5.7%)	
No	Family and relatives (4.1%)	
Presence of chronic disease		
Yes	Radio/TV (43.4%)	**p<0.001**
No	Others (78.8%)	

Chi-squared test
SSI: Social security insurance, TCM: Traditional and complementary medicine

Arab participants mostly used traditional medicine and herbal treatments, whereas Jews used dietary products and dietary supplements more. Other studies indicated that the most preferred TCM methods were vitamin supplements, massage, and traditional Chinese medicine (15-17). In studies conducted in Turkey, in a study in Izmir, prayers, and in a study in Kayseri, thermals were mentioned as the most frequently used TCMs (18,19). The reason why the patients mostly prefer herbal products may be because their advertisements are more prominent, because of their easy accessibility and cheapness, and because they may be harmless because they are obtained naturally (14). The TCM method's usage is affected by the region where the patient lives, cultural differences, and health or disease beliefs. In this study, we found the reasons why herbal therapy was preferred over other methods were the lack of sufficient knowledge about these methods and the high costs.

While the most common reason for using TCM is cough and immune system weakness, lemon and linden are the most commonly used herbs for herbal treatment. Those who use lemon and mint have difficulty applying to the health institution, and those who use linden prefer this method because it is cheaper. In a study that investigated the use of TCM in individuals with chronic disease, the rate of TCM use was found to be 62.3%, and 58.5% were using herbal products similar to our study. Similar to our study, the most commonly used herbal products were lemon, garlic, and linden. The purposes of use are defined as disease and pain problems in a systematic review (20). In a study conducted in Korea, the most common uses were gastrointestinal and dental diseases (16). In the study by Nural et al. (21), the most common reasons for using TCM were lowering blood pressure (38.8%) and reducing pain (30.2%). There are national and regional differences in their use, and our study is different from other study results. This may be because the study was conducted on a wider population, not just people with a particular disease.

In our study, the most common reason for using TCM was hearing that it was beneficial (72.7%), that it was thought to be reliable (30.7%), and that it was used due to drug side effects (29.9%). Similar to our study, the most common reason for using TCM in some studies was to believe that TCM is beneficial (1,17). Recently, people have turned to natural methods and moved away from modern methods. This is valid for both our country and the world. As a result, people believe, find, and use TCM more effectively because they find TCM more natural than modern medicine methods and believe that it is harmless and will not have side effects like medicines.

In our study, in accordance with the studies in the literature, there were people who suffered from the use of TCM in or around the participants (19,21).

When TCM is heard and used according to various variables, it is found that people who are more educated, younger, live in centers, and have better economic status know these methods at a higher rate (12). While the rate of knowing TCM in individuals in Saudi Arabia is 88.8%, this rate was found to be 69.7% in a study conducted on people over 60 years of age in a rural part of Izmir (17,19). The perception of TCM as beneficial, being a primary school graduate, having high health awareness, having positive attitudes toward TCM, and having more information about TCM have been positively associated with the use of TCM (19).

The 18-29 age group has the most faith in TCM's effectiveness and has benefited from it in the past. Although the most known and used method among the age groups is herbal therapy, the age group that knows and uses this method the most is the 30-50 age group. In studies, it was found that the use of TCM increased in middle and advanced ages (14,21). In individuals with chronic disease, TCM use was found to be significantly higher in patients aged 65 years and over (12,21,22). Although different studies have shown that the use of TCM is higher in young patients or that there is no age effect on the use of TCM (12,21), in our study, in parallel with this, the youngest group believes that the effectiveness of TCM is the greatest, but the middle-aged group uses it the most. The relationship between advanced age and the use of TCM can be attributed to the increase in chronic diseases as people grow older and seek solutions other than modern treatment methods.

While there was no difference in our study in terms of methods used between genders and believing in the effectiveness of TCM, it was significantly higher for women in the past to benefit from TCM, and women use TCM more. Although there are studies in the literature that do not find any difference between genders in terms of TCM use (13,21,22), there are also many studies supporting women using TCM in accordance with our findings (23,24). Although it is clearly shown in most studies that women use TCM more than men, national and regional differences are remarkable in terms of the method used. The most commonly used TCM method in our study was herbal therapy, and the majority of women in our study group may have caused this result.

In terms of educational status, it was determined that university graduates knew more about TCM and high school graduates used herbal therapy more. Although there is no difference, the group that believes in the

effectiveness of TCM is the group of university graduates, while the group that has benefited from TCM in the past is the group of primary school graduates. Although there are many studies in the literature showing that the use of TCM increases as the level of education increases (23-25), unlike the literature, low education level and TCM use were found to be related in another study (13). Among the reasons for the use of TCM among educated people is to have more information and to search for reliable alternative methods to improve their medical condition (25).

When evaluated in terms of job, the group that did not work knew the herbal therapy better and believed more in the effectiveness of TCM. In this group, the rate of using a TCM that has been beneficial in the past is higher. While the working group used more herbal treatments, there was no difference between the statistically working and non-working groups. Although some studies (24-26) have shown that the working group uses TCM more than the non-working group, TCM is used mostly by the working group in our study. In the study of Erci (27), it was shown that the group who did not work against TCM had a positive attitude and the officers had a negative attitude (26). The explanation of TCM being used more by the working group may be that this group investigates, knows the TCM methods more, and shares this information with each other in the workplace, because of which they are affected.

Those who have chronic illnesses but do not use drugs regularly have a higher rate of benefit from TCM in the past. Many people with chronic illnesses are afraid of drug side effects, so they cannot take their medication regularly or quit. As a result, they turn to TCM, which they find more natural and reliable.

When socio-demographic characteristics were evaluated with those who used any TCM and benefited from this treatment, a statistical difference was found only in the presence of chronic disease. More than half (52.2%) of those with chronic diseases have previously used this treatment and benefited from it. Although some studies (24-26) stated that healthy people develop negative attitudes toward TCM and use less, in our study, healthy people without chronic disease wanted more information about this issue and suggested more TCM in their environment.

The desire to obtain information about TCM was found more in the 30-50 age group: women, married people, children with children, primary school graduates, workers, housewives, SSIs, and those without chronic diseases. Those living in eastern provinces, women aged 18-29 years, divorced, people with children, university graduates, non-employed, green card holders, those without chronic illness, and drug users want information about TCM.

Study Limitations

Our study was conducted in various provinces across different regions of Turkey; however, it may not fully represent the entire country. Another limitation of our study is that we did not inquire about the utilization of TCM by family physicians. This omission stems from the fact that the surveys are typically administered by family physicians themselves, raising concerns about potential bias. Our research results are limited to certain cities with patients in FHCs and cannot be generalized to all of Turkey.

One of the strengths of our study lies in its broad geographical scope, which encompasses diverse provinces across Turkey. However, it is important to acknowledge that our study may not offer a comprehensive representation of the entire country. In addition, we took a cautious approach by not investigating the use of TCM among family physicians, as this decision was driven by concerns about potential bias inherent in surveys administered by the physicians themselves.

Conclusion

The use of TCM is very common in Turkey. The most known and used form of TCM is herbal therapy in primary care. Young people believe in the effectiveness of TCM more, whereas middle-aged people use TCM more. While university graduates know more about TCM, collage graduates use it more. While those without children know more about TCM, women have benefited more from using TCM in the past. The non-working group (housewives, students) had a better understanding of herbal treatment, believed more in the effectiveness of TCM, and the rate of using a TCM that has been beneficial in the past was higher in this group. SSI members have more information about TCM. Information about TCM is obtained from family members. The desire to obtain information about TCM was found more in the 30-50 age group, women, married people, who have children, primary school graduates, workers, housewives, SSIs, and those without chronic diseases. In this respect, family physicians have special importance and should be able to direct patients who want to receive information correctly and safely. Family physicians are actually advantageous in this respect, as patients who want information are more frequently referred to FHCs. Therefore, health policies and academic knowledge should be developed in this context.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the ethics committee of the Akdeniz University Faculty of Medicine Clinical Research for the study (approval number: 309, date: 01.06.2016).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: R.S.G., Design: R.S.G., Data Collection or Processing: R.S.G., M.C., E.C., O.A., S.H.K.S., M.A., Ahef Bilim Kurulu, Analysis or Interpretation: A.D., Literature Search: P.B., R.S.G., D.A.B., Writing: P.B., R.S.G., D.A.B.

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Original Article

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Medial Open Reduction via Anteromedial Approach in Developmental Hip Dysplasia: Long-term Clinical and Radiological Outcomes

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Abstract

Aim: The anteromedial approach in medial open reduction techniques is rarely used to treat developmental dysplasia of the hip (DDH). The objective of this study was to present the clinical and radiological outcomes of DDH patients treated with the anteromedial approach.

Methods: Fifty-nine hips of 52 patients aged between 6 and 18 months who underwent medial open reduction between 2009 and 2017 through an anteromedial approach and who had at least 5 years of follow-up were retrospectively evaluated. Results were reviewed in terms of avascular necrosis (AVN) rates and the need for further surgery.

Results: At the last follow-up, the rate of clinically significant AVN was 11.9%. Additional corrective surgery was performed on 20.3% of the patients. According to the modified McKay classification, 91.5% of the patients had excellent results. Radiologically, 93.2% of the patients were classified as Severin type 1. The mean age at operation time and initial Tönnis type of patients were significantly higher in patients who required advanced corrective surgery than in those who did not (p=0.042 and p=0.018, respectively).

Conclusion: The anteromedial approach is safe and practical for improving radiological outcomes and reducing the need for further surgery. Long-term studies focusing on the period after bone formation are required.

Keywords: Anteromedial approach, avascular necrosis, developmental dysplasia of the hip, medial open reduction, further surgery

Introduction

The primary goal of developmental dysplasia of the hip (DDH) treatment is to enable healthy joint development to provide a functionally congruent hip joint (1). Further goals of treatment are to prevent avascular necrosis (AVN) of the femoral head and to avoid the need for further corrective surgery (FCS) (1). In the first 6 months of infancy, closed reduction of the hip using an abduction othosis such as the Pavlik harness is considered to be the primary treatment modality (2). When nonsurgical treatment fails to achieve sustained reduction, the surgeon may proceed with open reduction. In this age group, soft tissue procedures are preferred for the surgical treatment of DDH. The surgical approach for reduction, however, is contentious (3). Anterior and medial approaches have been defined, with some advantages and disadvantages compared with each other. Smaller incision, shorter operation time, less soft tissue dissection, less blood loss, and direct visualization of anatomic structures such as the contracted inferior joint capsule, transverse acetabular ligament, and thickened and elongated ligamentum teres are the major advantages of the medial approach; however,there is an ongoing debate on the relatively longer learning curve and a higher rate of AVN of the femoral head (4).

The anterior approach is generally reserved for older children after the walking age and has the advantage of capsular plication when an elongated capsule leads to joint instability after reduction of the femoral head. In addition, acetabular procedures may be enclosed with an open reduction procedure through the same approach (5). Avascular necrosis is a well-known complication of both anterior and medial approaches (6).

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Ludloff was the first to describe the medial approach for open reduction of the hip joint (7). Ferguson refined this method by crossing the space posterior to the adductor longus (8). Weinstein and Ponseti modified the anteromedial method (9). The rates of AVN and FCS associated with open reduction of the hip joint vary widely in the literature, with the medial approach being more commonly associated with AVN and FCS (2).

The purpose of this study was to compare the mid-term clinical and radiographic results of the anteromedial Weinstein approach in children with DDH aged between 6 and 18 months.

Methods

Compliance with Ethical Standards

This study was conducted retrospectively in accordance with the standards of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (date: 11.05.2022, and approval number: 06-2022) and the 1975 Declaration of Helsinki, which was revised in 2013. Between May and October 2022, from the date of ethical committee permission, the study was conducted using a retrospective data collection. Parents who agreed to participate in the study were informed that the data would only be used in scientific research, and a written informed consent form was signed during the final visit.

Study Design

A total of 89 consecutive patients who underwent medial open reduction for DDH from 2009 to 2017 were retrospectively reviewed. The inclusion criteria for this study were patients who had Weinstein anteromedial open reduction for DDH with a minimum follow-up of 5 years. The exclusion criteria for this study were patients with a diagnosis of neuromuscular disease, teratologic hip dislocation, or skeletal dysplasia, and those who had undergone postomedial Ferguson or Ludloff medial open reductions. The remaining 59 hips of 52 children were enrolled in the trial after 37 children were excluded based on the inclusion criteria.

Surgical Technique

All procedures were performed by a single senior surgeon. Before open reduction, an arthrogram was performed. All patients with insufficient consentic reduction were operated on using the anteromedial approach described by Weinstein (Figure 1) (6). Bilateral dislocations were treated simultaneously.

Following transverse incision and adductor longus release, the iliopsoas tendon and medial joint capsule were identified between the pectineus muscle and the neurovascular bundle, as described by Weinstein (Figure 2). After careful release of the iliopsoas tendon (Figure 3), the medial cicumflex artery (Figure 4) was identified and saved before opening the joint capsule. We believe that the medial circumflex artery and medial joint capsule can be better identified, and thus, a possible insult to the artery, which may facilitate vascular necrosis, may

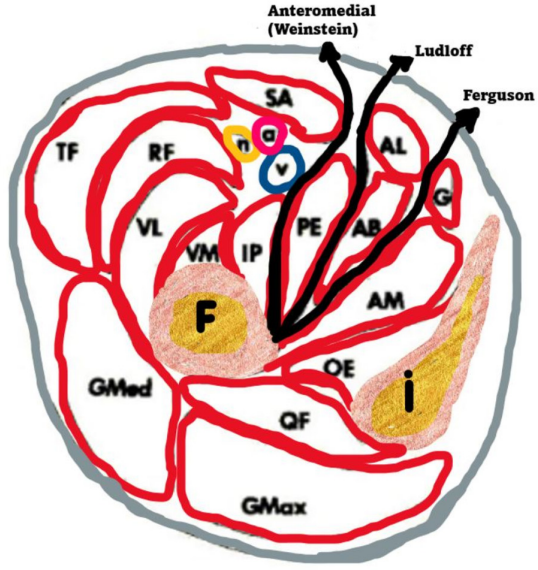

Figure 1. The various intervals used for medial open reduction are shown in this illustration

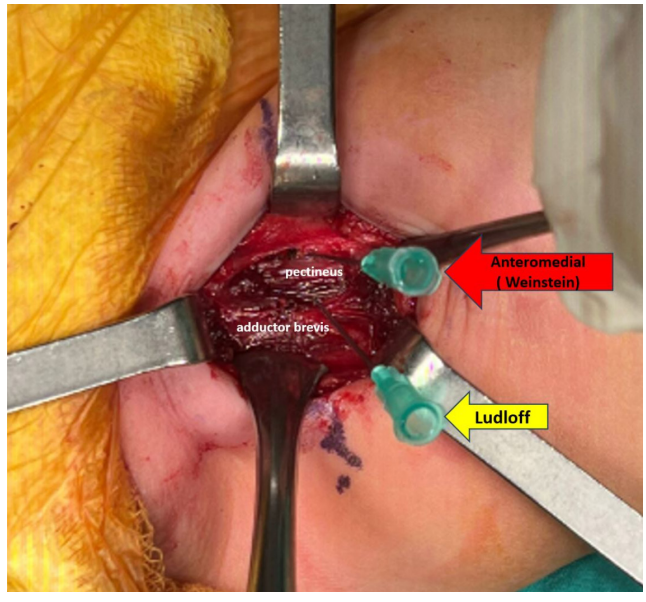

Figure 2. Intraoperative imaging of the anteromedial and Ludloff intervals relative to the pectineus and adductor brevis muscles

be better avoided by this approach. After opening the medial capsule, the ligamentum trees and pulvinar were identified and excised, the transverse acetabular ligament was released, and concentric reduction of the femoral head was achieved. The capsule was closed with loose sutures, and a hip spica cast was applied in the human position.

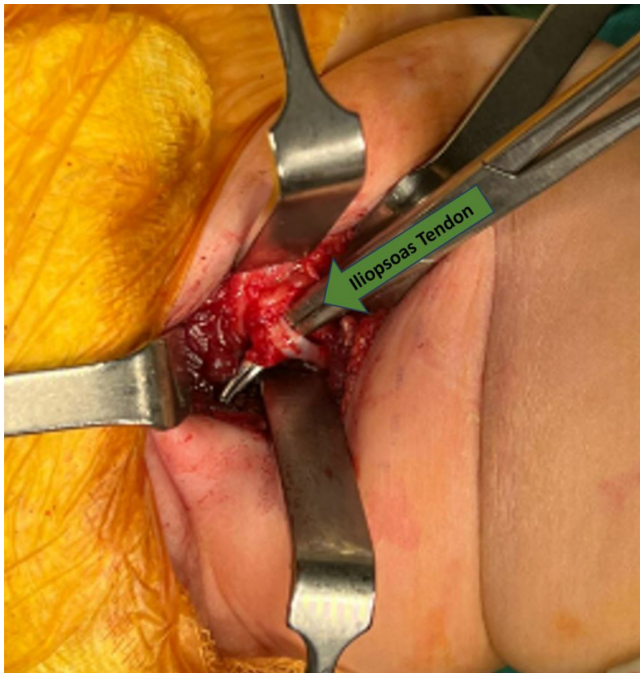

Figure 3. The iliopsoas tendon is identified in the intraoperative picture

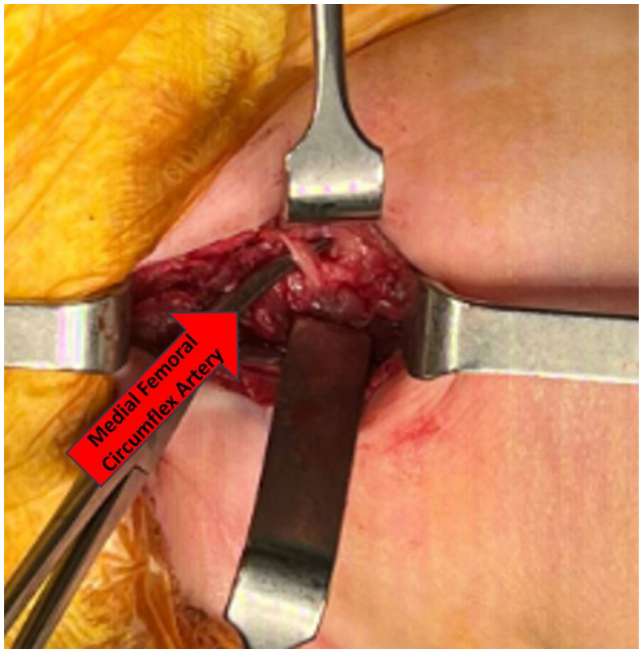

Figure 4. Intraoperative image identifies the medial femoral circumflex artery

At the sixth week postoperatively, the spica cast was removed in the operating room, and a new spica cast was applied after gentle manipulation of the hip joints. The total time in the spica cast was 3 months for all patients. If there was any doubt regarding concentric reduction after postoperative pelvic X-rays, a computed tomography scan was used to assess reduction, but it was not performed routinely. Following removal of the spica cast, an abduction brace was administered for an additional 3 months to treat residual acetabular dysplasia.

Clinical Evaluation

After taking a detailed patient history, a physical examination was performed to assess active symptoms, hip range of motion, pain and limping status, functional status, motion restriction, and gait pattern. Clinical and functional results of the patients were evaluated according to the modified Mckay clinical scoring system. The Iowa hip score questionnaire was filled out by the patient's parents for patients aged ten years or younger; for patients aged 11 to 18, the questionnaire was filled out by the patient.

Radiological Evaluation

Preoperative radiological evaluation of pelvic radiographs was performed according to the Tönnis classification. The Kalamchi and MacEwen classification was used to assess AVN at one year and at the latest follow-up. The center-edge (CE) angle was measured five years after surgery and at the most recent follow-up to allow Severin classification of the hips. Severin types I and II were considered to represent a good result, and types III, IV, V, and VI were considered to represent a poor result.

Patients who underwent FCS were identified by examination of their surgical records. Patients who required additional open reduction, pelvic osteotomy, and femoral osteotomy were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 for Windows (IBM Corp., Armonk, New York). Descriptive statistics were provided, including the mean, standard deviation, minimum and maximum values for numerical variables, and numbers and percentages for categorical variables. When the normal distribution condition was satisfied, the Student's t-test was used to compare numerical variables between two independent groups. When the condition was not satisfied, the Mann-Whitney U test was used. Two dependent group analyses were analyzed using the paired t-test because the differences in numerical variables provided the normal distribution condition. The relationships between numerical variables

were analyzed by Pearson correlation analysis when the parametric test condition was met and by Spearman correlation analysis when the condition was not met. The rates in the groups were compared using the chi-square test. P≤0.05 were considered statistically significant.

Results

The patient's baseline characteristics are shown in Table 1. The mean follow-up of the patients was 86.9±30.7 months. The mean age of the patients at the last follow-up was 97.7±31.3 months. In 66% of the patients, there was no initial hip screening with ultrasonography. The average age at the time of surgery was 10.4 months.

A total of 17 children (32%) had previously failed conservative treatment that included a Pavlik harness in eleven cases, a double diaper in two cases, and a closed reduction in four cases; 35 children had no previous treatment.

Preoperative radiological evaluation findings are demonstrated in Table 2. Prior to surgery, the mean AI of the affected hip was 37.4°±6.7° (19-50°) and remained significantly higher than that of the unaffected side five years later (p<0.001). At the final follow-up, the mean CE angle was 27.1°±7°, significantly lower on the affected side (p<0.05), and within normal ranges.

Final follow-up clinical and radiological evaluation findings are presented in Table 3. The overall final follow-up revealed excellent or good results in 57 hips (96.6%), of which Severin type I was found in 55 hips (93.2%) and type II in 2 hips (3.4%). A total of two hips (3.4%) were Severin type III, which had a poor outcome; no type IV, type V, or type VI hips existed.

Clinically significant (Type 2 and above) AVN rates were determined to be Type 2 in 5 (8.5%) hips, Type 3 in 1 (1.7%) hip, and Type 4 in 1 (1.7%) hip. According to the Kalamchi and MacEwen classification, the clinically significant AVN rate in this study was 11.9%.

Table 1. Baseline characteristics of patients in the study

Characteristic	Total n=52 (hips, n=59)
Female gender, n (%)	41 (79)
Side, n (%)	
Left	28 (54)
Right	17 (32)
Bilateral	7 (14)
Mean age at surgery, months (SD)	10.4±4.2
Mean age at final follow-up, maths (SD)	97.7±31.3
Mean follow-up time, ms (SD)	86.9±30.7

SD: Standard deviation

Table 2. Preoperative radiological evaluation findings

Characteristic	Hips, n
Tonnis classification	
Grade II	1
Grade III	32
Grade IV	26
Mean AI degree (°) (range)	
Affected hip	37° (19 to 50)
Contralateral stable hip	25° (13 to 40)

AI: Acetabular index

Table 3. Latest follow-up clinical and radiological evaluation findings

Characteristic			
AI at the final follow-up* degree (°)		19.4±6.7 (6,7-40)	
Final CEA** degree (°)		27.1±7.0 (2-42)	
Modified Mc-Kay Criteria; n (%)	Excellent Good Fair Poor	54 (91) 4 (6) 1 (2) 0	
Severin's Radiographic Classification Class; n (%)	I II III IV	55 (93) 2 (3.5) 2 (3.5) 0	
Presence of AVN n (%)	Yes No	7 (12) 52 (88)	
Kalamchi and MacEwen Criteria**** Type I-IV; n (%)	II III IV	5 (8) 1 (2) 1 (2)	
Further corrective surgery n (%)	Yes No	12 (20) 47 (80)	
Type of revision surgery n (%)	Salter osteotomy Femoral osteotomy	11(18) 1 (2)	

*AI acetabular index, **CEA center-edge angle, ***The presence of clinically significant AVN based on the Kalamchi and MacEwen criteria, ****Severity of AVN according to Kalamchi and MacEwen criteria

At the final follow-up, patients clinical status was assessed using the McKay functional classification system. Fifty (91.5%) hips were classified as Type 1 (excellent), four (7%) hips were classified as Type 2 (good), and one (1.7%) hip was classified as Type 3 (poor) (moderate).

Further corrective surgery was administered to 12 (20%) hips. Figure 5 shows normal anatomical development of the hip after MAR, and Figure 6 includes examples of patients who underwent Salter osteotomies for residual dysplasia after MAR. Salter osteotomies were performed in 11 hips, and femoral valgization and derotation osteotomies were performed in one patient (Figure 7).

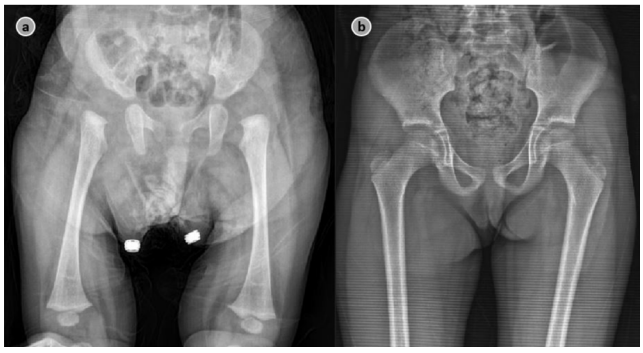

Figure 5. Radiographic views of bilateral hips undergoing MOR. AP radiographs of a 10-month-old female with bilateral DDH before and 9 years following anteromedial open reduction
DDH: Developmental dysplasia of the hip, AP: Anterior posterior

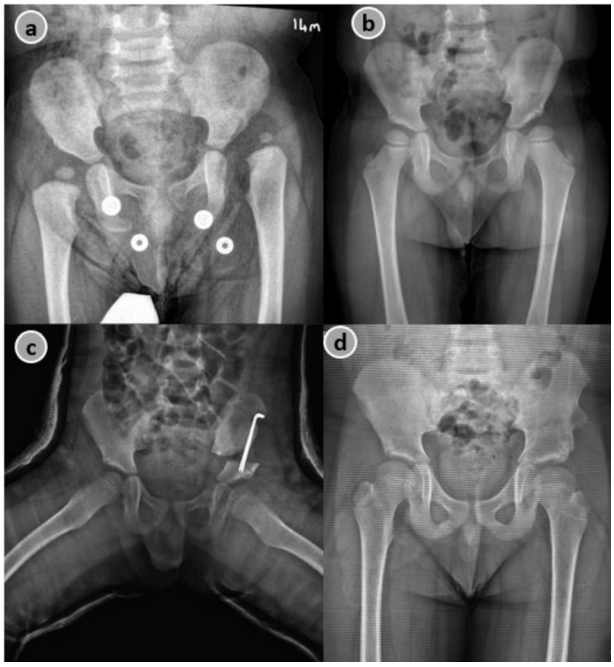

Figure 6. Radiographic views of a hip undergoing MOR and Salter osteotomy. Anteroposterior radiographs of a 14-month-old male with left DDH before (a), 2 years after MOR with left residual dysplasia of the hip (b), 3 years after MOR undergoing Salter osteotomy (c), 11 years following MOR (d)
DDH: Developmental dysplasia of the hipç

At the last follow-up, CE angle was found to be negatively correlated with age at the time and stage of preoperative Tönnis classification (p=0.015 and p=0.033, respectively) (Table 4). The preoperative Tönnis Type 4 ratio of hips requiring FCS was significantly higher (p=0.018) (Table 5).

In this study, wound complications related to casting occurred in two patients. Debridement and recasting were performed on these patients. All patients were discharged on the second day after surgery.

Discussion

During early childhood, open reduction of DDH via the medial approach is an effective surgical treatment method. Two main medial intervention methods are currently being applied: Ludloff's method (anteromedial) and Ferguson's method (posteromedical) (10). Ludloff described an interval between the pectineus and adductor brevis called the anteromedial approach.

Weinstein and Ponseti reported a method similar to that described by Ludloff. They used the interval via the pectineus and femoral vessel nerve bundles to reach the capsule. To protect the medial circumflex artery, which crosses the operative field, the femoral vessel nerve pack

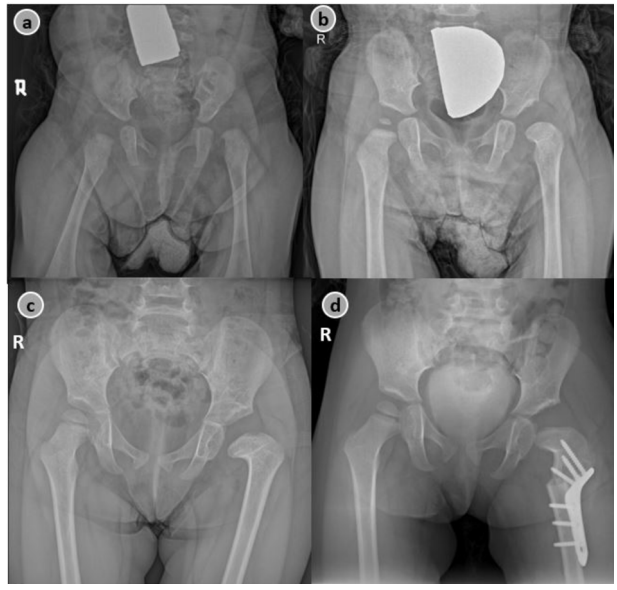

Figure 7. Radiographic views of a hip that developed AVN after MOR and is undergoing valgization osteotomy. Anteroposterior radiographs of a 7-month-old female with left DDH (a), AVN development in the left hip in the first year postoperatively (b), 2 years following MOR (c), and 4 years after MOR, valgisation osteotomy was performed (d)
AVN: Avascular necrosis, DDH: Developmental dysplasia of the hip

Table 4. Relationship between age at the time of surgery and preoperative hip stage in patients final AI and final CEAs				
	Mean age at surgery, months (SD)		Preoperative Tönnis Hip Classification	
	r	p	r	p
Final AI	0.123	0.366	0.091	0.505
Final CEA	-0.322	0.015	-0.286	0.033
AI: Acetabular index, CEA: Center-edge angle, SD: Standard deviation				

Table 5. Association between age at the time of surgery and preoperative hip stage in patients requiring FCS				
		Mean age at surgery, months (SD)	Preoperative Tönnis Hip Classification	
			Grade 3	Grade 4
		Mean ± SD	n (%)	n (%)
FCS	No	10.2±4.1	29 (63.0)	17 (37.0)
	Yes	12.7±4.5	3 (25.0)	9 (75.0)
	p	0.067	0.059	0.018
FCS: Further corrective surgery, SD: Standard deviation				

must be gently identified and laterally retracted with an elevator. The medial circumflex artery provides the major blood supply to the femoral head, and any insult during the intervention may lead to AVN.

The literature reports an upper age limit of 18 months for open reduction with the medial approach. Ferguson increased this limit to 24 months (8). Weinstein stated that it can be used until the age of 3 years, while Herring set the upper age limit at 12 months (9,10). There have been studies published in Turkey in which the authors claim that it can be used safely for up to 24 months (11). In this study, we found a statistically significant increase in poor results due to residual dysplasia as the patients got older at the time of surgery. We also found a statistically significant decrease in the CE angle with increasing patient age at the last follow-up. Similar articles have found that a greater age at the time of reduction has a significant adverse effect on radiological outcomes (6). Okano et al. (12) also demonstrated the importance of a younger age for medial open reduction in their research.

Avascular necrosis and residual dysplasia are two important complications for treating DDH. Damage to the medial circumflex artery, in particular, may result in AVN, one of the most feared complications during treatment. Dysplasia of the hip appears to be the leading cause of adult hip arthroplasty. Clinically significant AVN rates of up to 67% have been reported in studies, with an intensity of 10-30% in medial open reduction (4). In a recent meta-analysis, the rates of AVN in open reduction alone in patients younger than three years of age were 94.4%; however, this meta-analysis included transient AVN results as well as permanent AVN findings (13). Transient AVN findings in the early stages of DDH may regress over time. There have been studies that show the need for advanced corrective surgery after MOR ranges from 23 to 54%, but the reported rates are variable. Medial approaches are preferred because they provide direct access to structures, resulting in less blood loss, no damage to the iliac apophysis and abductor muscles, and better cosmetic results.

Among the medial approaches, the Ludloff and Ferguson approaches are frequently preferred, according to the literature. In different studies, it is stated that successful results were obtained with various modifications of limited postermedical and medial approaches (11,14).

We prefer the anteromedial Weinstein approach in our practice, which is less popular than the other medial approaches. We believe that this approach allows for more direct access to the hip joint and allows us to identify and protect the medial femoral circumflex artery more easily compared with the Ludloff and Ferguson approaches. According to our hypothesis, lower AVN rates are expected.

In this study, we found a clinically significant AVN rate of 12%, and the rate of further advanced corrective surgery was 20%. Cummings et al. (15) found a 1/3 requirement for corrective surgery in patients following open reduction in a recent study. It was discovered that the rate of postoperative AVN increased with the stage of hip dislocation. Similarly, we discovered that the rate of AVN increased with the stage of preoperative tennis hip dislocation in our study.

Koizumi et al. (16), in their study of 35 hips in 1996, reported a 42% incidence of AVN. Further corrective surgery rates were %46. They had 19.4 years of follow-up. In 1997, Morcuende et al. (17) revealed a 41% AVN rate in their series of 93 hips who had anteromedial open reduction, a mean follow-up of 11 years, and a FCS rate of 17%. Okano et al. (18), in their series of 45 hips with 16.4 years of follow-up in 2009, reported 29% AVN, and Yamada in 2013, reported 28% AVN and 64% FCS in their series of 115 hips with 20.3 years of follow-up.

Pollet et al. (6) reported 19% AVN and 22% FCS in their series of 58 hips with 12.7 years of follow-up. Ozkut et al. (19) performed postermedial limited surgery on 62 hips in 47 patients and found the clinically significant AVN rate to be 1% and the need for corrective surgery to be 3.2%.

Erturk et al. (20) published the results of 35 hips from 24 patients operated on using the Weinstein approach, which is similar to our study. The author reported a 14.2% need for advanced hip surgery and a 17.1% incidence of AVN (20).

Study Limitations

The most important limitation of studies on DDH is that most are retrospective. Kiani et al. (21) found an AVN rate of 44% and residual dysplasia of 55% in short-term follow-up in a large and prospective study. These results are higher than those of other studies. Transient AVN and residual dysplasia can be seen at a high rate in the early period of DDH treatment, but the development of the hip continues, and more moderate results can be obtained in long-term follow-ups.

The major limitations of this study are that it is a retrospective study and some patients have not yet reached skeletal maturity at the final evaluation. It should be considered that the development of the acetabulum will continue until it reaches skeletal maturity, and the results may vary after skeletal maturation. A relatively smaller study group and shorter mean follow-up compared with the literature are other limitations. The fact that all patients are operated on by a single surgeon with experience in pediatric orthopedics is advantageous in terms of consistency in results. This study is one of the few in the literature that examines the outcomes of Weinstein's anteromedial open reduction in DDH, despite its limitations.

Conclusion

In this study, one in every five children required additional corrective surgery, and one in every eight children developed clinically significant AVN. Medial open reduction via the anteromedial approach yields excellent clinical and radiological outcomes for treating DDH. Anteromedial open reduction for conservatively irreducible hips in young children is a safe and feasible intervention to achieve better radiological results and reduce the need for additional corrective surgery. To achieve better results without AVN and the need for FSC, medical open reduction should be performed early in the appropriate indication and age group. Long-term studies focusing on the period after bone formation are required.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (date: 11.05.2022, and approval number: 06-2022).

Informed Consent: Written informed consent form was signed during the final visit.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.S., Concept: E.G., Design: E.G., I.S., Data Collection or Processing: E.G., Analysis or Interpretation: E.G., I.S., Literature Search: E.G., I.S., Writing: E.G., I.S.

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

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Original Article

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Comprehensive Analysis of Prognostic Factors Affecting Postoperative Mortality in Adult Patients Undergoing Lower Extremity Amputation due to Diabetic Foot Ulcer

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Abstract

Aim: Mortality is significantly increased in patients undergoing amputation for diabetic foot ulcers (DFUs). The new biomarkers prognostic nutritional index (PNI), C-reactive protein (CRP)/albumin ratio, and comorbidities may help predict prognosis. This study aimed to determine the factors affecting mortality in DFU patients undergoing amputation.

Methods: This study is a retrospective case series of patients who underwent lower extremity amputation due to DFU between 2016 and 2018. Data on demographics, clinical information, laboratory test results, comorbidities, hospital stays, re-amputations, and complications were recorded. PNI was calculated using serum albumin concentration and lymphocyte count.

Results: A total of 97 patients (21 females and 76 males) were analyzed in the study, with 18 patients having bilateral lower extremity amputations (foot amputation, below-knee amputation, and above-knee amputation). The mean age was 64.48 years, and the mean follow-up period was 34.27 months. The mean length of hospital stay was 19.09 days, with a mean of 1.34 days spent in the intensive care unit. Preoperative laboratory test results showed a mean creatinine level of 1.4 mg/dL, a urea level of 55.22 mg/dL, an albumin level of 2.8 g/L, and a fasting blood glucose level of 168.8 mg/dL. The mean preoperative PNI was 39.31, and the mean CRP/albumin ratio was 42.51. Intensive care unit admission, CRP/albumin ratio, and CRP levels significantly affect 1-year postoperative mortality. The cut-off value for CRP as determined by receiver operating characteristic analysis was 89.9 mg/L. No significant association was found between comorbidities and mortality.

Conclusion: We demonstrated that comorbidities and the new biomarker PNI did not affect mortality. CRP levels, intensive care unit admission, and the new predictor CRP/albumin ratio significantly affected 1-year mortality.

Keywords: Diabetic foot ulcer, amputation, prognostic nutritional index, C-reactive protein, C-reactive protein/albumin ratio

Introduction

Diabetic foot ulcer (DFU) is one of the most difficult diseases to manage among emergency department admissions. DFU is a serious complication of diabetes mellitus that affects millions of individuals worldwide (1). It is characterized by the formation of chronic wounds on the feet, often leading to severe infections and tissue damage. In some cases, amputation becomes necessary to prevent the spread of infection and improve the patient's quality of life (2). However, amputation is associated with significant postoperative mortality rates, making it crucial to identify prognostic factors that influence patient outcomes (3).

It has been claimed that comorbidities affect postoperative mortality in patients with DFU (4). Conditions such as cardiovascular disease, chronic kidney disease, peripheral arterial disease, and chronic obstructive pulmonary disease contribute to increased surgical risk, delayed wound healing, and higher rates of infection, ultimately leading to a higher mortality risk (4). Managing and optimizing the control of these comorbidities before and after amputation is essential for improving patient outcomes.

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Infection is a major complication of DFUs and strongly influences postoperative mortality. The presence of infection at the time of amputation, particularly deep-seated or systemic infections, is associated with poorer outcomes and increased mortality rates (5). Furthermore, elevated levels of inflammatory markers, such as C-reactive protein (CRP), have been linked to a higher mortality risk in patients with DFU undergoing amputation (6,7). Early detection and management of infections, along with monitoring of inflammatory markers, are crucial for reducing postoperative mortality rates. We believe that promising new biochemical values [such as prognostic nutritional index (PNI) and CRP/albumin ratio], which are also used to predict other complications of diabetes, may provide guidance in predicting survival after amputation (8).

The aims of this study were (1) to investigate the relationship between biomarkers, comorbidities, length of intensive care unit (ICU) stay, and mortality, and (2) to examine the factors affecting the need for re-amputation in a single tertiary referral center. This study provides a comprehensive analysis of the prognostic factors affecting postoperative mortality in patients undergoing amputation due to DFUs.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2022/89, date: May 11, 2022) and conducted in accordance with the principles of the Helsinki Declaration. The participants were informed that the data would only be used for scientific purposes.

Study Design

The medical records of 109 patients who underwent lower extremity amputation due to DFUs between 2016 and 2018 at our institution were retrospectively identified. The inclusion criteria for the study were: (1) patients with DFUs (2) patients undergoing lower extremity amputation (foot amputation, below-knee amputation, and above-knee amputation), and (3) complete clinical and radiographic data. The exclusion criteria were: (1) patients who underwent surgery for reasons other than diabetes foot ulcers; (2) lost to follow-up; and (3) inadequate medical records.

Based on the above eligibility criteria, after excluding 12 patients, the remaining 97 patients were included in the study (Figure 1). Demographic and clinical data were collected from the hospital's electronic database and medical records, including gender and follow-up duration. The study was designed in two parts. In the first part, the relationship between laboratory test results, comorbidities, ICU length of stay, and 1- and 5-year survival was investigated. The PNI was calculated using serum albumin concentrations and lymphocyte counts in the peripheral blood. In the second part, the factors affecting re-amputation were reviewed.

Intra- and postoperative complications were recorded. Patients who underwent revision surgery are noted.

Statistical Analysis

Statistical analysis was performed using the SPSS (IBM, Armonk, New York, USA) version 24.0 statistical software. Descriptive statistical methods were used to evaluate the study data. A Kaplan-Meier survival analysis was performed. Furthermore, potential prognostic factors were identified by univariate Cox regression analysis. Elements with p values (two-sided) of 0.05 were included in the multivariate Cox proportional hazard model to identify independent variables in a stepwise fashion. Receiver operating characteristic curves were generated to determine the accuracy of the data. Differences with $p \leq 0.05$ were considered statistically significant.

Results

The demographic data of the patients is presented in Table 1. According to the Kaplan-Meier analysis, the 1-year and 5-year survival rates of patients were 70% (68/97) and 43% (42/97), respectively (Figure 2).

In part 1, preoperative mean creatine was 1.4±1.5 mg/dL and urea was 55.22±38.16 mg/dL. The mean

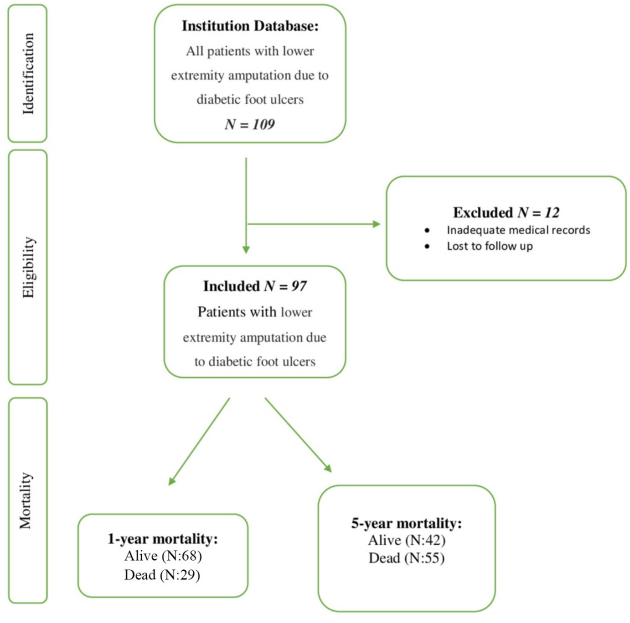

Figure 1. Flow chart of the study

preoperative albumin level was 2.8 2.8±0.6 g/L. The mean preoperative fasting blood glucose of the patients was measured 168.8±78.1 mg/dL. The mean preoperative PNI and CRP/albumin ratios of the patients were 39.31±16.1 and 42.51±42.89 respectively. In the statistical analysis, it was found that the CRP/albumin ratio (p=0.045) and CRP levels (p=0.032) significantly affected the 1-year mortality of the patients in the postoperative period. Receiver operating characteristic analysis was performed, and the cut-off value for CRP was found to be 89.9 mg/L (Figure 3). The mean length of hospital stay was 19.09±15.94 days, and the mean length of stay in ICU was 1.34±3.37 days (range, 0-14). We observed that the length of stay in the intensive care unit (p=0.002) was an independent risk factor for 1-year mortality. When comorbidities were examined, no correlation was found between hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, peripheral artery disease, coronary artery disease, renal disease, dementia, and mortality. When the relationship between comorbidities, laboratory test results, and 5-year survival was analyzed, we observed that the factors examined had no effect on mortality.

In part 2, when the relationship between the aforementioned parameters and re-amputation was examined, we found that ICU length of stay (p=0.014), preoperative platelet/lymphocyte ratio (PLR) (p=0.014), and preoperative fasting blood glucose (p=0.032) were independent risk factors.

Discussion

Diabetes mellitus is a systemic disease that simultaneously affects many systems in the body and is associated with an increased incidence of morbidity and mortality. DFU is one of the most difficult and serious complications of diabetes mellitus and has a direct impact on survival. The current literature focuses mainly on the progression of diabetic wounds, but we have chosen to focus on the factors that influence mortality after lower extremity amputation. The findings highlight the importance of identifying and addressing these factors in clinical practice, revealing several key factors that significantly influence patient outcomes.

While there are many studies examining mortality after DFU in the literature, there are very few studies examining mortality after amputation. In our study, our mortality rates after amputation were found to be compatible with those reported in the literature (9). Elderly patients often present with reduced physiological reserves and a higher burden of comorbidities, which may impair their ability to tolerate and recover from surgery. Contrary to previous studies, advanced age does not have a significant effect on increasing postoperative mortality in patients with DFU undergoing amputation (10).

Table 1. The demographic data of the patients	
Number of patients	**97**
Age (years)	64.48±11.41 (range, 38-90)
Gender (Female/Male)	21/76
Bilateral/unilateral amputation	18/79
Follow up period (months)	34.27±24.05 (range, 0.03-99.8)

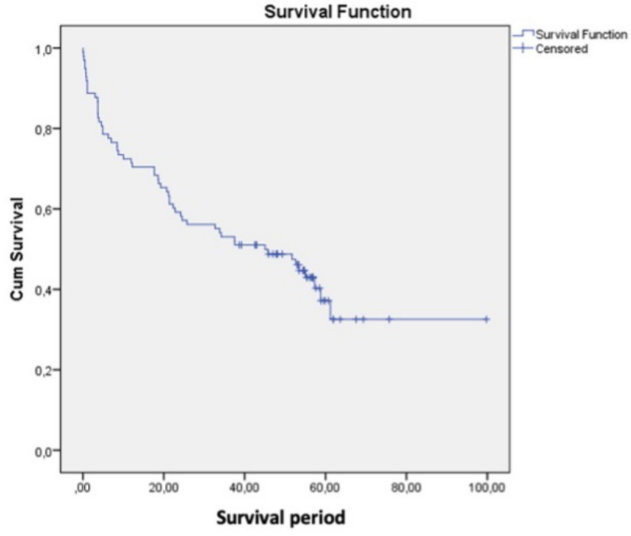

Figure 2. The Kaplan-Meier curves illustrating the survival

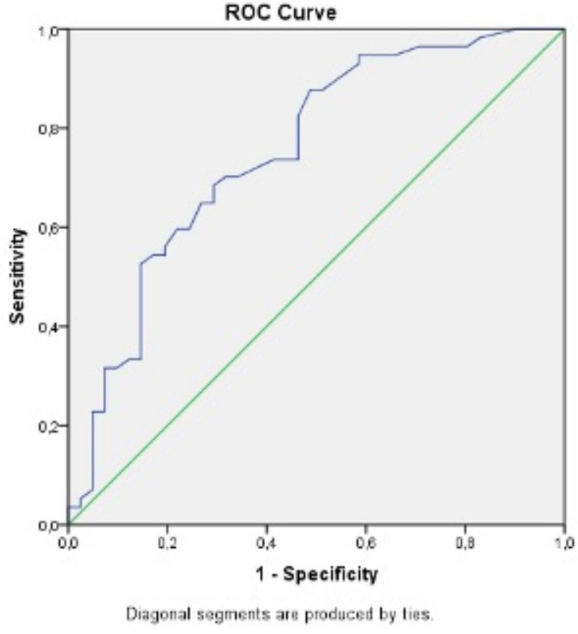

Figure 3. ROC curve for CRP levels (cut off-89,9, sensitivity: 0.702 specificity: 0.683)
ROC: Receiver operating characteristic, CRP: C-reactive protein

Table 2. Laboratory test results at the time of admission to the emergency department	
	Mean ± SD
CRP (C-reactive protein) (mg/L)	104.96±87.84
Hemoglobin (g/dL)	10.41±1.83
HbA1c (%)	9.39±2.29
WBC (White blood cells)	12.13±5.97
Neutrophil	9.97±8.25
Lymphocyte	2.25±3.05
NLR (Neutrophil to lymphocyte ratio)	6.21±4.78
RDW (Red blood cell distribution width)	34.09±184.01
PLT (Platelet count)	351.22±150.04
PLR (Platelet/lymphocyte ratio)	220.38±130.93
Urea (mg/dL)	55.27±37.97
Creatine (mg/dL)	1.42±1.52
Fasting blood glucose (mg/dL)	167.24±78.18
Albumin (g/L)	2.80±0.57
PNI (Prognostic nutritional index)	39.31±16.10
CRP/albumin	42.51±42.89
CRP/PNI	3.07±3.04
SD: Standard deviation	

It has been claimed many times in the literature that the presence of comorbidities such as cardiovascular disease, chronic kidney disease, peripheral artery disease, and chronic obstructive pulmonary disease increases postoperative mortality rates (4). These comorbidities create additional risks for the surgical procedure, delay wound healing, and increase susceptibility to infections. Unlike the literature, we did not find a relationship between these comorbidities and mortality. However, it is imperative that healthcare providers comprehensively evaluate and manage these conditions preoperatively to optimize patient outcomes.

Infection remains a major complication in patients with DFU and has a significant impact on postoperative mortality. Worse outcomes and higher mortality rates were observed in patients with deeply located or systemic infections (5). High levels of inflammatory markers, including CRP, have been found to predict increased mortality risk (6,11-14). In our study, we also revealed that CRP has a clear effect on survival. Timely detection, rapid management of infections, and careful monitoring of inflammatory markers are critical for reducing postoperative mortality rates.

The PNI, which is evaluated by peripheral blood lymphocyte count and serum albumin, is a new biomarker that shows the patient's immune status and adaptation to infection and diseases. We did not observe a relationship between PNI and mortality in our study. However, both CRP and the CRP/albumin ratio are biomarkers that have started to be used in the follow-up of diabetic complications. Receiver operating characteristic analysis revealed that the cut-off value for CRP was 89.9, and mortality increased for CRP values ≥90. In our study, we also revealed that these markers are significant predictive factors of survival in DFU follow-up (15).

The relationship between length of hospital stay and diabetes-related amputation has been studied, but to our knowledge, no study has investigated the relationship between length of stay in the ICU and amputation due to diabetes (16). The length of stay in the ICU is an independent risk factor affecting mortality after amputation due to DFU.

Although studies have shown a relationship between cerebrovascular disease, sex, chronic renal failure, and 5-year mortality, we could not find a relationship between 5-year mortality and any of the parameters examined in our study (17).

Studies have been conducted to investigate the causes of re-amputation in patients with diabetes (18). In our study, we found a relationship between re-amputation and the length of intensive care unit stay, preoperative PLR, and pre-operative fasting blood glucose.

Study Limitations

The findings of this study should be interpreted in light of its potential limitations. The most important limitation of the study was that it was retrospective, had a limited sample size, and lacked a case series for comparison. In addition, many surgeons participated in the surgeries. Despite these limitations, the current investigation has several strengths. To the best of my knowledge, this is the first study in the literature showing that the CRP/albumin ratio is effective in predicting mortality after amputation due to DFU, whereas PNI is not effective. In addition, this is one of the rare studies that determined a cut-off value for CRP. All surgeries were performed at a single tertiary referral center. Prospective randomized comparative studies are required in the future.

Conclusion

This comprehensive analysis highlights the importance of considering multiple prognostic factors in evaluating postoperative mortality in patients undergoing amputation due to DFUs. CRP levels, ICU length of stay, and CRP/albumin ratio are independent risk factors for 1-year mortality. Understanding and addressing these prognostic factors is crucial for healthcare professionals to optimize patient care, accelerate wound healing, reduce complications, and ultimately reduce mortality in this vulnerable patient population.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2022/89, date: May 11, 2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.E., M.Ek., M.Y., Design: M.E., M.Ek., M.Y., Data Collection and/or Processing: M.E., M.Ek., E.G., K.A.C., Analysis and/or Interpretation: M.E., M.Ek., Literature Research: M.E., M.Ek., Writing: M.E., M.Ek.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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The Effect of Subcutaneous Teriparatide Treatment on Mobility, Back Pain, and Patient Satisfaction in Patients with Vertebral Osteoporotic Fractures: A Cross-Sectional Study with 36-Month Follow-up

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Abstract

Aim: Although the effectiveness of teriparatide on bone mineral density (BMD), fracture risk, and back pain in severe osteoporosis is known, no comprehensive study has been conducted in the Turkish population regarding its impact on mobility and patient satisfaction. This study aimed to evaluate the effectiveness of teriparatide treatment on mobility, back pain, and patient satisfaction in patients with osteoporotic vertebral fractures, as well as its side effects in midterm follow-up.

Methods: The study was designed as a retrospective, cross-sectional study. Between February 2018 and April 2023, 50 consecutive patients (mean age 69.9±9.0 years; range, 53 to 94 years) who were diagnosed with vertebral fractures due to severe osteoporosis and had received 20 µg/day subcutaneous teriparatide (median, 18 months) were included in the study. The patients were evaluated using BMD measurements, blood tests, radiological imaging, a visual pain score (VAS-pain), mobility assessments [Functional Ambulation Classification (FAC)], and patient satisfaction levels at baseline, 6th, and 18th months.

Results: At 6 and 18 months, a significant decrease in VAS-pain and a significant increase in BMD and FAC were observed ($p<0.001$ for all values). The improvement observed at 6 months continued to increase until the 18th month. 96% of the patients reported being satisfied or very satisfied with the treatment. The treatment of three patients (6%) was discontinued because of side effects in the 15th month of treatment. After the completion of teriparatide treatment, two patients developed clinical vertebral fractures during follow-up. No life-threatening side effects or laboratory abnormalities were observed in any patient.

Conclusion: Teriparatide treatment in severe osteoporotic vertebral fractures with back pain has shown a dramatic reduction in pain and significant improvement in ambulation levels, providing high patient satisfaction with reasonable side effects.

Keywords: Fractures, osteoporosis, teriparatide, back pain, mobility, patient satisfaction

Introduction

Osteoporosis is a chronic, progressive, and most common metabolic bone disease characterized by an imbalance between bone formation and resorption, leading to low bone mass and deterioration of bone microarchitecture, resulting in an increased risk of bone fractures (1). The diagnosis of osteoporosis is based on dual-energy X-ray absorptiometry. The prevalence of osteoporosis increases with age. The rising life expectancy worldwide has made osteoporosis a significant global health and economic problem (2). In Turkey, it is estimated that the prevalence of osteoporosis is over 20% among individuals aged 50 years. However, the diagnostic rate is reported to be approximately 25%, and it is stated that more than three-quarters of the patients are not receiving pharmacological treatment (3).

The most severe and dreaded consequences of osteoporosis are hip and vertebral fractures. Additionally,

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height loss, spinal deformities, including kyphosis and scoliosis, and back pain may occur, leading to restricted mobility. The primary goal of osteoporosis treatment is to prevent new bone fractures by increasing or at least preserving bone mass and quality (1,3). While antiresorptive drugs known as bisphosphonates, which reduce osteoclastic activity, have been widely used for many years, the role of anabolic agents that promote bone formation has recently started to gain prominence in treatment (4). Teriparatide, a recombinant human parathyroid hormone [PTH (1-34)], is the first and only available anabolic agent used for treating postmenopausal osteoporosis, male osteoporosis, and steroid-induced osteoporosis in Turkey (3,5,6). Subcutaneously administered teriparatide, at a daily dose of 20 µg/day, is frequently used in clinical practice for osteoporotic vertebral fractures and is taken daily for 18-24 months (5,6).

In studies evaluating the clinical efficacy of teriparatide, it has been demonstrated that it increases bone density, reduces fracture risk, and improves and decrease back pain and improves quality of life, showing different mechanisms of action from bisphosphonates (6-8). However, the number of significant and comprehensive studies on its impact on mobility and patient satisfaction is limited (8,9). The use of teriparatide in Turkey is restricted because of its narrow indications compared with other antiresorptive agents, high treatment costs, and limited clinical experience related to the follow-up process. In this context, this study aimed to investigate the effects of teriparatide treatment on mobility, back pain, bone mineral density (BMD), and patient satisfaction levels in patients with severe osteoporosis-related painful vertebral fractures, as well as the side effects during midterm follow-up.

Methods

Compliance with Ethical Standards

This study was a cross-sectional study which is a type of observational studies conducted at a tertiary care hospital. Study approval was obtained from the KTO Karatay University Non-Pharmaceutical and Non-Medical Device Research Ethics Committee (date: April 4, 2023, and approval number: 2023/044). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki.

Study Design and Data Collection

Between February 2018 and April 2023, 50 consecutive patients (mean age 69.9±9.0 years; range, 53 to 94 years) who were diagnosed with vertebral fractures due to severe osteoporosis in the Physical Medicine and Rehabilitation outpatient clinics and had received 20 µg/day subcutaneous teriparatide (Forsteo®; Eli Lilly and Company, Indianapolis, IN, USA) treatment were retrospectively examined by reviewing hospital and physician records. During this period, teriparatide treatment was initiated in 51 patients diagnosed with vertebral fractures and severe osteoporosis. Only one patient discontinued follow-up for unknown reasons, resulting in the completion of the study with 50 patients (Figure 1).

The study included patients who presented with acute back pain and had osteoporotic compression fractures detected on thoracolumbar magnetic resonance imaging (MRI) and/or computed tomography (CT) imaging and had a BMD T-score of -1.50 or lower at the lumbar spine, femoral neck, or total hip. In accordance with the literature, patients with radiologically detected vertebral compression fractures corresponding to at least grade 1 according to the Genant classification and showing a minimum of 20% reduction in vertebral height were considered to have osteoporotic fractures (10). Patients with hypercalcemia, hyperparathyroidism, or Paget's disease of bone, those with hyperthyroidism, chronic kidney and liver failure, malabsorption, atypical femur fracture,

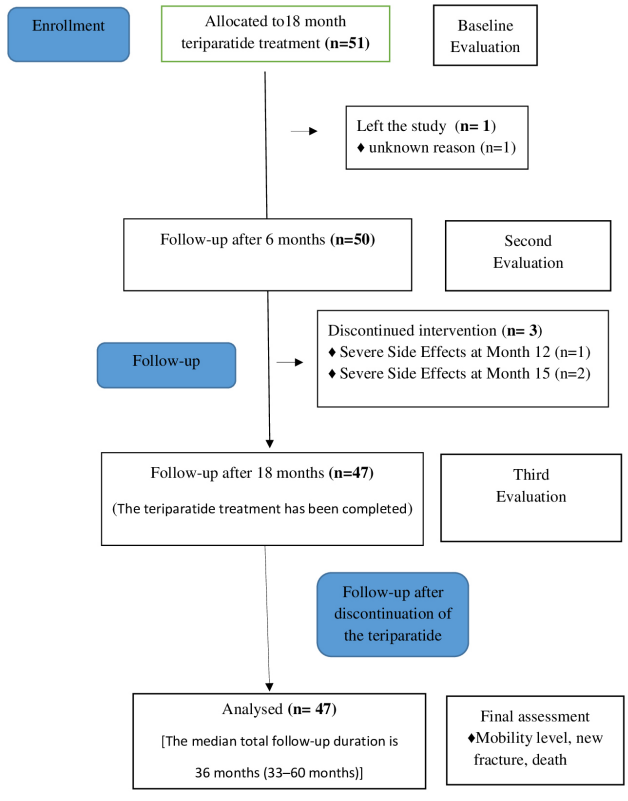

Figure 1. Flow chart of the study

jaw osteonecrosis, direct trauma history in the last 6 months, any other conditions explaining back pain besides osteoporosis, as well as those with unexplained elevation in alkaline phosphatase (ALP) levels, bone malignancies, or metastases, and those who have undergone radiation therapy to the bone, were excluded from the study (6). Additionally, patients who had received zoledronic acid infusion in the last 12 months, denosumab in the last 6 months, or ibandronate intravenous treatment in the last 3 months were also excluded from the study.

Patients' socio-demographic data, such as age, gender, marital status, body mass index, clinical history, medications used for osteoporosis, comorbidities, presence of polypharmacy (≥5 medications), and smoking and alcohol use, were recorded. All patients received daily subcutaneous treatment with 20 µg of teriparatide for a duration of 12 to 18 months. In addition, all patients were administered 1000 mg/day of calcium (Ca), and those with vitamin D deficiency (25-hydroxyvitamin D <20 ng/mL) received additional oral cholecalciferol supplementation. Baseline and follow-up laboratory blood values (hemogram, creatinine, alanine aminotransferase, Ca, P, ALP, albumin, vitamin D, and PTH) and BMD (DXA: lumbar and femoral T-score) measurements taken at the 6th and 18th months were recorded. Fractures detected in radiological imaging (radiographs, MRI, and/or CT) were noted according to the Genant classification (Grade 0-3) (10). Patients' mobility assistive devices and mobility levels, ranging from 1 to 5, were assessed using the Functional Ambulation Classification (FAC) (Level 0, non-ambulation; Level 5, independent, all surfaces) (11). The severity of back pain was recorded using the visual analogue scale (VAS, 0-10) (9). At the end of the treatment, patients' satisfaction levels were determined using the Likert scale, ranging from 1 to 5 (12). Patients' satisfaction levels were assessed using a 5-point Likert scale as follows: 1, "no satisfaction at all"; 2, "low satisfaction"; 3, neutral (neither satisfied nor dissatisfied); 4, "satisfied"; and 5, "very satisfied". Throughout the follow-up period, DXA results, VAS pain scores, biochemical tests, medication-related side effects, patients who underwent vertebroplasty or kyphoplasty, and those with new fractures were recorded.

Statistical Analysis

Statistical analyses were performed using IBM® SPSS Statistics 22 software (Armonk, NY, USA). The frequency and percentage of categorical data are given as n (%); numerical data are given as the median and interquartile range or mean ± standard deviation. The Shapiro-Wilk test was used to determine whether the data were normally distributed. In the dependent group with repeated measures, Friedman's test was applied. The Wilcoxon signed-rank test was used to calculate the difference between two non-parametric measurements at different time points. Spearman's rho test was used for correlating non-parametric data that did not have a normal distribution. All statistical analyzes were performed in two directions, at the 5% significance limit and 95% confidence interval.

Results

The demographic and clinical characteristics of the patients are presented in Table 1. Mild symptoms such as

Table 1. Demographic and clinical characteristics of patients

		N (%) or mean ± SD
Age, y		69.9±9.0
Sex	Female Male	40 (80) 10 (20)
Age at menopause, y		39.3±8.1 40.3±5.1
BMI (kg/m^2)		28.7±4.9
Marital status	Married Single or widow	44 (88) 6 (12)
Comorbidity	Yes No	47 (94) 3 (6)
Polypharmacy	Yes No	37 (74) 13 (26)
Smoking	Yes No	7 (14) 43 (86)
Number of old vertebral fracture Number of new vertebral fracture		2.6±1.2 1.3±0.9
Genant classification	Grade 1 Grade 2 Grade 3	5 (10) 25 (50) 20 (40)
Use of mobility assistive devices	Wheelchair Walker Cane	5 (10) 14 (28) 31 (62)
FAC level	0 (non-ambulatuar) 1 2 3 4 5 (independent, fully)	8 (16) 1 (2) 6 (12) 29 (58) 6 (12) 0
Previous oral bisphosphonate use* Previous denosumab use*		16 (32) 1 (2)
Teriparatide treatment duration, m Total follow-up duration, y Post-teriparatide treatment Denosumab Zoledronic acid Alendronate Ibandronate		17.8±1.0 3.6±1.3 49 (98) 38 (76) 7 (14) 3 (6) 1 (2)

*Duration of bisphosphonate use was one to eight years, while denosumab was used for two years.
SD: Standard deviation, BMI: Body mass index, FAC: Functional ambulation classification, m: Months, y: Years

nausea, headache, fatigue, arm-leg pain, and leg cramps were reported in 32% of the patients. Only 3 (6%) patients discontinued the treatment at the 15th month because of severe side effects, including hypotension, dizziness, palpitations, limb pain, and extreme fatigue. There were no deaths during the treatment period, but three patients experienced fatal outcomes after 6 months, 3 years, and 3.5 years following treatment because of cardiac and respiratory failure, which were pre-existing comorbidities. Eleven (22%) patients had undergone one- or two-level vertebroplasty surgery in the neurosurgical clinic within the past month because of acutely painful vertebral osteoporotic compression fractures and were referred to our clinic for postoperative osteoporosis treatment. In contrast, in nine (18%) patients who were newly referred to our Physical Medicine and Rehabilitation clinic and started teriparatide treatment, vertebroplasty surgery was performed because of their severe clinical condition and the intensity of compression and edema observed on MRI. Table 1 presents the demographic and clinical characteristics of the patients.

The mean baseline lumbar vertebral and femoral neck T-scores of the patients were -3.73±0.72 and -2.98±0.82, respectively (Table 2). After treatment, a significant increase was observed in both T-scores at 6 and 18 months, according to DXA values ($p<0.001$). Significant improvement in back pain and ambulation levels was detected in patients at 6 and 18 months after treatment ($p<0.001$ for all values). The changes in clinical evaluation parameters and laboratory values of the patients during the 18-month follow-up are summarized in Table 2.

At the end of teriparatide treatment, patients' satisfaction levels were quite high (Figure 2). The two patients who were neutral in treatment satisfaction were among the three patients who experienced significant side effects. No patient was dissatisfied with the treatment. Among the patients who completed teriparatide treatment, 38 (76%) switched to denosumab, 7 (14%) to zoledronic acid, 3 to alendronate, and 1 to ibandronate. One patient did not wish to receive maintenance antiresorptive medication.

During teriparatide treatment and after switching to antiresorptive treatment, no patient experienced life-threatening side effects or hypercalcemia. A mild increase in pain was observed in some patients in the months following the completion of teriparatide treatment.

However, two patients who switched to denosumab after completing 18 months of teriparatide treatment developed new clinically painful vertebral fractures. At the end of the follow-up period after teriparatide treatment, all patients were mobilized. No significant correlation was found between patients' pain or treatment satisfaction levels and the number of fractures or Genant stages.

Discussion

Osteoporotic fractures are a major concern that can lead to severe pain, disability, and even death, imposing significant economic burdens on healthcare systems. More than three-quarters of these fractures occur in women, with the highest prevalence observed in the thoracolumbar vertebrae (13). Unfortunately, there is currently no treatment for osteoporosis that exhibits strong efficacy and provides a permanent cure. Therefore, primary and secondary prevention are of great importance. Current evidence suggests that the most potent drugs for high-risk osteoporosis and osteoporotic fractures are teriparatide, denosumab, and romosozumab (14). However, the effectiveness of these drugs also diminishes shortly after discontinuation of treatment, which does not eliminate the need for continuous therapy (14,15).

Table 2. Changes in clinical and laboratory evaluation parameters over the course of treatment

Evaluation parameters	Baseline	At 6 months of treatment	At 18 months of treatment	p-value
VAS-pain (0-10)	8 (7-9)	2 (2-3)	1 (1-1)	<0.001[a]
Lumbar T-score Femoral neck T-score	-3.7 (-3.2 - -4.0) -2.9 (-2.5 - -3.5)	-3.2 (-2.6 - -3.5) -2.6 (-2.1 - -3.1)	-2.6 (-2.1 - -3.0) -2.5 (-1.9 - -2.8)	<0.001[a] <0.001[a]
DXA BMD (g/cm^2) Posterior-anterior spine Femoral neck	 0.621 (0.565-0.666) 0.743 (0.673-0.796)	 0.721 (0.626-0.757) 0.790 (0.747-0.829)	 0.794 (0.736-0.865) 0.824 (0.747-0.880)	 <0.001[a] <0.001[a]
Ca (mg/dL) P (mg/dL) ALP	8.8 (8.4-9.2) 3.05 (2.8-3.4) 80.0 (62.3-103.5)	8.5 (8.2- 8.8) 3.1 (2.9-3.4) -	8.3 (8.1-8.6) 3.2 (3.0-3.5) 78.0 (65.3-89.0)	<0.001[a] <0.001[a] 0.082[b]
25-hydroxyvitamin D (ng/mL)	11.0 (4.2-15.0)	23.5 (8.5-33.0)	38.0 (30.0-45.8)	<0.001[a]
PTH (mg/dL)	68.0 (56.0-85.8)	54.5 (45.0-70.8)	51.0 (39.0-62.0)	<0.001[a]
FAC level	3 (2-3)	4 (3-4)	4 (4-4)	<0.001[a]

[a]Friedman test; [b]Wilcoxon-Signed Ranks test; mean ± SD values for normal distribution and median (interquartile range) for non-normal distribution values were used.
BMD: Bone mineral density, DXA: Dual-energy X-ray absorptiometry, SD: Standard deviation, VAS: Visual analogue scale (for back pain), FAC: Functional ambulation classification, Ca: Calcium, P: Phosphorus, ALP: Alkaline phosphatase

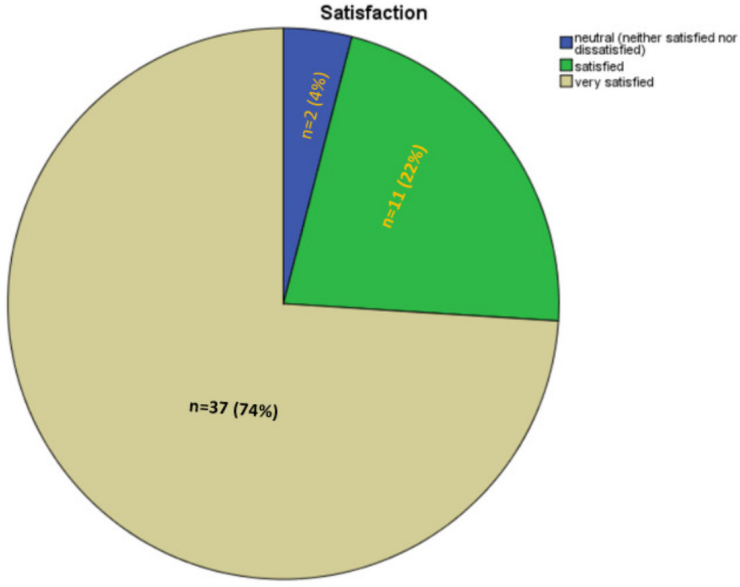

Figure 2. Patient satisfaction levels at the end of teriparatide treatment

Teriparatide exhibits dual effects on bone formation and bone resorption, which are time-dependent. The intermittent use of recombinant teriparatide in osteoporosis treatment directly enhances osteoblast activity and indirectly promotes bone resorption (16). Teriparatide, with its anabolic effect, can rapidly increase bone mass, and in clinical practice, it is more commonly used for post-fracture treatment than for fracture prevention (17). In Turkey, health insurance covers teriparatide treatment only for managing osteoporotic fractures. We investigated the effectiveness and safety of teriparatide in painful, severe osteoporotic vertebral fractures in accordance with the general terms of use. To the best of our knowledge, this study is highly valuable as it represents the most comprehensive reporting of teriparatide treatment results in a single center in Turkey.

Çevikol et al. (18) examined the effects of teriparatide treatment in 15 patients with severe osteoporosis who were unresponsive to bisphosphonate therapy. In their study, a 12-month treatment with teriparatide resulted in an increase in bone density and quality of life, as well as a significant reduction in back pain. In their study, due to financial constraints and side effects, only six of 15 patients could complete the treatment for up to 18 months. In two more recent single-center studies with a similar methodology, one including 13 severe osteoporosis cases and the other including 21 cases, the results of teriparatide were reported (19,20). Teriparatide was found to be effective on DXA, back pain, and quality of life, whereas it was reported to be ineffective on spinal deformity (20). One notable difference in our study compared with these studies is the much longer follow-up period of patients and the absence of the high treatment discontinuation rate seen in those studies. Indeed, the fact that our study was conducted in a private hospital might have eliminated the financial reasons that could have led to the discontinuation of treatment.

Studies in the literature have reported high adherence to teriparatide treatment with a relatively low occurrence of side effects (21-23). The high cost of the treatment and daily subcutaneous injection administration appear to be the main factors that disrupt treatment adherence. After sequential treatment with teriparatide followed by denosumab or zoledronic acid, an increase in BMD and bone strength occurs (24,25). Additionally, denosumab, with its subcutaneous administration every 6 months, and zoledronic acid, with its annual intravenous usage, are high-compliance anti-resorptive agents (26,27). Therefore, in the present study, the majority of patients received denosumab or zoledronic acid after teriparatide treatment.

Teriparatide is effective in severe osteoporosis, increases both trabecular and cortical bone density, dramatically reduces low back pain, and does not adversely affect blood values (23,28). In this context, the results obtained in our study are compatible with the literature. Surprisingly, there are few and narrow studies in the literature on the effect of teriparatide on ambulation. However, the most significant cause of morbidity and mortality associated with osteoporotic fractures is immobility and related complications. Kim et al. (29), in a systematic review, reported the effect of teriparatide on fracture healing, functional recovery, and mobility. In the present study, the significant improvement in patients' FAC levels throughout the follow-up period demonstrated the concrete functional

contribution of the treatment. In patients receiving teriparatide treatment, the occurrence of approximately 5-10% new vertebral fractures can be expected (6). The absence of any clinical vertebral fractures in any of our patients during the 18-month treatment period in our study may be attributed to the relatively small sample size. The two new vertebral fractures observed in two patients during the follow-up period after the completion of teriparatide treatment agree with the overall risk and expectations.

In recent years, both in Turkey and globally, patient satisfaction has become a crucial aspect of evaluating treatment outcomes. The increasing patient expectations and the rise of patient-centered approaches have led to the recognition of patient satisfaction as a highly prioritized value in the healthcare domain (9,30). In osteoporosis treatment as well, patient satisfaction and preferences emerge as significant factors (31,32). In this context, our study examined patient satisfaction and observed that teriparatide provided a high level of satisfaction among patients. We believe that the effectiveness of relieving acute, severe pain played a critical role in achieving this high level of satisfaction. Additionally, economic considerations and care standards might have also influenced overall satisfaction.

Study Limitations

The most important limitation of our study was its retrospective and single-center design. In addition, the fact that some patients had undergone vertebroplasty may have influenced the results of teriparatide. However, the observation of similar outcomes in studies where vertebroplasty was not performed might support the insignificance of this effect. Despite these limitations, we believe that our study makes a valuable clinical contribution to the literature because of its presentation of long-term follow-up data exceeding the duration of teriparatide treatment and involving a significant number of patients that can be considered high for previous studies. Moreover, being the only study investigating both changes in patients' mobility levels and patient satisfaction adds to the strength and uniqueness of our research.

Conclusion

Teriparatide treatment in severe osteoporotic vertebral fractures with back pain has shown a dramatic reduction in pain and significant improvement in ambulation levels, providing a high level of patient satisfaction. Teriparatide treatment can be considered safe in terms of side effects; however, close clinical and laboratory monitoring of patients is essential. To further substantiate the existing findings, multicenter and prospective studies are required.

Ethics

Ethics Committee Approval: Study approval was obtained from the KTO Karatay University Non-Pharmaceutical and Non-Medical Device Research Ethics Committee (date: April 4, 2023, and approval number: 2023/044).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: R.Y., S.B., Design: R.Y., S.B., Data Collection and/or Processing: R.Y., S.B., Analysis and/or Interpretation: R.Y., S.B., Literature Research: R.Y., Writing: R.Y., S.B.

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Original Article

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Impact of Direct and Indirect Cat Allergen Exposure Patterns on Allergic Rhinitis and Asthma in Cat-Sensitized Patients

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Abstract

Aim: Cat allergen hypersensitivity is a clinical condition that can affect patients across a wide spectrum, ranging from mild allergic rhinitis to severe asthma. Since cat hypersensitivity can occur through indirect exposure, non-cat owners also have the risk of developing cat allergies. The aim of this study was to investigate the effects of direct and indirect exposure patterns on the clinical features of allergic rhinitis and allergic asthma in patients with cat hypersensitivity.

Methods: In our study, designed as a retrospective cohort, the demographic and clinical characteristics of 257 patients diagnosed with cat allergy and allergic rhinitis who were followed up and treated between January 2022 and March 2023 were evaluated. Cat and non-cat owner patients were compared in terms of symptoms of allergic rhinitis, treatment steps for allergic rhinitis, and frequency, control and treatment steps for allergic asthma.

Results: The median (interquartile range) age of the patients was 29 (23-38), and 182 of them were female (70.8%). The visual analogue scale symptom scores of cat owners were significantly higher than those of non-cat owners (p=0.022 and p=0.023, respectively). The rate of moderate or severe allergic rhinitis that persisted despite treatment was higher in cat owners (31.8%) than in non-cat owners (17.8%). Additionally, allergic asthma frequency in cat owners with moderate or severe allergic rhinitis symptoms despite medical treatment was more common than in cat owners with mild rhinitis (p=0.026).

Conclusion: Direct exposure to cat allergens is associated with poor control of allergic rhinitis symptoms. These patients should avoid contact with cats. If avoidance is not possible, the clinical condition of these patients should be closely monitored, as they may have treatment-resistant respiratory allergies.

Keywords: Allergic, asthma, rhinitis

Introduction

Cat allergens are the second-most common indoor allergens, following house dust mites. The prevalence of cat allergies is estimated to be around 10-20% of the global population, and it reaches up to 20-30% in individuals with respiratory allergies (1-4).

Cat allergen hypersensitivity is commonly observed not only in cat owners but also in individuals who do not own cats (5,6). In Turkey, cats are often cared for in public spaces. Thus, it can be expected that the incidence of cat allergies will be higher among individuals who do not own cats. A previous study conducted in Izmir/Turkey revealed that 44.7% of non-cat owners with respiratory allergies exhibited cat sensitivity (6). This finding suggests that in individuals without direct contact with cats, the significant presence of cat sensitivity can be attributed to substantial indirect exposure to cat allergens. Cat allergy has emerged as a significant health concern for both cat owners and non-owners, as it can lead to various and serious clinical conditions ranging from allergic rhinitis to asthma (5,7-10).

The severity of the symptoms of allergic rhinitis and asthma can vary depending on the level of exposure to allergens. Although cat owners often resist the idea of avoiding their cats, the primary management strategy in managing cat allergies is allergen avoidance, as in managing other allergies (1,5,11,12). However, in regions with a high indirect exposure risk to cat allergens,

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complete avoidance of cat allergens may not always be possible, even for individuals who do not own cats (6).

Investigating the effects of different cat allergen exposure patterns on allergic rhinitis and asthma in individuals with cat hypersensitivity can be beneficial for managing cat allergies. In this study, we aimed to explore the effects of both direct (cat owners) and indirect (non-cat owners) patterns of cat allergen exposure on the characteristics of allergic rhinitis and asthma.

Methods

Compliance with Ethical Standards

The study was started after obtaining approval from the Ethics Committee of the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (approval no: KAEK/2023.05.205, date: 26.05.2023). The medical records of the patients with allergic rhinitis between January 2022 and March 2023 in the Adult Immunology and Allergy Clinic of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital were researched, and patients who had cat allergen sensitivity were evaluated. Informed consent was obtained from the patients participating in the study.

Study Design

All laboratory and clinical evaluation results used in the study were routinely obtained during patient examinations and were scanned retrospectively from medical records.

Skin prick test results, serum specific immunoglobulin E (IgE) levels, blood eosinophil counts, serum total IgE levels, pulmonary function test results, asthma control test (ACT) scores, and rhinitis visual analogue scale (VAS) symptom scores were all recorded on patient follow-up forms. Patients with a VAS symptom score less than 5 were considered to have mild rhinitis, and those with at least 5 were considered to have moderate to severe rhinitis (13). The Allergic Rhinitis and Its Impact on Asthma guideline was used to assess the severity of rhinitis and to determine the rhinitis treatment step (13). The Global Initiative for Asthma guideline was used to determine the asthma treatment step (14,15). The treatment steps for allergic rhinitis are shown in Table 1.

Comparisons were conducted between cat and non-cat owners in terms of allergic rhinitis symptoms, allergic rhinitis treatment steps, and asthma frequency, control and treatment steps.

Statistical Analysis

All analyses were performed with the IBM Statistical Package for Social Science version 25.0 (SPSS Inc., Chicago, IL, USA) for MacOS. Figures were developed in GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA) for MacOS. Descriptive data were given as percentages and as medians [interquartile range (IQR) 25-75]. The comparisons of VAS symptom scores, ACT scores, pulmonary function test results, blood eosinophil counts, serum total IgE, rhinitis medication scores, and asthma treatment step levels between the cat owners and non-cat owners were all performed with the Mann-Whitney U test. A comparison of rhinitis VAS symptom scores before and after medication was performed using the Wilcoxon test. Categorical variables were analyzed with the chi-square test. The results were assessed at a significant level of $p<0.05$.

Results

Clinical and Demographic Characteristics of the Patients

A total of 257 patients with allergic rhinitis and cat allergen sensitivity were included in the study. The median (IQR) age of the patients was 29 (23-38), and 182 of them were female (70.8%). Sixty-eight (26.5%) patients had a concomitant diagnosis of asthma. While 66 (25.7%) patients were cat owners, 191 (74.3%) did not have any pets. Fifty-eight (22.6%) patients were only sensitive to cat allergens, while 169 (65.9%) had additional hypersensitivity (Table 2).

Effect of Medical Treatment on the Symptom Scores of Allergic Rhinitis

Before medical treatment, the median (IQR) VAS symptom score for allergic rhinitis was 7.0 (6.0-8.0) for all patients, 7.5 (6.0-9.0) for cat owners, and 7.0 (6.0-8.0) for noncat owners. After the treatment, the same score was observed: median (IQR) 3.0 (1.0-4.0) for all patients, median (IQR) 3.0 (2.0-5.0) for cat owners, and median (IQR) 2.0 (1.0-4.0) for non-cat owners. Post-treatment median (IQR) VAS scores for all groups were lower than before the treatment ($p<0.001$ for each comparison) (Figure 1).

Table 1. Classification of treatments used in patients with allergic rhinitis (13,16)

1	Non-sedating H1-antihistamine (oral, intranasal, and ocular), leukotriene receptor antagonists, or promotes (intranasal and ocular)
2	INCSs
3	INCSs + intranasal azelastine
4	Oral corticosteroid as a short course and an add-on treatment
5	Consider referral to a specialist and allergen immunotherapy

INCSs: Intranasal corticosteroids

Table 2. Clinical and demographic characteristics of the patients	
Gender, n (%)	
Female	182 (70.8%)
Male	75 (29.2%)
Median age (IQR)	29 (23-38)
Concomitant asthma (%)	
Yes	68 (26.5%)
No	189 (73.5%)
Cat owners, n (%)	
Yes	66 (25.7%)
No	191 (74.3%)
Atopies of the patients, n (%)	
Cat	58 (22.6%)
Cat and house dust mites	45 (17.5%)
Cats and pollens	20 (7.8%)
Cat, house dust mites and pollens	67 (26.1%)
Cat and dog	7 (2.7%)
Cats, house dust mites, pollens and dog	23 (8.9%)
Cat and *Blatella* spp.	3 (1.2%)
Cats, house dust mites, pollens, and *Blatella* spp.	14 (5.4%)
Cats, house dust mites, pollen, dogs, and *Blatella* spp.	20 (7.8%)
IQR: Interquartile range	

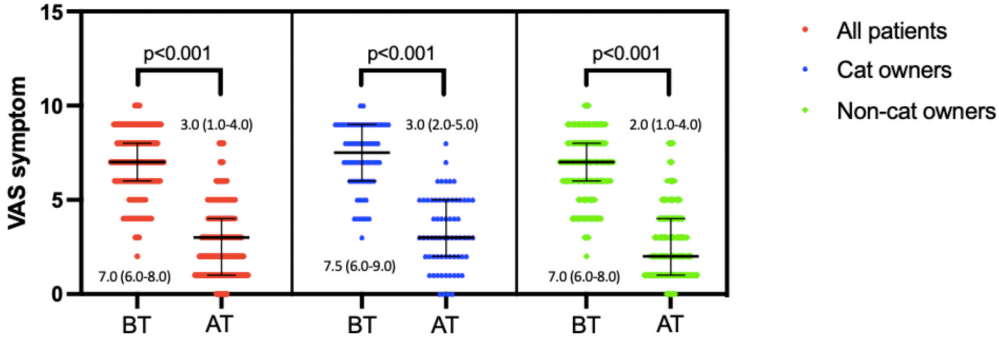

Figure 1. Effects of medical treatment on VAS symptom scores of allergic rhinitis The figure shows the changes in symptom severity measured by VAS for patients diagnosed with allergic rhinitis before and after treatment. A decrease in VAS symptom scores was observed in all patient groups following allergic rhinitis treatment. Statistical analyses were conducted using the Wilcoxon test
AT: After treatment, BT: Before treatment, VAS: Visual analogue scale

The Effects of Being a Cat Owner on the Allergic Rhinitis Symptoms and Medication Scores

The initial and post-treatment VAS symptom scores of cat owners were significantly higher than those who do not have cats (p=0.022 and p=0.023, respectively) (Figure 2). On the other hand, while there was no relationship between the presence of moderate or severe rhinitis before medical treatment and direct exposure to cat allergens, patients with moderate or severe allergic rhinitis after treatment were mostly cat owners (p>0.05, p=0.017, respectively). Among cat owners, 31.8% had moderate or severe allergic rhinitis symptoms after receiving medical treatment, whereas among non-cat owners, the rate was 17.8%. In addition, cat owners with moderate or severe rhinitis symptoms after medical treatment had a higher incidence of asthma than cat owners with mild rhinitis (p=0.026). The median (IQR) rhinitis medication scores were similar between cat owners 2.5 (2.0-3.0) and non-cat owners 2.0 (2.0-3.0) (p>0.05).

The Effects of Being a Cat Owner on Allergic Asthma

There was no difference between cat owners and non-cat owners in terms of asthma frequency, ACT scores, asthma treatment step, FEV1% predicted, FEV1/

FVC values, blood eosinophil count, and total IgE values (p>0.05 for each comparison) (Table 3).

The Effects of Patients Atopy Characteristics on Allergic Rhinitis and Asthma

The rate of monosensitization to cat allergen was higher in individuals who owned cats (34.8%) compared with those who did not own cats (18.3%) (p=0.006). However, being monosensitive to cat allergens or polysensitive to additional allergens did not show any significant impact on asthma frequency, ACT scores, or median (IQR) rhinitis VAS symptom scores (p>0.05 for each comparison).

Discussion

The study found that both pre-treatment and post-treatment rhinitis symptom scores were higher in cases of direct cat allergen exposure compared with indirect exposure. Additionally, among cat owners, a significant proportion continued to experience moderate to severe allergic rhinitis despite receiving medical treatment, and these individuals also demonstrated an increased frequency of asthma.

Cat allergy contributes to a wide range of allergic diseases, including allergic rhinitis and asthma (5,11). The high prevalence of exposure to cat allergens has made cat allergies a significant health concern not only among cat owners but also among individuals who do not have direct contact with cats (6,17). A previous study in the Istanbul region found that cat sensitivity in non-cat owners was a risk factor for poor quality of life in allergic rhinitis (17). In our study, since we did not include a group of patients without cat sensitivity, we did not obtain similar results. However, we demonstrated that cat owners with more direct cat allergen contact had higher allergic rhinitis symptom scores compared with non-cat owners. Data from studies conducted in the Istanbul region, where high rates of indirect cat allergen exposure are expected due to the high population of street cats, are particularly relevant for clinicians specializing in respiratory allergies in this region. Clinicians can potentially achieve improvements in symptom scores by advising measures to avoid cat allergen exposure, including implementing household precautions, in this patient group.

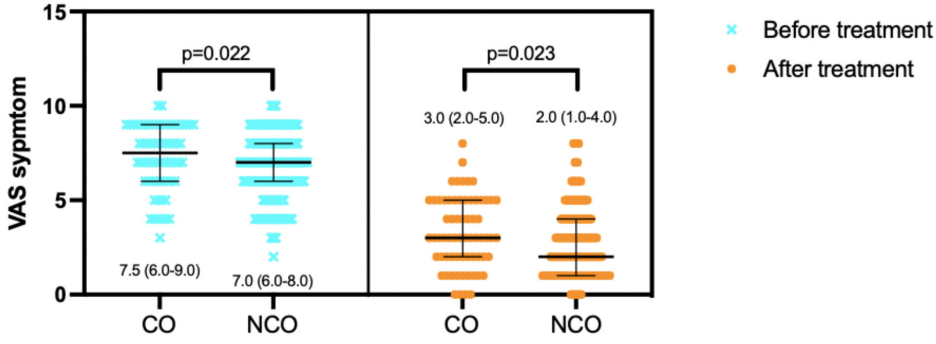

Figure 2: Effects of being a cat owner on the VAS symptom scores of allergic rhinitis The figure demonstrates the difference in symptom severity of allergic rhinitis measured by VAS between cat and non-cat owners. Both before and after medical treatment, cat owners had higher allergic rhinitis VAS symptom scores compared with those who did not own cats. Statistical analyses were conducted using the Mann-Whitney U test

CO: Cat owner, NCO: Non-cat owner, VAS: Visual analogue scale

Table 3. The effects of being a cat owner on asthma

	Cat owners	Non-cat owners	p-value
Concomitant asthma (%)			
Yes	23 (8.9%)	45 (17.5%)	NS
No	43 (16.7%)	146 (56.8%)	
Asthma control test score	22.0 (20.0-24.0)	23.5 (20.0-25.0)	NS
Asthma treatment step	3.0 (2.0-4.0)	3.0 (1.0-3.0)	NS
FEV1 (% predicted)	95.5 (90.3%-102.0%)	92.0 (85.8%-101.3%)	NS
FEV1/FVC	85.0 (84.0-90.0)	84.5 (76.3-89.5)	NS
Blood eosinophil count (cell/mcL)	135.0 (52.0-537.0)	210.0 (90.0-620.0)	NS
Total IgE (kU/L)	261.5 (7.5-1705.8)	215.0 (30.0-874.0)	NS

There were no significant differences observed between cat and non-cat owners in terms of concomitant asthma, ACT score, asthma treatment step, pulmonary function test results, blood eosinophil count, and serum total IgE level

FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, IgE: Immunoglobulin E, NS: Not significant

In recent studies, although pet animal feeding is not listed among the risk factors for asthma, exposure to triggers is considered one of the factors that disrupt asthma control (18-24). It is expected that direct exposure through intense contact may have a greater negative impact on asthma control compared with indirect exposure. However, our study did not find any significant differences between the direct and indirect exposure groups in terms of asthma severity, control, or frequency, unlike the differences observed in allergic rhinitis. On the other hand, cat owners with moderate or severe rhinitis had a higher prevalence of asthma compared with those with mild rhinitis. The absence of this relationship in the group with indirect exposure suggests that more intense contact with cat allergens may also contribute to an increased number of individuals with asthma who have comorbid moderate or severe allergic rhinitis.

The population of street cats is high not only in Istanbul but also in many other cities in Turkey. In a previous study from Ankara/Turkey, cat allergen sensitivity was shown to be a risk factor for increased timothy allergen sensitivity (25). However, we could not have a similar encounter because there were no non-cat allergen-sensitive individuals in our study group. On the other hand, when we looked at the effect of monosensitization with cats or polysensitization with a concomitant allergen on the clinical conditions of asthma or rhinitis, we did not observe any difference.

When evaluating other clinical characteristics based on cat allergen exposure patterns, there was no significant difference in medical treatment scores among patients diagnosed with asthma and/or rhinitis ($p>0.05$ for each comparison). In both groups, allergic rhinitis symptom scores significantly improved after medical treatment ($p<0.001$ for each comparison). However, the prevalence of moderate or severe rhinitis despite the treatment was significantly higher in cat owners (31.8%) compared with non-cat owners (17.8%) ($p=0.017$).

Study Limitations

A potential limitation of this study is its retrospective design. Additionally, the lack of a patient group without cat allergen hypersensitivity hindered the comparison between individuals with and without cat allergies. On the other hand, our study used a large dataset of atients and yielded valuable data on allergen exposure patterns. To the best of our knowledge, this is the first study conducted with a large number of patients diagnosed with cat allergy and allergic rhinitis, aiming to investigate the effects of cat allergen exposure patterns on both allergic rhinitis and asthma in the Istanbul region.

Conclusion

When individuals have cat allergen hypersensitivity and continue to own a cat, it is associated with poorer control of allergic rhinitis symptoms and a higher prevalence of asthma in those with moderate to severe allergic rhinitis. It is recommended that these patients avoid contact with cats if possible. However, for those who cannot comply with this recommendation, their clinical condition should be closely monitored, as they may have treatment-resistant respiratory allergies. Additionally, it should be kept in mind that even among patients who do not own cats, there may be a high prevalence of cat allergen hypersensitivity due to indirect exposure, and an increase in direct contact with cats may lead to poor symptom control in these patients.

Ethics

Ethics Committee Approval: The study was started after obtaining approval from the Ethics Committee of the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (approval no: KAEK/2023.05.205, date: 26.05.2023).

Informed Consent: Informed consent was obtained from the patients participating in the study.

Peer-review: Externally peer-reviewed.

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

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Original Article

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Comparison of Treatment Options for Enthesitis-Related Arthritis with the Juvenile Spondyloarthritis Disease Activity Index

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Abstract

Aim: The Juvenile Spondyloarthritis Disease Activity Index (JSpADA) is the only disease activity score specifically validated for children with enthesitis-associated arthritis (ERA). It was developed to address the need for an effective measurement tool to assess disease activity in this population. We aimed to evaluate the clinical course of patients with ERA using JSpADA and to compare the effects of treatment modalities using JSpADA.

Methods: This cross-sectional observational study enrolled 61 patients with ERA who were followed up between January 2020 and 2023. Clinical features, treatment options, and JSpADA were noted in electronic medical files. The effectiveness of treatment modalities was compared by JSpADA.

Results: The median age of onset of the group was 10 [interquartile range (IQR), 9-15] years. The study cohort included three groups of patients: 1) DMARD received (n=34); 2) biologic drug received (n=14); 3) DMARD and biological combination received (n=13). Forty-three cases (70%) presented with peripheral arthritis, including enthesitis, whereas 18 (30%) patients had axial involvement. At disease onset, the median JSpADA scores were 2 (IQR, 2-3), 2.5 (IQR, 2-3), and 3.5 (IQR, 2.5-5) in groups 1, 2, and 3, respectively (p=0.27). At the first year of follow-up, there was a significant improvement in the disease activity of groups 1 and 2 (p=0.02 and p=0.04). However, there was no significant reduction in JSpADA values in the third group.

Conclusion: In patients with ERA, intermittent JSpADA evaluation during visits can guide the objective and accurate follow-up and treatment response of patients.

Keywords: Biologic drug, enthesopathy, spondyloarthritis

Introduction

Enthesitis-associated arthritis (ERA) is a subcategory of juvenile idiopathic arthritis (JIA) characterized by enthesitis and sacroiliitis that can affect peripheral and axial joints. According to previous studies, peripheral involvement is more common in pediatric patients than in adults. Because the course, long-term complications, and treatment responses of the disease may differ, cases with peripheral and axial involvement are thought to be on different spectrums of ERA (1-4).

As in all diseases, detailed anamnesis is still considered to be the best parameter in the diagnosis, evaluation of disease activity, and follow-up of ERA. Clinicians' opinions and experiences come to the fore in the interpretation of subjective symptoms such as inflammatory low back pain or morning stiffness. For laboratory evaluation, inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are assessed in the follow-up of patients with ERA. However, there is still an effort among clinicians to create a practical method for disease follow-up by combining objective measurements and subjective findings with various composite scales. Because the Juvenile Arthritis Disease Activity Score (JADAS) is insufficient to evaluate axial involvement in JIA, which is more specific to ERA, the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) was developed specifically for the patient group diagnosed with ERA. It is the first disease activity assessment tool constructed for children with spondyloarthropathy (5-8).

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Juvenile Spondyloarthritis Disease Activity Index evaluates disease components, including active joint and enthesitis count, morning stiffness, back mobility, clinical sacroiliitis, uveitis, patient pain assessment, and inflammatory markers. Although there are studies on the validation of JSpADA and whether it can reliably predict the duration of clinical remission, further research on real-life data for clinical use is required.

ERA is considered to have a poorer prognosis than other JIA categories in terms of its resistant course and treatment response. Although non-steroidal anti-inflammatory drugs are prescribed as first-line treatment, second-line disease-modifying antirheumatic drugs (DMARDs) are usually required during follow-up with patients. Biological drugs, particularly tumor necrosis factor inhibitors (anti-TNF), are considered in patients who are resistant and usually have axial involvement. In our country, due to the health system circumstances, a switch to biological drugs can be achieved after using conventional DMARDs for at least 3 months.

Treatment response and reaching and maintaining remission in ERA can be more challenging than in other JIA categories (9,10). In patients with ERA, intermittent JSpADA evaluation during visits can guide the objective and accurate follow-up and treatment response of the patients. We evaluated the clinical course of patients with ERA through JSpADA and compared the effects of treatment modalities by comparing JSpADA in these patients.

Methods

Compliance with Ethical Standards

Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethical Committee (date: 17.05.2022, and approval number: 871316). Written informed consent was obtained from parents or patients as appropriate.

Study Design

Patients treated in a tertiary pediatric rheumatology department between January 2020 and 2023 were included in the study. All patients met the diagnosis of ERA according to the International League of Associations for Rheumatology (ILAR) criteria. According to the ILAR criteria, ERA is defined as arthritis and enthesitis of ≥6 weeks' duration in children aged <16 years, or arthritis or enthesitis plus two of the following: sacroiliac tenderness or inflammatory spinal pain, HLA-B27 positivity, onset of arthritis in boys aged more than 6 years, anterior uveitis associated with pain, redness, or photophobia, and family history of HLA-B27-associated disease. Psoriasis or a history of psoriasis in the patient or a first-degree relative, the presence of IgM RF on at least two occasions at least 3 months apart, systemic JIA findings in the patient, and a follow-up period of less than 6 months were exclusion criteria (2).

The patients were followed up in the outpatient clinic at 3-month intervals. Juvenile Spondyloarthritis Disease Activity Index scores, clinical findings, laboratory parameters, and treatments were noted at each visit.

Enthesitis was defined as localized tenderness at the enthese points or the demonstration of inflammation of the enthesal sites of the respective extremities demonstrated by ultrasonography.

Axial ERA was diagnosed if the patient met the Assessment of SpondyloArthritis International Society criteria. Axial involvement includes the following characteristic features: presence of inflammatory back pain for more than 3 months, detection of sacroiliitis on imaging, and one additional spondylarthropathy feature (11).

The items of JSpADA were as follows: (1) active joint count (0 joint=0 points, ≤2 joints=0.5 points, >2 joints=1 point), (2) active enthesitis number (0 entheses=0 points, ≤2 entheses=0.5 points, >2 entheses=1 point), (3) patient global assessment of well-being (0=0 points, <5=0.5 points, ≥5=1 point), (4) ESR or CRP related to SpA activity (normal=0, ≤2 times normal=0.5 points, >2 times normal=1 point), (5) morning stiffness >15 min (present=1 point), (6) clinical sacroiliitis (present=1 point), (7) uveitis (present=1 point), (8) modified Schober test (abnormal=1 point). The range of scores is between 0 and 8, with higher scores indicating more active disease. There are still no validated cut-off values for JSpADA (5,6,8).

Patients were categorized into three groups according to the type of treatment received. Group 1 included patients who received only conventional DMARDs; Group 2 consisted of patients who received biological drugs; and cases in Group 3 required DMARD and biological combination therapy during the disease course.

Statistical Analysis

Data analysis was performed using IBM SPSS (IBM Corp., Armonk, NY) version 26. The distribution of normality was evaluated using the Shapiro-Wilk test. Descriptive statistics are defined for numerical variables as mean and SD if normal distributed and median and interquartile range (IQR) if non-normal distributed. Frequency and percentages were used for categorical variables. Comparisons between groups were made by the Student's t-test for normally distributed numerical variables, the Mann-Whitney U test for non-normally distributed numerical variables, and the χ^2 or Fisher's exact test for categorical data. A statistically significant difference is considered if $p \leq 0.05$.

Results

Demographics Features

In this study, the data of 66 patients with ERA was retrospectively analyzed. Five patients with a follow-up period of <6 months were excluded. The remaining 61 cases were enrolled in the study and grouped according to the treatments prescribed (Figure 1).

The study cohort included 12 (19.6%) female and 49 (80.3%) male patients. The median duration of illness of patients in group 1 who received only DMARDs was significantly shorter than that of patients in groups 2 and 3. Eleven patients (18%) had a family history of ankylosing spondylitis. Table 1 summarizes the demographic features of the cohort.

Clinical Findings

When the findings of the systems questioned in the routine visits were examined, morning stiffness (33, 54%), heel pain (31, 51%), and hip pain (25, 41%) were the most common complaints. At disease onset, peripheral arthritis and enthesitis were in 35 (57%) and 31 (51%) subjects, respectively. At the time of diagnosis, 43 (70.4%) patients presented with peripheral involvement, and 27 (44.2%) had isolated peripheral involvement. Sacroiliitis was in 15 (24.5%) patients. Heel pain was significantly more common in group 1 than in the other groups, and sacroiliitis was seen more frequently in group 3 among the three groups. Clinical features at disease onset are shown in Table 2.

Treatment

Nonsteroidal anti-inflammatory drugs were prescribed as the first-line treatment in almost half of the patients. Sulfasalazine (n=37, 61%) was the most commonly preferred conventional DMARD for the groups, and methotrexate (n=24, 39%) was the second most common DMARD choice. In the whole cohort, sulfasalazine was the most widely used concomitant DMARD for biological therapy. The median duration of receiving DMARDs was 6 (IQR: 4-24) months.

Biologic DMARDs were prescribed to 22 (36%) patients with axial involvement and 5 (8.1%) patients with peripheral involvement. The two main biologics preferred were etanercept (22; 36%) and adalimumab (5; 8.1%). Adalimumab and etanercept were prescribed at similar rates for peripheral and axial involvement.

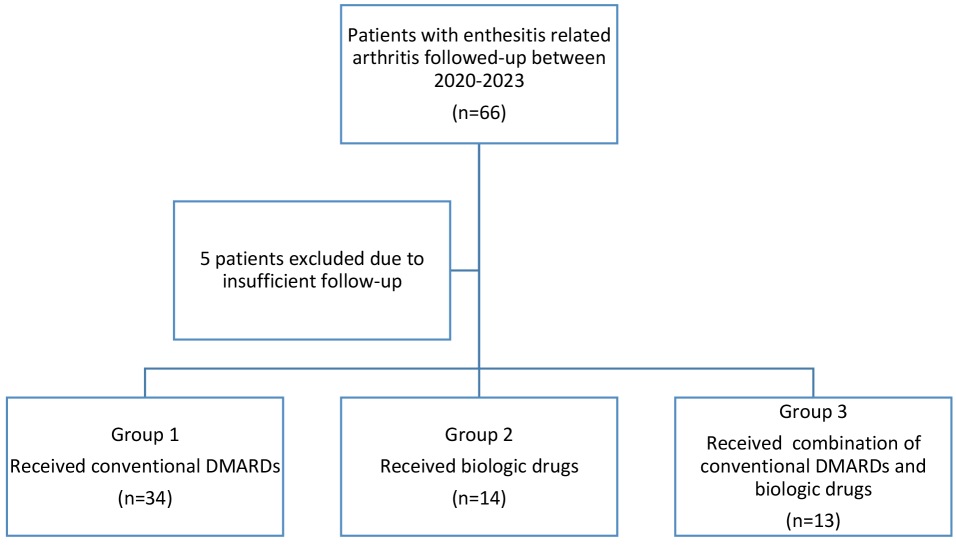

Figure 1. Study population

Table 1. Demographics of cohort (n=61)

Features	Group 1 (n=34)	Group 2 (n=14)	Group 3 (n=13)	p-value*
Gender (male), n, %	27 (73.5%)	10 (71.4%)	12 (92%)	0.3
Age, median (IQR 25-75), years	16 (11-17)	15 (10-12)	15 (11-18)	0.09
Age of onset of disease, median (IQR 25-75), years	11 (10-15)	8 (7-14)	9 (7.5-12)	0.2
Duration of illness, median (IQR 25-75), months	10 (8-15)	11.5 (9-22)	12.5 (10-22.5)	0.001*
Rheumatologic disease history in family n, %	5 (8.1%)	3 (21.4%)	3 (23%)	0.07

*p<0.05 is considered significant Mann-Whitney U test, IQR: Interquartile range

Comparison of the Groups

A comparison of the three groups in terms of JSpADA indexes revealed no difference in JSpADA (p=0.27) at the time of disease onset. At the sixth month and first year evaluations, JSpADA scores showed significant improvement for groups 1 and 2 (p=0.02 and p=0.04). During the disease course, there was no significant reduction in JSpADA values in the 3rd group (p=0.8). Juvenile Spondyloarthritis Disease Activity Index values are summarized in Table 3 for three groups at disease onset: 6 months, first year, and last visit.

Discussion

In this study, the efficacy of treatments used in ERA on clinical outcomes was examined using the JSpADA index. Our results revealed that patients who received a combination of biologics and conventional DMARDs had more severe disease, more frequent axial involvement, and higher activity indexes. Furthermore, this study shows that the JSpADA index is a practical and convenient tool for the follow-up of ERA patients.

Methotrexate is the most commonly prescribed DMARD for children with JIA (12,13). However, it has a limited role for treating enthesitis, sacroiliitis, and axial involvement of the ERA subtype (7) and is usually prescribed for peripheral involvement of the disease. Among conventional DMARDs, sulfasalazine is the most commonly recommended onegin axial ERA. Kısaarslan et al. (14) performed a study evaluating the response to conventional DMARDs in 52 patients with ERA. Twenty-seven patients (52%) achieved remission with DMARDs, whereas 25 (48%) patients could not achieve. Methotrexate and sulfasalazine were prescribed in 41 (78.8%) and 33 (63.5%) patients, respectively. In their cohort, the JSpADA score at disease onset had a mean value of 3.49±1.09 (1.5-5.5). They reported that the absence of factors affecting the duration of DMARD application showed that DMARDs might still be applied as the first line of treatment. Consistent with this study, the first choice for ERA treatment in our cohort was conventional DMARDs, both as monotherapy and along with biologics. However, in our study, sulfasalazine was preferred twice as frequently as methotrexate, and the scores were lower at the onset of the disease. The reason why methotrexate use was low despite the higher peripheral involvement in our study is that DMARD selection may vary depending on the clinical experience of

Table 2. Clinical manifestations of groups at the disease onset

Characteristic	Group 1 (n=34)	Group 2 (n=14)	Group 3 (n=13)	p-value*
Hip pain n, %	11 (32%)	6 (42.8%)	8 (61.5%)	0.8
Inflammatory back pain n, %	10 (29.4%)	5 (35.7%)	5 (38.4%)	0.3
Heel pain n, %	24 (70.5%)	4 (28.8%)	3 (23%)	0.03*
Morning stiffness ≥15 minutes n, %	20 (59%)	6 (42.8%)	7 (53.8%)	0.06
Arthritis n, %	22 (64.7%)	8 (57.1%)	5 (38.4%)	0.8
Enthesitis n, %	21 (61.7%)	6 (42.8%)	4 (30.7%)	0.8
Sacroiliitis n, %	6 (17.6%)	3 (21.4%)	6 (46%)	0.01*
Uveitis n, %	0	0	0	
JSpADA, median (min-max)	2 (2-3)	2.5 (2-3)	3.5 (2.5-5)	0.27
HLA-B27 positivity n, %	14 (41.1%)	5 (35.7%)	5 (48.4%)	0.08
Increasing in acute phase reactants n, %	18 (52.9%)	6 (42.8%)	7 (53.8%)	0.08
MRI findings n, % Peripheral arthritis Peripheral arthritis and sacroiliitis Sacroiliitis	 20 (58.8%) 4 (11.7%) 4 (11.7%)	 4 (28.5%) 2 (14.2%) 2 (14.2%)	 3 (23%) 1 (7.7%) 5 (38.4%)	 0.7 0.9 0.7

*p<0.05 is considered significant- Pearson X^2 test, JSpADA: The Juvenile Spondyloarthritis Disease Activity Index, HLA: Human leukocyte antigen, MRI: Magnetic resonance imaging, min-max: Minimum-maximum

Table 3. Comparison of disease activity indexes among groups

JSpADA, median (min-max)	Group 1 (n=34)	Group 2 (n=14)	Group 3 (n=13)	p-value*
Disease onset	2 (2-3)	2.5 (2-3)	3.5 (2.5-5)	0.27
6-month follow-up	0.5 (0-1)	0.5 (0-2)	2.5 (1-3)	0.2
12-month follow-up	0 (0-1)	0.5 (0-1.5)	1.5 (1-2)	0.1
Last visit	0 (0-1)	0 (0-1)	1.5 (1-2)	0.1

*By Mann-Whitney U test and p<0.05 is considered significant, JSpADA: The Juvenile Spondyloarthritis Disease Activity Index, min-max: Minimum-maximum

the centers and the course of the disease. In this respect, intermittent recording of JSpADA scores during follow-up visits can be considered for managing the disease and deciding whether a second-line medication such as biologics is needed. Additionally, clinicians caring for adult patients with spondyloarthropathy claim that biologics can be the initial therapy for adults in many cases, whereas traditional DMARDs are still the first-line treatment option for patients with ERA.

In 2018, JSpADA was prospectively validated in 127 children with ERA (6). Researchers also assessed the performance of adult SpA scores. They pointed out that exclusion of back mobility from JSpADA may increase its applicability, and adult scores, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score-ESR, showed good construct validity and good correlation with JSpADA. The results of this study provide the opportunity to use the same score in the future to follow these patients into adulthood, thus eliminating the need to switch to separate adult scores. Although our study did not make a comparison with adult scores, the fact that the scores are higher in cases requiring biological drugs during clinical follow-up suggests that JSpADA is effective in indicating the severity of the disease.

In children with ERA, axial involvement, including the hip and sacroiliac joint, may require more aggressive treatment than peripheral involvement. Because the presence of hip arthritis and sacroiliitis at disease onset has poorer prognoses, decreased clinical remission rates and thus increased biological drug requirements have been reported in previous studies (15-17). In this context, TNF-α inhibitors can significantly improve the clinical manifestations of axial ERA (15,18). However, no significant difference in long-term follow-up was detected in patients who initially had high JSpADA scores (19). A recent study by Shipa et al. investigated the drug survival of adalimumab and etanercept (and their biosimilars) in biologic-naïve patients with ERA (20). They assessed disease activity using BASDAI and JADAS-CRP. Following an initial positive primary response, continuing methotrexate with adalimumab was associated with the longest drug survival compared with adalimumab monotherapy or etanercept-based regimens. In their study, axialERA was associated with poorer drug survival, consistent with our study. They reported that elevated baseline CRP and axial disease were associated with an unfavorable initial response to TNFi, whereas patients with concomitant methotrexate were more likely to show an initial response to TNFi. In our results, patients treated with monotherapy had low JSpADA levels at disease onset, whereas combination therapy was preferred in those with high scores. There was improvement in the scores of all three groups during follow-up, but the most significant improvement was observed in groups 1 and 2. These results suggest that having low disease activity at the onset of the disease and the use of DMARDs mono- or combination therapy may facilitate disease management. A study by Zhang et al. (15) showed that anti-TNF therapy was effective in children with ERA after 18 months of diagnosis. They compared magnetic resonance imaging (MRI) and clinical manifestations of joint inflammation in children before and after TNF-α inhibition and reported significant improvement ($p<0.013$). They also speculated that children with ERA, who have no characteristic symptoms of the disease, might show inflammatory reactions during MRI re-examination in the subclinical affected joints. In our study, comparisons of the three groups revealed that patients in groups 2 and 3 had more frequent axial involvement and thus required biological drugs. The JSpADA scores of these two groups were also higher than those of group 1. Comparable with previous studies (13,21-23), cases in our research with active disease scores during the follow-up had more sacroilities and required more frequent biological drugs. Eventually, axial ERA is a risk factor for poor prognosis, the need for combination therapy, and high activity indexes. MRI can also be considered in the follow-up of cases with severe and refractory disease (24).

Study Limitations

The retrospective and single-center design are the main limitations of our study. Because the patients are from a reference center for pediatric rheumatology, the possibility of including cases with severe and active disease seems to be more frequent. Despite these limitations, this study demonstrates the practicality, importance, and value of JSPADA in evaluating ERA treatment options and managing the disease with sufficient patients for a single center.

Conclusion

Evaluation of treatment response and reaching and maintaining inactive disease in ERA patients can be more challenging than in other JIA categories. Because the clinical picture of ERA is highly variable, treatment strategies may vary in parallel, and it becomes difficult to standardize. In addition to JSpADA at the time of diagnosis, high JSpADA values that do not decrease during follow-up may indicate the severity of the disease and the need for more aggressive treatment. Multicenter studies are needed to reveal the use of disease activity measures such as JSpADA developed for children in the follow-up of ERA patients on treatment decisions.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethical Committee (date: 17.05.2022, and approval number: 871316).

Informed Consent: Written informed consent was obtained from parents or patients as appropriate.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: F.G.D., O.A., V.G., N.A.A., Design: F.G.D., O.A., V.G., N.A.A., Data Collection or Processing: F.G.D., O.A., V.G., N.A.A., Analysis or Interpretation: F.G.D., O.A., V.G., N.A.A., Literature Search: F.G.D., O.A., V.G., N.A.A., Writing: F.G.D., O.A., V.G., N.A.A.

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Original Article

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Serum Copeptin Levels in Adult Patients with a Migraine Attack: A Cross-Sectional Study

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Abstract

Aim: This study investigated the potential role of serum copeptin, a mediator of acute pain via sympathetic stress stimulation, as a biomarker of varying degrees of migraine-related disability. Specifically, we aimed to analyze whether the serum copeptin level can be used to differentiate migraine types (e.g., with and without aura).

Methods: The study population included 80 consecutively consenting adult patients who had migraine attacks and attended the emergency department from June 2020 through November 2020, as well as 80 age- and sex-matched healthy controls. Using the Migraine Disability Assessment Scale (MIDAS), the same medical professional assessed each patient's level of headache-related disability. Based on their MIDAS scores, the patients were separated into four groups: no disability (score 0-5; group MIDAS-I); mild disability (score 6-10; group MIDAS-II); moderate impairment (score 11-20; group MIDAS-III); and severe disability (score >20; group MIDAS-IV). There were also two categories of migraineurs: those with auras and those without auras. Upon admission, comparisons were made between the groups' serum copeptin values.

Results: In comparison to the control group, the patient group's serum copeptin levels were noticeably higher (2113.30±206.20 vs. 1383.40±488.40; p<0.001). The study of the receiving operator's characteristics showed that the cut-off copeptin level was 1898.5 pg/mL, with 90% sensitivity and 82.4% specificity for distinguishing patients from controls. There were no noticeable differences in the mean serum copeptin levels between the patient groups when compared by MIDAS score. Additionally, patients with and without aura did not differ notably in terms of mean serum copeptin levels. (2118.70±211.60 vs. 2071.10±160.40).

Conclusion: Serum copeptin levels may be used as a diagnostic aid to help anticipate migraine-related headache attacks when combined with clinical signs and symptoms.

Keywords: Copeptin, migraine, biomarker, headache

Introduction

Migraine is a primary headache disorder recognized by the International Headache Society (IHS). It is neurovascular in origin, caused by mechanisms involving neurogenic inflammation, cerebral vasomotor dysfunction, and cerebrovascular inflammation (1). Among the factors responsible for migraine are neuroinflammatory conditions, cytokines, numerous neuropeptides, and vasomotor changes. With the onset of a migraine attack, vasoactive peptides are formed as a result of trigeminal nerve stimulation, resulting in an increase in blood flow, leakage of proteins from the vessels, and neurogenic (2). However, the etiology of migraines is still not fully understood.

Unlike in other diseases, in which the identification and validation of biochemical markers have greatly improved, there are currently no accepted biochemical markers for chronic or episodic migraine attacks (3,4). The peptide arginine-vasopressin (AVP) is an important hypothalamic stress hormone released from the hypothalamus. The 39-amino-acid glycopeptide copeptin is a precursor of AVP and forms the C-terminal part of the 164 amino acid pre-provasopressin molecule (5). Copeptin is an easily measured biochemical marker of AVP released in response

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to many physiological and pathological stimuli, including pain, hypoglycemia, hypoxemia, stroke, infection, shock, and stress (6). It may thus serve as a biochemical marker of acute pain triggered by sympathetic stress stimulation (7). Nonetheless, there has been little research on the relationship between the serum copeptin level and acute migraine episodes (8). Clarification of this relationship may contribute to the prevention of unnecessary and excessive radiological examination requests in terms of the approach to diagnosis.

We hypothesized that serum copeptin levels may have predictive value in migraineurs who were admitted to the ED with complaints of headache. In this study, we investigated the correlation between the serum copeptin level and the Migraine Disability Assessment Score (MIDAS) in these patients. We also examined the predictive value of serum copeptin levels for differentiating between migraine with aura and migraine without aura (e.g., with and without aura).

Methods

Compliance with Ethical Standards

Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (trial registration no. 2020/68). This study was conducted in accordance with the 1989 Declaration of Helsinki.

Patient Population

Eighty consecutive adult patients (61 females and 19 males, aged 18-56 years) who attended our emergency department with a migraine episode in the ictal phase were included in this cross-sectional study. The flowchart of the study is shown in Figure 1. The control group consisted of 80 age- and sex-matched, healthy volunteers. After their vital functions were measured, the patients were monitored in an isolated area in the ED, and they or their authorized representatives provided signed informed consent. Prior to their involvement in the study, all of the healthy participants were told about the protocol and provided with signed consent.

The third edition criteria of the Headache Classification Committee of the IHS and the patient's medical history were used to diagnose migraine (1). A migraine is characterized as having at least five headache attacks with a duration of 4 to 72 hours (untreated or inadequately treated) and at least two of the following symptoms: One of the following conditions must be present: unilateral location, pulsing quality, moderate or severe pain intensity, or exacerbation brought on by or resulting in the avoidance of regular physical activity (such as walking or ascending stairs). The same medical professional used the MIDAS to evaluate patients entering the emergency department for headache-related impairment. The questionnaire's score was derived to assess how a migraine headache affected the patient's capacity for functioning at work, in the house, and in everyday life (9). The following data were recorded for each patient: age, sex, symptoms, comorbidities [e.g., hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD)], accompanying aura (e.g., visual, sensory, speech and/or language, motor, brainstem, retinal), duration of symptoms, MIDAS score, and serum copeptin level at admission. The people who had migraines were then separated into four groups depending on their MIDAS scores. There are four categories of disability: none (score 0-5; MIDAS-I group MIDAS-I), mild (score 6-10; group MIDAS-II), moderate (score 11-20; group MIDAS-III), and severe (score >20; group MIDAS-IV). In addition, migraineurs were divided into two subgroups, with and without aura. Serum copeptin levels on admission were compared between the groups.

Blood Sampling

Patients' venous blood samples (5 mL) were taken from the antecubital vein at the time of admission without the administration of any drugs, serum infusions, or imaging procedures that would have influenced the serum copeptin level. Blood samples were drawn into heparinized tubes and put right away in a freezer at 4 °C. Before usage, plasma was separated by centrifugation at 4,000 rpm for 5 min. It was then kept at 40 °C. Prior to analysis, the temperature of each serum sample was raised to room temperature.

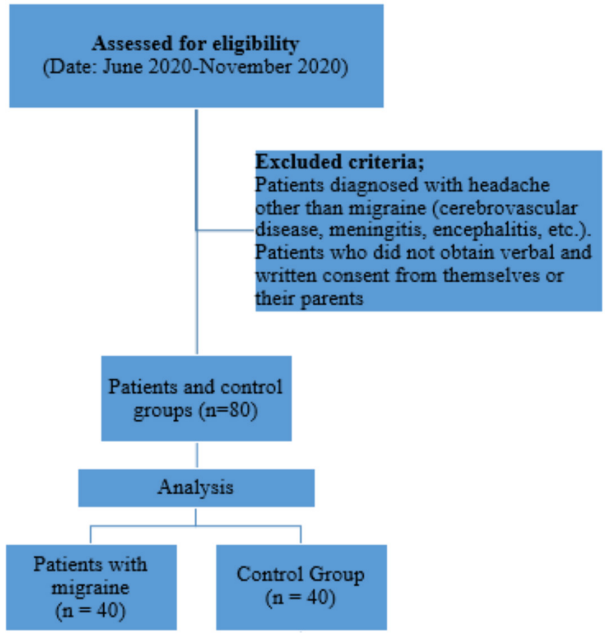

Figure 1. Flowchart of study

Measurement of Serum Copeptin

Using a human copeptin antibody, an enzyme-linked immunosorbent assay was used to determine the levels of serum copeptin (Catalogue No. YLA 1139HU; Shanghai YL Biotech Co.).

Calculation of the MIDAS Score

The MIDAS is used to determine how seriously a migraine affects the patient's quality of life. The MIDAS score has been related to clinical trials determining the need for medical care and has been demonstrated to have moderate test-retest reliability for headache patients (9).

Statistical Analysis

SPSS statistical software (version 15.0 for Windows; IBM Corp., NY, USA) was used to analyze the data. Categorical variables (such as sex and age) are reported as numbers (n) and a percentage (%); numerical data (such as copeptin values) are expressed as the mean (standard deviation), minimum, maximum, and median. The Mann-Whitney U test was used for non-normally distributed data, and chi-squared and Student's t-tests were used for intergroup comparisons (controls vs. patients). To calculate the cut-off copeptin level, predictive factors were identified using logistic regression analysis using the forward approach. Correlations between copeptin values and age, symptom duration, and MIDAS score were evaluated based on Spearman's rank correlation coefficient (rho) tests. The significance level was set at $p \leq 0.05$.

Results

The mean age of the 80 patients included in this study was 36.70±9.80 years (range: 18-56 years), and 61 were female (76.20%). The average age of the 80 healthy volunteers was 38.60±10.60 years (range: 19-57 years), and 61 were female (76.20%). Age and sex between patients and controls did not significantly differ from each other. Although the mean serum copeptin level was much higher in patients than in controls (1383.40±488.44 vs. 213.30±206.20) (Figure 2), it was not statistically significant. Comparing the patient and control groups in terms of demographics and serum copeptin levels is shown in Table 1.

A cut-off copeptin level of 1898.50 pg/mL was determined by receiver operating characteristic (ROC) analysis to be 90% sensitive and 82.4% specific for differentiating patients from controls [area under the curve (AUC) 0.923; 95% confidence interval (CI), 0.877-0.969] (Table 2 and Figure 3).

Using the MIDAS score, patients were categorized based on the degree of migraine-related disability; most of them participated in the MIDAS-II (n=31, 38.75%) and MIDAS-III (n=31, 38.75%) groups. Eleven patients (13.75%) were in the MIDAS-I group and seven (8.75%) in the MIDAS-IV group. Nine patients (11.3%) had auras, and 70 (88.7%) had none. The most common aura in patients was photophobia, which occurred in 55 patients (68.8%), followed by nausea (58.8%) in 47 patients, phonophobia in 42 patients (52.5%), anorexia in 13 patients (16.3%), vomiting in 6 patients (7.5%), and diarrhea in 3 patients (3.8%). The mean duration of symptoms according to the patients was 9.90±5.90 h. The minimum duration of symptoms was 2 h, and the maximum was 36 h.

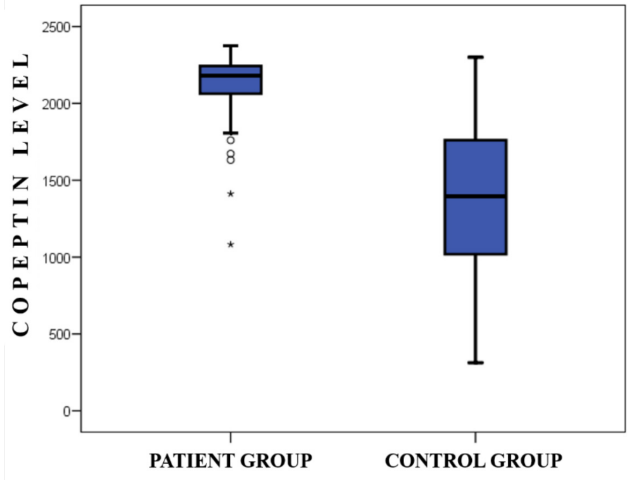

Figure 2. Serum copeptin levels (pg/mL) in patients and control groups

Table 1. Demographic data (age and gender) and plasma measures of 80 adult patients with migraine-related headache and 80 healthy controls

		Patients	Controls	
Characteristics		**% (n)**	**% (n)**	**p-value***
Gender	**Male** **Female**	23.8 (19) 76.2 (61)	23.8 (19) 76.2 (61)	0.189
		Mean±SD	Mean±SD	
Age		36.70±9.80	38.60±10.60	0.851
Copeptin (pg/mL)		2,113.30±206.20	1383.40±488.44	<0.001

Data are expressed as numbers (n), percentages (%), mean ± standard deviation (SD). *Intergroup comparisons (controls versus patients) were conducted using the chi-square, independent samples t-test, and Mann-Whitney U tests where appropriate

Table 2. Specificity and sensitivity ratios for serum copeptin levels to predict the patient with migrain-related headache in ROC curve analysis

Copeptin (pg/mL)		
Equal or higher value	Sensitivity	Specificity
1,756.50	0.950	0.750
1,764	0.938	0.750
1,783	0.938	0,.65
1,802	0.938	0.779
1,817.5	0.925	0.779
1,841.5	0.925	0.794
1,874	0.900	0.794
1,898.5	**0.900**	**0.824**
1,915.5	0.863	0.824
1,936.5	0.863	0.838
1,950	0.863	0.853
1,968	0.850	0.853
1,994.5	0.850	0.897
ROC: Receiver operating characteristic		

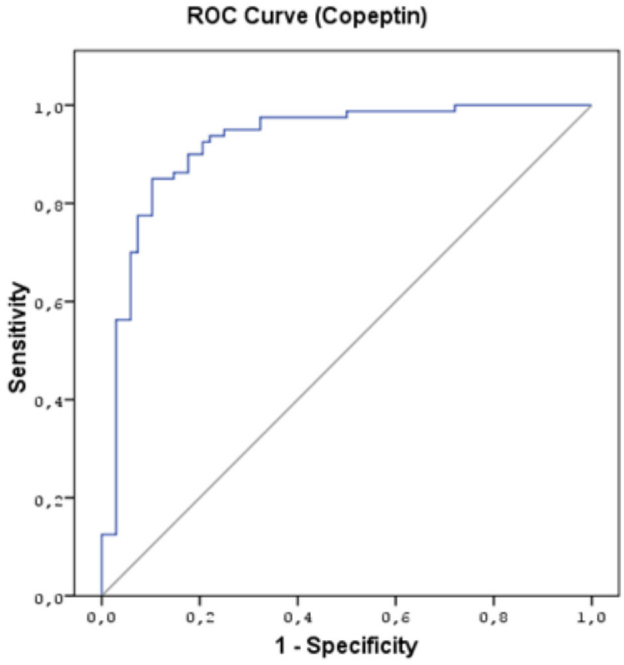

Figure 3. Specificity and sensitivity of the serum copeptin level for distinguishing patients with migrain attack from the controls using receiver operating characteristics curves (AUC 0.923; 95% CI 0.877-0.969)

AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristics

Comorbidities were reported by 41.2% (n=33) of the patients and included HT (8.7%, n=7), DM (7.5%, n=6), CAD (5%, n=4), COPD (2.5%, n=2), and others (gastroesophageal reflux disease, hypothyroidism, anemia, asthma, and multiple sclerosis; 17.5%, n=14).

There was no statistically significant difference in the mean serum copeptin levels of the four MIDAS groups, nor was there a significant correlation (rho=-0.017 and p=0.883) between the serum copeptin level and the MIDAS score. Male and female patients also did not significantly differ in terms of the mean serum copeptin level. Although migraine patients without aura had greater mean serum copeptin levels than those with aura, the difference was not statistically significant (2,118.70±211.60 vs. 2,071.01±160.04) (Table 3).

Discussion

Migraines can occur at any age, including during childhood but especially during adolescence (10), and are approximately three times more common in women than in men (11). With increasing age, the number of early migraine attacks decreases. Migraines without aura are more frequent than migraines with aura (12). Consistent with those studies (10-12), in the present study, the prevalence of migraine varied according to age and sex. The mean age of the patients was 36.70 (±9.80, range 18-56) years, corresponding to middle age, and 76.2% were female, whereas 23.8% were male, a three-fold difference.

In the study of Yılmaz et al. (8), based on 52 migraineurs and 51 healthy individuals, the mean copeptin level in the patient group during the attack and non-attack periods was 689.28 pg/mL and 576.68 pg/mL, respectively, compared with 608.68 pg/mL in the control group. The difference in the mean copeptin level during the attack and attack-free periods was significant (p=0.026). The copeptin cut-off level was 388.67 pg/mL, which had 58.8% sensitivity and 60.7% specificity. In the study by Yılmaz et al. (8),

Table 3. Distrubution of serum copeptin levels according to gender, aura symptoms, and MIDAS score groups

		Copeptin (pg/mL)			
Characteristics		**Mean±SD**	**Minimum-Maximum**	**Median**	**p-value***
Gender	Male	2,128.30±117.09	1,854-2,307	2,180	0.532
	Female	2,108.70±227.40	1,082-2,375	2,180	
Aura	No	2,118.70±211.60	1,082-2,375	2,180	0.160
	Yes	2,071.01±160.04	1,806-2,307	2,121	
MIDAS	I	2,118.60±164.00	1,760-2,307	2,180	0.972
	II	2,097.80±256.30	1,082-2,375	2,180	
	III	2,127,30±177.90	1,412-2,307	2,180	
	IV	2,111.70±161.50	1,806-2,307	2,180	

Data are expressed as numbers (n), percentages (%), mean±standard deviation, median, or minimum and maximum values. *Mann-Whitney U test, MIDAS score: No disability (MIDAS; score 0-5 MIDAS-I group), mild disability (MIDAS; score: 6-10; MIDAS-II group), moderate disability (MIDAS score: 11-20; MIDAS-III group), severe disability (MIDAS: >20; MIDAS-IV group)
MIDAS: Migraine Disability Assessment Scale, SD: Standard deviation

although serum copeptin levels were not of diagnostic value, their use in the management of migraineurs in the ED was proposed.

Kazanasmaz et al. (13) measured copeptin in the plasma samples of 61 migraine patients and 60 paired healthy controls to determine the value of copeptin in predicting migraines in the young. Copeptin's level (mean 298.25 pg/mL) in the patients was significantly higher than that in the controls (194.35 pg/mL). The threshold was 249.5 pg/dL, which in the diagnosis of migraine had a sensitivity of 64% and a specificity of 67%.

Blum et al. (14) evaluated 391 patients who presented to the ED with headaches: 219 (56%) had primary headaches and 172 (44%) had secondary headaches. Among the latter, 75 (19%) were considered serious. The copeptin level in the group with a severe headache was significantly higher than that in the group with a milder headache (6.44 pmol/L vs. 3.89 pmol/L; p<0.0001). In addition to the underlying disease in secondary headache and the associated stress, the pain itself may have contributed to an increase in the copeptin level, which would explain the very high copeptin values in some patients with migraine.

Similar to that, in the current investigation, patients' mean serum copeptin levels were considerably greater than those of the controls. (1,383.40±488.44 pg/mL vs. 213.30±206.20 pg/mL). ROC analysis identified a copeptin cut-off level of 1898.50 pg/mL with 90% sensitivity and 82.4% specificity (AUC 0.923; 95% CI, 0.877-0.969) for distinguishing the two groups. However, there was no statistically significant difference in the mean serum copeptin levels between the groups as measured by the MIDAS score (p=0.972), nor was there a significant correlation between the serum copeptin level and the MIDAS value (rho=-0.017; p=0.883).

Study Limitations

There were several limitations to this study. First, it was conducted at a single center. Second, when patients first arrived at the emergency department, migraine-related pain severity was not assessed for each patient using a visual analogue scale (VAS). This made it impossible to compare changes in serum copeptin levels in patients with migraine based on the intensity of their pain as measured by the VAS score. Third, copeptin may have an impact on long-term results; however, the levels were not examined at a time when the patients were not experiencing headaches after being hospitalized. Future research should consider these factors. Despite these limitations, this is the first clinical study that, to our knowledge, has investigated the relationship between the level of serum copeptin and the severity of migraine-related disability as measured by the MIDAS score.

Conclusion

Serum copeptin levels in patients diagnosed with migraine attacks are not useful in predicting the degree of migraine-related disability as assessed by the MIDAS score. However, it may be useful in predicting headaches associated with a migraine attack in conjunction with clinical signs and symptoms. More clinical trials with larger samples are required to confirm these results.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (trial registration no. 2020/68).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.D.S., O.K., S.C., Design: I.E., O.D.S., O.K., Data Collection or Processing: I.E., O.D.S., O.K., Analysis or Interpretation: O.K., S.C., O.S., Literature Search: I.E., O.D.S., H.E., Writing: I.E., O.D.S., O.K., O.S.

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

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Original Article

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Predictive Value of Preoperative De-Ritis Ratio at Tumor Staging in Testicular Germ Cell Tumors

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Abstract

Aim: The de-ritis ratio (DRR), which refers to the ratio of aspartate transaminase (AST) to alanine transaminase (ALT), is used in the assessment of several malignancies. Preoperative prediction of tumor anvasiveness remains an important issue. The aim of this study was to investigate the possible association between tumor progression and the DRR (AST/ALT).

Methods: The medical records of 103 patients who underwent radical orchiectomy because of testicular cancer between January 2010 and January 2020 in a single tertiary center were retrospectively assessed in this cross-sectional study. Parameters including age, blood parameters including AST, ALT, beta-human chorionic gonadotropin (B-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), complete blood count, pathology results, treatment schemes, imaging results, preoperative and postoperative DRR (AST/ALT), and tumor stage were noted.

Results: The mean age of the 103 patients was 34.9±10.45. The pathological T-stage was T1 for 26 (25.2%), T2 for 65 (63.1%), and T3 for 12 (11.6%). The mean follow-up of the patients was 31.44±10.32 (13-53) months. The risk of retroperitoneal lymph node involvement and metastasis at a DRR was calculated as 1.37 (area under the curve, 0.853 with a sensitivity of 90% and specificity of 89%; 95% confidence interval, 0.689-0.897). Preoperative B-hCG level and LDH were statistically significantly higher in the AST/ALT>1.37 group (p=0.002 and p=0.012). Thirty-five (30.4%) of patients with NSGHT had an AST/ALT>1.37. Seminoma was observed in 25.6% (n=21) of patients with AST/ALT>1.37 (p=0.107). The higher stage was significantly associated with an elevated DRR (p=0.019).

Conclusion: The DRR appears to be a useful and cost-effective preoperative marker for predicting localized and non-localized disease in Tca at the time of diagnosis.

Keywords: Testicular cancer, De-ritis ratio, Germ cell tumor, Aspartate transaminase, Alanine transaminase

Introduction

Testicular neoplasms account for approximately one percent of all malignancies in men (1). These malignancies are the most common solid tumors in men in the second to fourth decade of life (2). Germ cell tumors are seen in approximately 90-95% of all testicular tumors and are divided into two groups: seminomatous and non-seminomatous. The mortality rate of these tumors is low, but the economic, psychological, and physical problems caused by these tumors in young men are extremely important. Advancements in treatment modalities have improved the cure rate of testicular cancers regardless of the tumor's spread; therefore, the preoperative prediction of testicular cancer has recently become increasingly important. Currently, the five-year survival rates are around 97% (3,4).

In the clinical routine, serum tumor markers such as alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) have an extremely important role in definitive diagnosis, treatment, and follow-up. These markers have also been used for the risk stratification of patients with testicular cancer.

However, these markers have low specificity and sensitivity; therefore, several investigations have been conducted to establish more reliable markers (5). In addition to these markers, alternative tumor markers have also been investigated for predicting the prognosis of testicular tumors. Recent studies have reported that the neutrophil-to-lymphocyte ratio (NLR) and aspartate aminotransaminase (AST)-to-alanine aminotransaminase (ALT) ratio, also called the de-ritis ratio (DRR), could be used as predictive values for solid tumors (6,7).

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The AST/ALT ratio was first described in 1957 by Fernando De Ritis and was used in liver diseases, especially in viral hepatitis (8,9). In the past few years, this ratio has become more important for non-hepatic diseases such as peripheral arterial occlusive disease, acute ischemic stroke, and type 2 diabetes mellitus (7). Later, Wu et al. (7) found that the ratio is not only associated with hepatocellular damage and systemic diseases but also plays an important prognostic role for several cancer types, such as breast cancer, esophageal cancer, and pancreatic cancer. Recently, two studies have investigated the relationship between the prognosis of testicular germ cell tumors and the DRR (10,11). However, we believe that there is still a lack of literature investigating the role of the DRRand the association of tumor metastasis with testicular cancer.

In our study, we aimed to determine the prognostic role of the DRR for determining metastasis and lymph node involvement. Furthermore, we investigated the association between the DRR and progression-free survival (PFS).

Methods

Compliance with Ethical Standards

Informed consent was obtained from all patients, and ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Dr. Lutfi Kirdar City Hospital (approval no: 2020/514/184/3, dated: 26.08.2020).

Subjects and Study Design

The data of 133 patients who underwent radical orchiectomy because of testicular cancer between January 2010 and January 2020 in a single tertiary center was retrospectively retrieved from our medical records. Sixteen patients with non-germ cell tumors and 7 patients whose histopathological results were missing were excluded. Seven patients with a history of hematologic disease, secondary malignancy, hepatic disease, diabetes mellitus, liver-eliminated drugs, or liver hepatitis were excluded from the study (Figure 1). Follow-up with all patients was routinely performed according to the European Association of Urology Guidelines.

Patients' age and blood parameters, including pre-operative and postoperative AST, ALT, beta-hCG (B-hCG), AFP, LDH, and pre-operative and postoperative DRR, were noted. AST (U/L) and ALT were routinely analyzed on the pre-operative day and postoperative week 1. Complete blood count, AFP, LDH, and B-hCG were analyzed on the pre-operative day and the third postoperative week. All serum parameters were analyzed in the same laboratory. Tumor characteristics (tumor size, tumor type, surgical margin, rete testis invasion, spermatic cord invasion, and tumor stage) were evaluated according to the 2016 TNM classification. Patients were scanned using thoracoabdominal computed tomography for lymph nodes and distant organ metastases. Progression-free survival was calculated from the date of surgery to the date of progression.

Patients were divided into two groups according to TNM. Patients with pathological stage pT1 (stage 1) were classified as stage 1; pT2-T4 and 1S, including any regional lymph node positivity without distal organ metastasis, were defined as stage ≥2.

Patients are also divided into seminomatous and non-seminomatous germinatous testicular cancers. The association between the DRR and pathological outcomes was analyzed in detail and subjected to statistical analysis.

Statistical Analysis

Descriptive values for continuous variables are presented as mean ± standard deviation. Categorical variables are presented as numbers and percentages. The Shapiro-Wilk test was used to define the distribution of the variables. Categorical variables were analyzed using the chi-square test and the Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. The receiver operating characteristic (ROC) curve method was used to assess the diagnostic significance of AST/ALT for metastasis and lymph node involvement. A threshold with the highest sensitivity and specificity was determined using the ROC curve. Overall survival was estimated using the Kaplan-Meier method, with differences evaluated by the log-rank test. A 2-sided p-value <0.05 was considered statistically significant. IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analyses.

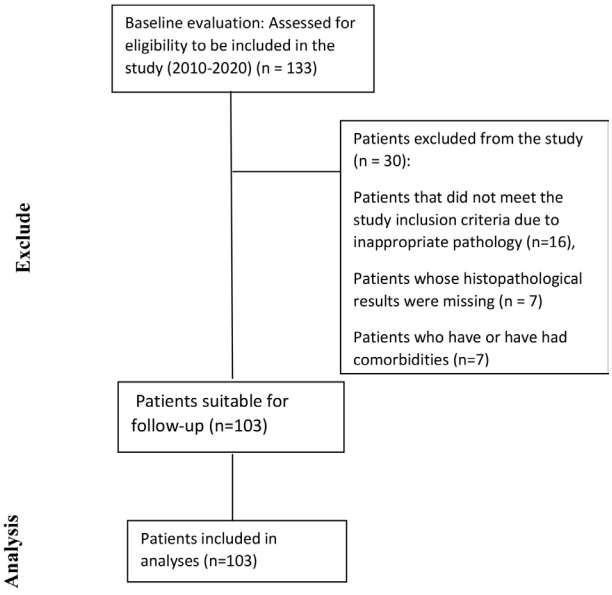

Figure 1. Flowchart of the study

Results

The mean age of the 103 patients was 34.9±10.45. The preoperative mean AST and ALT levels were 22.8 (14-81) U/L and 23.3 (8-145) U/L, respectively. Median preoperative serum beta-hCG, AFP, and LDH levels were 16.2 (0-245497) mIU/mL, 6.41 (1-21000) ng/mL, and 313.1 (23-2581) U/L, respectively. Further demographic and clinical data are summarized in Table 1.

The mean tumor size was 50.99±22.98 (6-130) mm. The pathological diagnosis was seminoma in 47 patients and non-seminomatous germ cell tumor in 56 patients. The pathological T stage was T1 for 26 (25.2%), T2 for 65 (63.1%), and T3 for 12 (11.6%) patients. The mean follow-up of the patients was 31.44±10.32 (13-53) months.

The risk of retroperitoneal lymph node involvement and metastasis at a DRR was calculated as 1.37 [area under the curve (AUC), 0.853 with a sensitivity of 90% and specificity of 89%; 95% confidence interval, 0.689-0.897] (Figure 2). Overall, forty-seven patients had an AST/ALT rate <1.37 and 56 patients had an AST/ALT rate >1.37. No statistical difference was determined between AST/ALT rate <1.37 and AST/ALT rate >1.37 in terms of age, tumor type, tumor size, and preoperative AFP (p=0.164, p=0.107, p=0.456, p=0.523, respectively).

Preoperative B-hCG level and LDH were statistically significantly higher in the AST/ALT>1.37 group (p=0.002 and p=0.012). 30.4% (n=35) of patients with NSGHT had an AST/ALT >1.37. Seminoma was observed in 25.6% (n=21) of patients with AST/ALT >1.37 (p=0.107) (Table 2).

A higher stage was statistically significantly associated with an elevated DRR (p=0.019). Overall, thirteen (13.9%) patients showed progression after a mean follow-up of 25.9±5.7 (15-36) months. Lower PFS was associated with a >1.37 DRR, as shown in Kaplan-Meier analysis (Figure 3).

Table 1. Demographic and clinical data of patients with testicular cancer (n=103)

Variable	Value
Age, mean ± SD (range)	34.9±10.45 (18-58)
Preoperative AST (U/L)	22.8 (14-81)
Preoperative ALT (U/L), median (range)	23.3 (8-145)
Preoperative de-Ritis ratio	1.23±0.47
Preoperative AFP (ng/mL)	6.41 (1-21000)
Preoperative hCG (mU/mL)	16.2 (0-245497)
Preoperative LDH (U/L)	313.1 (23-2581)
Pathological T stage, n (%) T0 T1 T2 T3 T4	 0 26 (25.2) 65 (63.1) 12 (11.6) 0
Stage Stage 1 Stage ≥2	 63 (61.3) 40 (38.7)
Tumor size, mm, mean ± SD (range)	50.99±22.98 (6-130)
Tumor type, n (%) Seminoma NSGHT	 47 (45.6) 56 (55.4)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, SD: Standard deviation, NSGHT: Non-seminomatous germ cell tumor

Table 2. Comparison of De-Ritis <1.37 and >1.37

Variable	AST/ALT <1.37	AST/ALT >1.37	p-value
Age, mean ± SD (range)*	35.94±9.95	33.92±9.1	0.164
Tumor type, n (%) Seminoma NSGHT^^	 26 (21.4) 21 (25.6)	 21 (25.6) 35 (30.4)	0.107
Preoperative AFP (ng/mL), median (range)*	4.35(1-3000)	9.2 (1-21000)	0.523
Preoperative HCG, (mU/mL)*	5.67 (1-7696)	32.78 (1-24547)	0.002
Preoperative LDH, (U/L), median (range)*	269.8 (23-1446)	469 (63-2581)	0.012
Stage^^ Stage 1 Stage ≥2	 35 (75.6) 12 (24.4)	 28(50) 28 (50)	0.019*
Tumor size, mm, mean ± SD (range)*	49.53±25.81	52.01±22.02	0.456

^^Chi-square test, *Mann-Whitney U test, SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, NSGHT: Non-seminomatous germ cell tumor

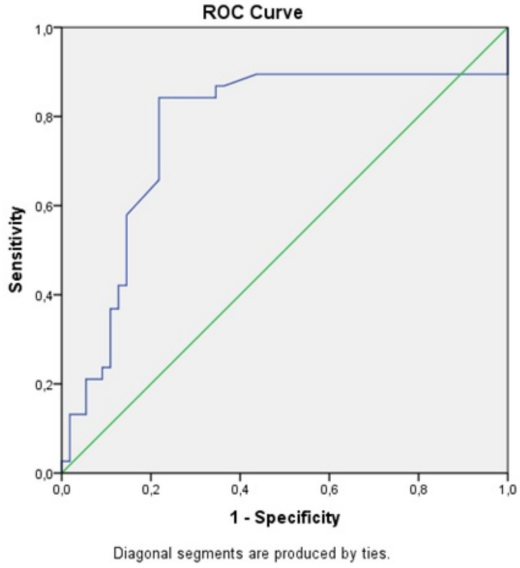

Figure 2. The risk of retroperitoneal lymph node involvement and metastasis in testicular cancer patients at a De-Ritis ratio level of 1.37 (area under the curve, 0.853; 95% confidence interval, 0.689-0.897)
ROC: Receiver operating characteristic curve

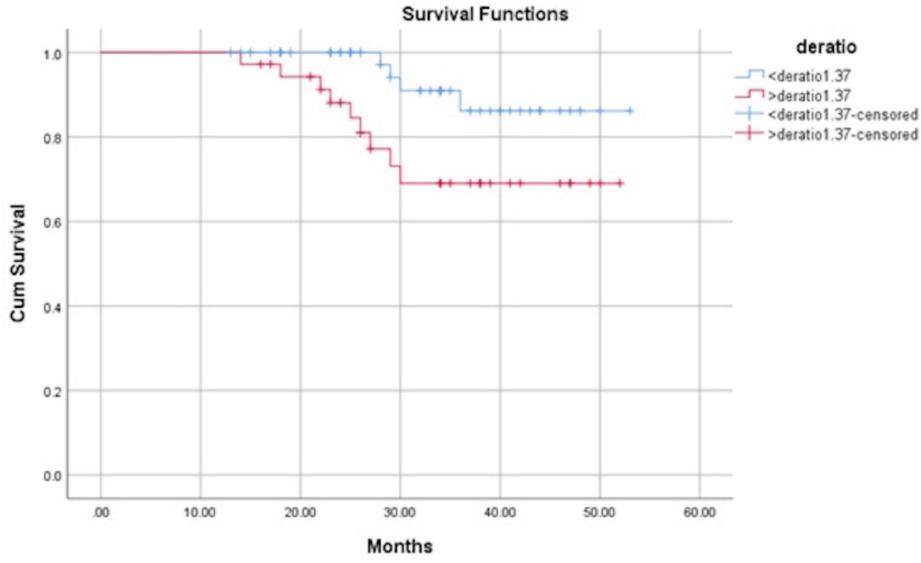

Figure 3. Kaplan Meier's analysis demonstrates the risk for progression free survival between the two groups

Discussion

Searching for preoperative predictive markers for cancer has been increasing recently and remains important. Cost-effectiveness plays an important role in the diagnosis and follow-up of oncological cases, and research on simple parameters is ongoing. AFP, B-hCG, and LDH are widely used for the diagnosis and prognosis of testicular cancer. These markers are cost-effective and easy to apply; however, they have low specificity and sensitivity. Furthermore, normalization of marker levels after orchiectomy does not rule out the presence of metastatic disease, whereas persistence of marker levels after orchiectomy may be associated with metastatic disease (12,13). In addition to these available biomarkers, the utility of microRNA in predicting testicular cancer prognosis has been investigated. MicroRNA has been reported to be a useful biomolecule for the diagnosis, prognosis, and treatment of testicular cancer (10). However, this biomolecule seems not to be useful for daily practice.

Aspartate aminotransaminase and alanine aminotransaminase are enzymes that mainly originate from liver cells and are released into the blood circulation. They are used in daily practice and are usually measured when planning anesthesia for surgery. Different tissues produce AST; however, ALT is liver-specific (14). Crucial metabolic interactions between protein and carbohydrate metabolism are the primary functions of both enzymes. These enzymes are crucial for cells with high metabolic activity, and aerobic glycolysis is dependent on AST (8). The role of AST in the glycolysis mechanism is to contribute to NADH/NAD+ conversion in the malate-aspartate pathway (15). Hsu and Sabatini (16) determined that aerobic glycolysis in malignant cells is higher than that in non-malignant cells. As a result, AST is hypothesized to increase abnormally in cancer cells because of the Warburg effect. Therefore, the AST/ALT ratio has been associated with tumor metabolism in many glucose-using malignancies (Botros). DRR has been reported as a biomarker in some studies previously (7).

Articles have been published on the relationship between the AST/ALT ratio and malignancy (7,15,17-20). Wu et al. (7) published a pooled analysis of 9400 patients for the prognostic value of the AST/ALT ratio in solid tumors in 2019. They included 18 major reviews on renal cell carcinoma, hepatocellular carcinoma, pancreatic cancer, bladder cancer, liver cancer, and urinary tract urothelial carcinoma in the meta-analysis. In the results, they found that the AST/ALT ratio is predictive of decreased overall survival and cancer-specific survival. Only in a subgroup that looked for races, there was no significant result for Caucasians (7).

To the best of our knowledge, only four studies have investigated the association between testicular cancer and the DRR until now (10-12,21). In a study by Gorgel et al. (11), the preoperative elevated DRR was defined as an independent prognostic factor for testicular tumors. Increased AST and ALT levels were strongly predictive of retroperitoneal lymph node involvement. The optimal threshold of the AST/ALT ratio for lymph node involvement and/or metastases was 1.30 in this study (0.674; 95% confidence interval, 0.563-0.786) (11). These authors reported that without the presence of retroperitoneal lymph node involvement or metastasis on radiological

examination, markers cannot reveal information for lymph node metastases and stated the evidence of the opposite for the DRR. We did not find any investigation in their study supporting this statement. Furthermore, these authors reported that increased preoperative hCG levels were predictive of retroperitoneal lymph node involvement and metastasis, as expected. Bozkurt et al. (12) found that DRR was an independent prognostic factor for lung metastasis. The optimal DRR threshold was 1.21 for lung metastasis [AUC: 0.724 with a sensitivity of 81% and specificity of 74%] (12). This study demonstrated that DRR is an inexpensive parameter that can be used not only for predicting testicular tumor stage but also for predicting lung metastasis (12). Guner et al. (10) suggested that the optimal threshold of DRR is 1.35 (AUC: 0.791 with a sensitivity of 80% and a specificity of 73%). The investigators concluded that the DRR was related to a higher stage and worse overall survival (10). Olcucu et al. (21) evaluated the relationship between testicular tumors and four preoperative inflammation markers, namely neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, neutrophil-monocyte ratio, and DRR. In this study, four preoperative inflammation markers were defined as predictive factors for metastasis, but no significant statistical difference was detected for DRR (21).

Although there is no established threshold for the DRR for testicular tumors, the optimal cut-off value for low and high DRRs was found to be 1.37. This threshold was similar to that in previous studies. Concordant with the aforementioned studies, a high DRR was associated with the occurrence of metastasis and retroperitoneal lymph node involvement. Moreover, we determined an association between DRR and PFS in the Kaplan-Meier analysis. Previously, Guner et al. (10) found that elevated DRR was associated with early-term mortality in a Kaplan-Meier analysis. Furthermore, the authors stated that a high DRR was associated with a higher stage. This result supports our findings. Individual pathological variables were not investigated in our study, as these variables were found not to be associated with DRR in previous studies (10).

In addition to the DRR, the association between the NLR and testicular germ cell tumors was investigated in previous studies. Similar to the DRR, NLR is an easily acquired, inflammatory, and inexpensive marker. The authors concluded that the use of NLR might be predictive of the distinction between localized and non-localized TGCT in the early postoperative period. A persistent value in NLR after orchiectomy indicated non-localized disease in their study (21,22).

Study Limitations

Despite our study providing important information about the association of progression and metastasis with the DDR, there are some limitations in the study that should be mentioned. The study was retrospectively designed and included a relatively small population of patients with testicular cancer. Second, we did not measure this ratio in the early postoperative period; therefore, we could not find the half-life or DRR. AST and ALT levels can be affected by many factors, such as undetected liver diseases, alcohol consumption, dietary habits, and drug interactions. Because of the low sample size and short follow-up period, the association of DRR with cancer-specific survival and overall survival could not be investigated.

Conclusion

The DRR appears to be a useful and cost-effective preoperative marker for predicting localized and non-localized disease in Tca at the time of diagnosis. Clinicians should be aware of metastasis and retroperitoneal node involvement in patients with elevated DRR before surgery. Furthermore, DRR may serve as a biomarker for predicting PFS. Prospective studies with large sample sizes are essential to reaching certain conclusions.

Ethics

Ethics Committee Approval: Ethical permission for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Dr. Lutfi Kirdar City Hospital (approval no: 2020/514/184/3, dated: 26.08.2020).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.C., E.D., O.O., Concept: C.C., O.O., Design: C.C., E.D., O.O., Data Collection or Processing: C.C., E.D., Analysis or Interpretation: C.C., Literature Search: C.C., E.D., Writing: E.D., O.O.

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

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Original Article

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The Relationship Between Peyronie's Disease and Serum Parathormone and Ionized Calcium Levels

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Abstract

Aim: Peyronie's disease's (PD) etiology is still unclear. Many factors that may cause the disease are being investigated. The objective of our study was to clarify the effect of serum parathormone and ionized calcium levels on the pathophysiology of PD.

Methods: The study was designed as a cross-sectional study. Demographic data, physical examinations, laboratory tests, and medical and sexual histories of patients between January 2017 and June 2020 were analyzed. Patients were divided into PD and control groups.

Results: By measuring serum calcium and parathormone levels of patients, we analyzed 38 PD and 40 control group patients and revealed that i) parathormone (p=0.321) and ionized calcium (p=0.286) levels are not related to PD, and ii) cardiovascular disease (p=0.037), diabetes mellitus (p=0.0001), and hypertension (p=0.001) are significantly associated with PD, whereas smoking, alcohol consumption, and dyslipidemia status are not.

Conclusion: The study shows that there is no relationship between serum parathormone and ionized calcium levels and the etiology of PD.

Keywords: Parathormone, Ionized calcium, Peyronie's disease

Introduction

Peyronie's disease (PD) springs from progressive fibrosis of the tunica albuginea that causes curvature or other deformities of the penis. It usually presents with a painful palpable plaque, more often on the dorsal surface of the penis and penile curvature (1). Prevalence rates range from 0.4% to 20.3% and usually increase with age (2). Although the precise etiology of PD remains obscure, the commonly accepted theory is recurrent microvascular injury or trauma to the tunica albuginea. Furthermore, diabetes mellitus (DM), hypertension, obesity, smoking, alcohol use, and dyslipidemia have been associated with PD in some studies (3). Histological findings resembling PD were observed when blood came into contact with the tunica albuginea of rats. In the tissue in contact with blood, the expression of transforming growth factor-β was increased. This finding suggests that changes in extracellular matrix remodeling are related to the pathophysiology of PD (4).

Parathyroid hormone (PTH) is a protein hormone released by the parathyroid glands and is one of several hormones that regulate ionized calcium levels by stimulating osteoclast activity in the bone matrix when blood ionized calcium levels decrease. The PTH level increases calcification in different organs by various mechanisms (5-7). Although the relationship between PTH and transforming growth factors is not fully known, its relationship with the TGF-β receptor has been shown (8). In a study examining fibrosis in the proximal tubules of patients with chronic kidney diseases, it was found that connective tissue growth factor expression in the kidney was increased in those administered PTH, and they proved that it has a noteworthy role in the pathophysiology of fibrosis (9). In addition, when mineralized Peyronie's plaques were examined with energy dispersive X-ray and micro-X-ray fluorescent spectroscopic maps, calcium densities were found to be similar to those of bone (10). By considering all this evidence, we hypothesize that

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there might be a relationship between serum PTH levels and PD.

In our study, we aimed to investigate whether PTH is effective in the etiology of PD because of its effect on serum calcium levels and possible inflammatory processes.

Methods

Compliance with Ethical Standards

University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinical Research Ethics Committee permission dated 18.03.2023 and numbered 2023.03.107 was obtained for this study.

Study Design

In this cross-sectional study, we performed retrospective analyses of patients who applied to our urology outpatient clinic due to PD between January 2017 and June 2020. Thirty-eight of 363 PD patients whose serum PTH and ionized calcium levels were measured for any reason were included in our study. As the control group, 40 patients who complained of a reason other than PD and whose serum PTH and ionized calcium levels were measured were randomly included in our study.

Patient Evaluation

Demographic data and the medical and sexual histories of the patients were obtained. This information includes several components such as smoking behavior, alcohol consumption, painful erection, degree and direction of penile curvature, ability to vaginal penetration, penile plaques, medications, and comorbidities. The International Index of Erectile Function Questionnaire (IIEF-5) was used to define the erection status of patients (11).

Disease-specific symptoms and the presence of penile fibrotic plaques (observed during the physical examination) help define the diagnosis of PD. By autophotography during erection or physical examination after intracavernosal alprostadil injection, the degree and direction of the concomitant penile curvature were diagnosed. The localization and size of the penile plaques were measured by penile ultrasound performed without intracavernosal injection.

Our sample excludes patients taking hypercalcemia medication. The PTH and serum calcium levels of 363 patients were enrolled retrospectively in the hospital information system. Three hundred and twenty-five of those patients had no serum PTH or ionized calcium level measurements, which made them inconvenient for our analyses, and they were excluded from our sample. The data of the control group was also retrospectively obtained from the hospital information system. Demographic data, comorbidities, smoking, and alcohol consumption were retrospectively obtained from patient files.

A blood test was obtained after 10-12 hours of fasting. The normal ranges for PTH and serum calcium were 10-55 pg/mL and 8.8-10.2 mg/dL, respectively. PTH levels were measured using a Cobas e601 autoanalyzer and a Roche intact PTH measurement kit (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

We performed analyses using the SPSS (Statistical Package Programme for Social Sciences 22.0) program. The distribution of continuous variables [age, body mass index (BMI), IIEF-5 scores, PTH, plasma calcium level] were assessed by performing the Kolmogorov-Smirnov test. To compare the groups, the t-test was used for BMI and plasma calcium level. The Mann-Whitney U test was performed for PTH, IIEF-5 scores, and age. To compare variables including smoking, alcohol consumption, and the presence of comorbidities such as DM, HT, dyslipidemia, and cardiovascular disease (CVD), a chi-square test was used. A p-value lower than 0.05 indicates statistical significance.

Results

We analyzed the data of 78 patients, 38 of whom belonged to the PD group, and the remaining 40 belonged to the control group. Table 1 shows the general characteristics of the two groups.

On the one hand, the difference between the PD group and the control group was not statistically significant for the variables age (p=0.217), body mass index (BMI) (p=0.438), smoking (p=0.286), and alcohol consumption (p=0.546). On the other hand, the differences between the PD and control groups revealed that DM (p=0.0001), hypertension (HT) (p=0.001), and CVD (p=0.037) rates were significantly higher in the PD group.

Table 2 and Figure 1 demonstrate the results of laboratory assessments. First, the mean PTH values of the PD and control groups were 31.92±10.6 pg/mL and 34.78±12.3 pg/mL, respectively, while the difference between these values was not statistically significant (p=0.321). Second, the mean serum calcium values of the PD and control groups were 9.56±0.56 mg/dL and 9.13±0.48 while the difference between these values was not statistically significant (p=0.286). Third, the mean IIEF-5 scores of the PD group and the control group were respectively 20.8±4.4 and 22.1±5.6, while the difference between these values was not statistically significant (p=0.536). Finally, the dyslipidemia difference between these groups was not statistically significant (p=0.376).

Discussion

Because of increased fibrosis in the tunica albuginea and ossification of plaques in PD, we believe that PTH may have a role in the pathophysiology of both mechanisms

Table 1. Characteristics of patients			
	Patients with Peyronie's disease n=38	**Controls n=40**	**p-value**
Age, years, mean ± SD	50.96±10.6 (28-73)	47.37±9.0 (25-76)	0.217*
BMI (kg/m^2), mean ± SD	28.65±4.7	27.92±4.3	0.438**
Smoking, no. (%)	13 (34.2%)	17 (42.5%)	0.286***
Alcohol, no. (%)	6 (15.7%)	5 (12.5%)	0.546***
IIEF-5 score	20.8 ± 4.4	22.1 ± 5.6	0.536*
Comorbidities			
Diabetes mellitus, no. (%)	10 (26.3%)	3 (7.5%)	0.0001***
Hypertension, no. (%)	12 (31.5%)	5 (12.5%)	0.001***
Dyslipidemia, no. (%)	4 (10.5%)	6 (15.0%)	0.376***
Cardiovascular disease, no. (%)	4 (10.5%)	1 (2.5%)	0.037***
Penile curvature, degrees, mean ± SD	35.9±18.6		
Plaque area, cm^2, mean ± SD	4.3±1.9		
SD: Standard deviation; BMI: Body mass index; *Mann-Whitney U; **T-test; ***Chi-square			

Table 2. Results of laboratory assessments			
Parameters (Reference range)	**Patients with Peyronie's disease n=38**	**Controls n=40**	**p-value**
PTH, pg/mL (10-55)	31.92±10.6 (18.75-42.21)	34.78±12.3 (12.23-51.12)	0.321*
Plasma calcium, mg/dL (8.8-10.2)	9.56±0.56 (8.58-10.0)	9.13±0.48 (8.62-9.87)	0.286**
PTH: Parathyroid hormone; *Mann-Whitney U; **T-test			

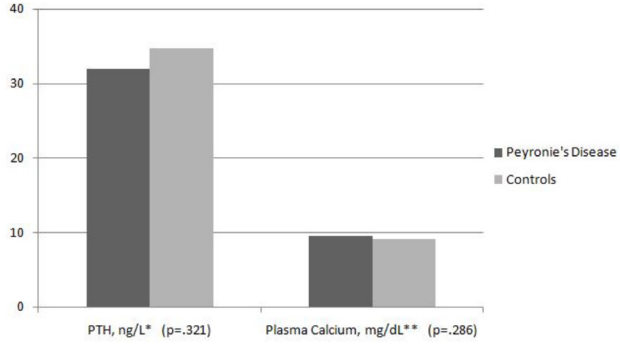

Figure 1. Results of laboratory assessments
PTH: Parathyroid hormone

by upregulating serum calcium levels and effects on connective tissue fibrosis.

TGF-β_1 and TGF-β_2 regulate tissue repair and inflammation through various pathways. After repetitive microtrauma of the tunica albuginea, inflammation occurs in the tissues. It is thought that increasing the amount of acetylated protein in inflamed tissues causes fibrosis by increasing TGF-β_2 expression (12). The relationship between PTH and TGF-β_2 can be demonstrated by the PTH type 1 receptor-transforming growth factor β type 2 receptor complex (8). Therefore, we based our initial hypothesis on the impact of parathormone on tissue inflammation and fibrosis.

Metabolic syndrome is diagnosed by meeting three of the following criteria: abdominal obesity, high blood pressure, high triglyceride, low high-density lipoprotein (HDL), and high blood sugar (13). A positive correlation was found between PTH levels and metabolic syndrome in morbidly obese and elderly patients (14). The link between increased PTH and metabolic syndrome may be explained by correlations with components one by one, such as HT (15), hyperglycemia (16), and low HDL levels (17). An association between PTH and metabolic syndrome has long been predicted. However, the depiction of interactions between metabolic syndrome and primary hyperparathyroidism is hampered by many factors (18). Given the possible association between PD, DM, and CVD, these comorbidities should be screened for in all at-risk PD patients (19). Based on this information, metabolic syndrome has a relationship with PD and PTH. Therefore, we built our second hypothesis on the possible role of PTH in PD. Although we found a significant association between HT, DM, CVD, and PD, we report no significant association between PTH and PD.

DM can cause systemic involvement, such as neuropathy, nephropathy, vasculopathy, and retinopathy. In

addition, DM has negative effects on wound healing (20). Myofibroblasts play a significant role not only in wound healing but also in collagen production. When wound healing is terminated, myofibroblasts undergo apoptosis. Abnormal wound healing may occur if this mechanism does not work. When myofibroblasts are activated due to paracrime interactions, they may contribute to the formation of Peyronie's plaques (21). Studies have shown that high blood glucose levels increase collagen synthesis (22). Moreover, a correlation was shown between the severity of PD and DM (23). In parallel with the literature, we found DM at a higher rate in the PD group.

Hypertension is a dimension of metabolic syndrome. However, mixed outcomes have been reported in recent studies regarding the relationship between HT and PD. While some studies did not show any relationship between HT and PD (24,25), some studies reported a significant relationship (26). We contributed to these mixed outcomes by finding a higher HT in the PD group than in the control group (p=0.001).

CVD is thought to cause weakness in vessel walls and facilitate vessel damage during sexual intercourse. Furthermore, according to previous studies, CVD is associated with PD (27,28). Analogously, we found higher CVD rates in the PD group.

Men with PD have higher rates of HT, DM, and smoking than men without PD (29). The alcohol consumption rate in Dupuytren's disease, which is frequently associated with PD, is higher than that in the normal population (30). Contrary to popular belief, we found no significant difference between smoking and alcohol consumption between patients with and without PD.

Despite many studies, the pathophysiology of PD is still not clearly known. In a study on the status of serum trace elements in PD, serum Mn, Cu, Zn, and Fe levels were reported to be significantly lower in the PD component (31). Calcium is an essential mineral with important physiological functions that cannot be synthesized in the body. PTH plays a critical role in the regulation of serum calcium levels through its effect on bone turnover. Calcium is the main factor in the fibrocalcification of plaques during plaque formation (32). However, we could not detect a significant relationship between serum calcium levels and PD.

Study Limitations

There are several limitations to our study. First, as we performed a retrospective study using data belonging to some patients obtained at a single center, our outcomes may not fully reflect the patient population in other centers. Second, in our study, serum vitamin D levels, which may affect ionized calcium levels and cavernosal TGF-β levels, were not evaluated. Despite these limitations, although it is a small-scale study, it can be considered a pioneering study analyzing the relationship between PTH and PD.

Conclusion

Many factors that may be risk factors for PD are still being investigated. The present study shows that there is no relationship between serum parathormone and ionized calcium levels and the etiology of PD.

Ethics

Ethics Committee Approval: Ethical permission for the study was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinical Research Ethics Committee (dated: 18.03.2023, and numbered: 2023.03.107).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.M.C., M.S., Design: M.M.C., M.S., Data Collection or Processing: M.M.C., M.S., Analysis or Interpretation: M.M.C., M.S., Literature Search: M.M.C., M.S., Writing: M.M.C., M.S.

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

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Original Article

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Evaluation of ABO/Rh Blood Group Distributions and Clinical Characteristics in Patients with Adrenal Incidentaloma: A Case-Control Study

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Abstract

Aim: Studies examining the relationship between endocrine organ diseases and ABO and Rh blood groups have been conducted, and some studies have shown that endocrine organ diseases may be associated with ABO/Rh blood groups. The aim of this study was to evaluate the ABO/Rh blood group distribution in patients with adrenal incidentaloma (AI) and its relationship with the clinical features of the patients.

Methods: The study was conducted as a retrospective case-control study. Patients with AI who were followed up in the outpatient clinic of a single tertiary center between 2019 and 2023 were included in the study. The clinical (age, gender), radiological (diagnostic method, radiological features, adenoma size, localization), and biochemical (catecholamines, cortisol, aldosterone, and plasma-renin activity) characteristics of the patients were determined. The ABO and Rh blood group distributions of the patients were compared with those of the healthy control group.

Results: The number of patients included in the study was 356 and the number of people in the healthy control group was 2,809,237. Adrenal incidentaloma was detected by computed tomography in 237 (67.1%) patients and was more often detected in the left adrenal gland (51.1%). The median size of the adrenal mass was 20 mm. Because of the hormonal evaluation, functional hormone production was detected in 16 (4.5%) patients. After further investigations, it was found that three (0.8%) patients had adrenal carcinoma and three (0.8%) patients had cancer metastases. ABO blood group distributions in the patients (42.7% A, 13.5% B, 9.6% AB, 34.3% O) and control groups (42% A, 16% B, 8% AB, 34% O) were found to be similar (p=0.9). Similar results were found in terms of the Rh factor (p=0.9). There was no statistically significant relationship between the distribution of ABO and Rh blood groups and clinical features such as age, gender, functional hormone release, mass size, and accompanying endocrine diseases.

Conclusion: The ABO/Rh blood group was not found to be a risk factor in patients with AI. In addition, no relationship was found between clinical features and the ABO/Rh blood group in patients with AI.

Keywords: Adrenal incidentaloma, ABO blood groups, Rh factors

Introduction

Adrenal incidentaloma (AI) is the detection of a mass in the adrenal gland because of radiological imaging performed for any reason. Today, with the development of imaging techniques, the incidence of AI in the adrenal glands is approximately 4-7% in patients undergoing computed tomography (1,2). This rate may increase even more in elderly individuals (3). Approximately 8-30% of patients with AI have a mass in the bilateral adrenal glands (4). The differential diagnosis of adrenal gland masses includes many diseases, such as adrenal carcinoma, metastasis, congenital adrenal hyperplasia, lymphoma, hemorrhage, and infection. All patients with AI should be carefully evaluated for malignancy and functional hormone secretion. There is a risk of malignancy in patients with an adrenal mass greater than 4 cm and a radiological Hounsfield unit greater than 10 units (5,6). Approximately 10% of patients with AI have hormone secretion, and all patients should be evaluated in this regard (7). Unilaretel adrenalectomy is the primary treatment method for unilateral malignant or hormone-secreting tumors;

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however, in patients with bilateral masses, the decision should be made according to the type of tumor and the type of hormone secreted.

Because of further investigations in patients with a diagnosis of AI, non-functional adenomas were detected in the majority of patients, but the underlying pathophysiological mechanism is not fully known. Although the frequency of AI detection increases with age, the risk factors have not been fully defined. Chromosome 9q34 contains the gene for the ABO blood group, which encodes glycosyltransferases (8). Glycosyltransferases produce ABO blood-type antigens by catalyzing However, blood group antigens were detected on the cell surfaces of bronchopulmonary, genital tract, epidermis, and gastrointestinal cells (9). Previous studies have demonstrated a connection between certain cancers, metabolic and autoimmune diseases, and ABO/Rh blood groups (10). In various investigations, the associations between ABO and Rh blood types and endocrine disorders were investigated. It is unknown whether the ABO and Rh blood groups are risk factors in patients with AI.

In this study, we aimed to compare the ABO/Rh blood group distribution in patients with AI with that in the healthy population. In addition, the relationship between clinical features and the ABO/Rh blood group in patients with AI was examined.

Methods

Compliance with Ethical Standards

Ethics committee approval (approval no: 60-2023, date: 29.03.2023) was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee before the study, and the study was conducted according to Turkish Medicines and Medical Devices Agency Good Clinical Practice Guidelines (revision no: 08).

Patients and Data Collection

This study was designed as a retrospective case-control study. Patients with AI who were followed up in the outpatient clinic of a single tertiary center between 2019 and 2023 were included in the study. The patients included in the study were identified using the hospital's data processing system. Inclusion criteria was determined as 1-being over the age of 18, 2-having a diagnosis of AI, and 3-knowing the ABO/Rh blood group (Figure 1). Patients with incomplete data and congenital adrenal hyperplasia were excluded from the study. The clinical, biochemical, and radiological data of the patients (mass characteristics, location, and size) were noted in the patients follow-up files and the Ministry of Health Patient Information System. The histories of other accompanying endocrine diseases of the patients, such as hypertension, diabetes mellitus, hyperparathyroidism, pituitary adenoma, and benign thyroid diseases (hypothyroidism, hyperthyroidism, and goiter), were recorded. The ABO and Rh blood groups of the patients were measured using the gel centrifugation test method.

All biochemical tests were performed in a standardized biochemistry laboratory. If the 1 mg dexamethasone suppression test is >1.8 mcg/dL, other screening tests (bedtime cortisol level, bedtime salivary cortisol level, 24-hour urine free cortisol level) and the 2 mg dexamethasone suppression test are performed, and if the results in these tests are above the normal limit, Cushing's syndrome

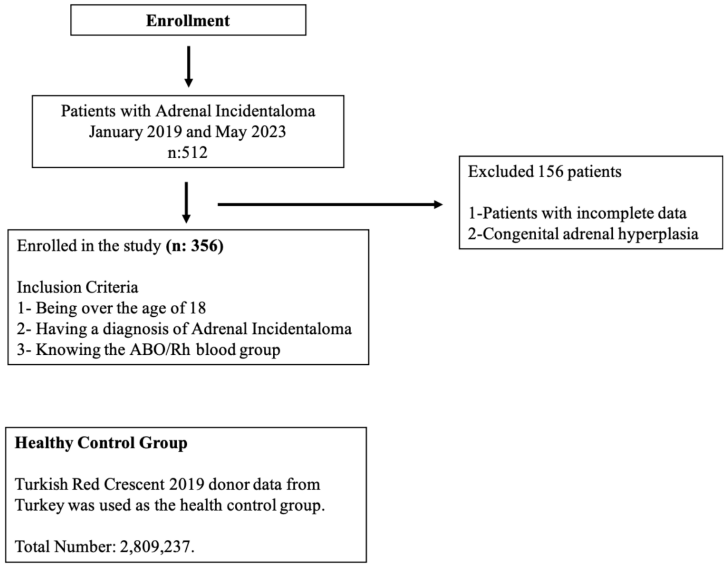

Figure 1. Flow chart of patient enrollment

is accepted. The levels of fractionated catecholamines (metanephrine and normetanephrine) in 24-hour urine were checked for the diagnosis of pheocromacytoma, and plasma and urinary catecholamines were re-evaluated in cases of abnormal values. If catecholamine levels were found to be three times higher than the normal value, a diagnosis of pheochromocytoma was made. Plasma renin activity (PRA) and plasma aldosterone levels were measured for hyperaldosteronism in patients with hypertension and/or hypokalemia. If the aldosterone/PRA ratio is >20, the diagnosis is confirmed by confirmatory tests (saline infusion test, oral salt loading test, and captopril test).

The ABO and Rh blood group distributions of the patients were compared as general or blood group-specific (such as A vs. non-A) with the blood group distribution of the healthy control group. Turkish Red Crescent 2019 donor data from Turkey was used as the health control group. The number of healthy individuals who were blood donors in 2019 was 2,809,237 (11). In addition, the relationship between ABO/Rh blood group distributions and patients' age, gender, functional hormone release, adrenal mass localization, and size was evaluated.

Statistical Analysis

The statistical analyses were performed using SPSS 29 (IBM, Armonk, NY, USA). Continuous variables in the study were represented by median (as well as minimum and maximum values) values, numbers, and percentages, while categorical variables were described by numbers and percentages. ABO/Rh blood group distributions in the patient group and healthy control group were compared using Fisher's exact test and the chi-square test. When the p-value was 0.05, the results were deemed statistically significant, and the probability ratio was calculated.

Results

Patient Characteristic

Study statistics were made by including data from 356 patients with AI. The patients were followed up for a median of 31.8 months. The median age at diagnosis was 59 (range, 19-85), and most patients were female (68.3%). The most common accompanying endocrine diseases were hypertension (53.1%), diabetes mellitus (26.4%), and benign thyroid diseases (24.4%). Thirty-seven (10.4%) patients had a history of cured cancer. None of the patients had a family history of AI. Most of the patients underwent radiological imaging because of a symptom (such as pain, swelling in the abdomen, or cough). The most common imaging method was computed tomography (67.1%). The median size of the adrenal mass was 20 mm, and the most common location was the left adrenal gland (51.1%). Functional hormone secretion was detected in 16 (4.5%) patients. After the radiological examinations, it was determined that most patients had an adrenal adenoma (91.6%). Table 1 shows the clinical, radiological, and biochemical characteristics of the patients.

Table 1. Clinical, pathological, and radiological features of patients with AI

	The number of patients (n=356)
Age at diagnosis	
60<	194 (54.5%)
60≥	162 (45.5%)
Gender	
Female	243 (68.3%)
Male	113 (31.7%)
The medical history of endocrine disease	
Hypertension	189 (53.1%)
Diabetes mellitus	94 (26.4%)
Benign thyroid disease	87 (24.4%)
Hyperparathyroidism	9 (2.5%)
Pituitary adenoma	7 (2%)
The history of cancer	
Yes	37 (10.4%)
No	319 (89.6%)
Insidentaloma localization	
Left sight	182 (51.1%)
Right sight	118 (33.1%)
Bilateral	56 (15.8%)
Radiological imaging causes	
Check-up examination for any symptoms	231 (92%)
Cancer screening	25 (8%)
Imaging method at diagnosis	
Computed tomography	239 (67.1%)
Magnetic resonance imaging	115 (32.2%)
PET Scan	2 (0.6%)
Adenoma size at diagnosis	
<2 cm	165 (46.3%)
2-4 cm	167 (46.9%)
>4 cm	21 (6%)
Missing	3 (0.8)
Hormone secretion status	
Non-functional	340 (95.5%)
Cushing's disease	9 (2.5%)
Primary aldosteronism	4 (1.1%)
Pheochromocytoma	3 (0.9%)
A definitive diagnosis of the adrenal mass	
Adenoma	326 (91.7%)
Myelolipoma	10 (2.9%)
Cyst	8 (2.2%)
Cancer metastasis	3 (0.8%)
Adrenal carcinoma	3 (0.8%)
Feocromasitoma	3 (0.8%)
Undefined	3 (0.8%)
Surgery for AI	
Yes	36 (10.1%)
No	320 (89.9%)

AI: Adrenal incidentaloma

ABO/Rh Blood Group Distribution

ABO and Rh blood groups were evaluated in general, and no statistical difference was found between the patient and healthy control groups (Table 2). In terms of ABO blood group distribution, patients (42.7% A, 13.5% B, 9.6% AB, 34.3% O) and the control group (42% A, 16% B, 8% AB, 34% O) were found to be similar (p=0.6). The Rh factor distribution was equal in both groups (p = 0.9) (Table 3). Although the frequency of the AB blood group was found to be increased compared with the nonAB blood group in patients with AI, it did not reach statistical significance [p=0.6, confidence interval (CI) 95%, odds ratio (OR): 1.25]. Although the frequency of the B blood group was found to be decreased compared with the NonB group, it was not statistically significant (p=0.6, CI 95%, OR: 0.86). In addition, no correlation was found between the distribution of ABO and Rh groups and features such as age, gender, functional hormone release, adrenal mass size, and localization in patients with AI.

Table 2. Distribution of ABO/Rh blood groups in patients with AI and control group

Blood antigens	Patients group (n=356) %	The control group (n=2,809,237) %	p-value
ARh+	38.6%	37%	0.6
ARh-	4.2%	5%	
BRh+	13.2%	14%	
BRh-	0.3%	2%	
ABRh+	8.4%	7%	
ABRh-	1.1%	1%	
ORh+	27.5%	30	
ORh-	6.7%	4%	
Total (%)	100	100	

Chi-square and Fisher's exact tests were used
AI: Adrenal incidentaloma

Discussion

In this study, we show the clinical, biochemical, and radiological features at the time of diagnosis in patients with AI. Thanks to advances in radiological imaging methods and high resolution, the frequency of AI detection is increasing daily. While the incidence of AI was 0.4% in patients who underwent computed tomography in the 1980s, this rate has increased to 7% today (12,13). It is necessary to evaluate these patients in terms of malignancy and functional hormone secretion and follow up in this regard (14). The pathophysiology of AI development has not been fully elucidated. Obesity is thought to be one of the possible pathophysiological mechanisms that may increase the frequency of AI due to insulin resistance and the effect of insulin on the adrenal glands (15,16). In a comparative study in which 601 patients were evaluated, the frequency of type 2 diabetes was found to be 31.8% in patients with AI, and the frequency of obesity increased in these patients. The multivariate analysis of this study showed that type 2 diabetes mellitus could be a statistically significant risk factor for the development of AI (13). In the TURDEP-II study, the prevalence of diabetes mellitus was found to be 16.5% in the Turkish population (17). In our study, the frequency of diabetes mellitus was found to be 26.4% in people with AI, which is quite high compared with the normal population.

Today, the number of studies examining the relationship between blood groups and various diseases is increasing. In a retrospective study of 41 years of data, including nearly 500,000 patients, a relationship was found between the ABO and RhD systems and tongue cancer, cervical cancer, osteoarthritis, asthma, HIV, and hepatitis B infections (18). In various investigations, the associations between ABO and Rh blood types and endocrine gland disorders were investigated. In the study examining the clinical manifestations of patients with multiple

Table 3. Odds ratios according to ABO/RH blood group distribution in patients with AI and controls group

	Patients group Total number: 356 (%)	The control group Total number: 2,809,237 (%)	p-value	Odds ratio 95% CI
A Non-A	42.7% 57.3%	42% 58%	P=0.8	1.02 (0.74-1.41)
B Non-B	13.5% 86.5%	16% 84%	P=0.6	0.86 (0.44-1.67)
AB Non-AB	9.6% 90.4%	8% 92%	P=0.6	1.25 (0.51-3.03)
O Non-O	34.3% 65.7%	34% 66%	P= 0.9	1.00 (0.74-1.37)
Rh- Rh+	12.4% 87.6%	12% 88%	P=0.9	1.03 (0.56-1.87)
Total (%)	100	100		

Chi-square and Fisher's exact tests were used
CI: Confidence interval, AI: Adrenal incidentaloma

endocrine neoplasia type 1, it was shown that 94% of the metastatic patients had O blood group, and O blood group was shown to be a risk factor for metastasis (19). In a different investigation, it was observed that patients with Hashimoto's hypothyroidism had an O blood group that was statistically considerably higher than that of other hypothyroid patients (20). In addition, in a recently published study on thyroid gland cancer, no relationship was found between thyroid gland papillary cancer and the ABO/Rh blood group (21). In a meta-analysis examining the ABO/Rh blood group relationship in patients with type 2 diabetes mellitus, it was determined that individuals in the AB blood group had the highest risk and those in the B blood group had the lowest risk of developing type 2 diabetes (22). The relationship between ovarian gland disorders and ABO blood groups has been the subject of several studies. In a study examining the connection between ovarian hyperstimulation syndrome and blood type, it was found that blood type A may be a risk factor for the disease (23). Another study that looked at 35,479 infertile women indicated that women with blood group B had a greater diminished ovarian reserve than women with blood group O (24). The relationship between ABO and Rh blood types and the development of cancer, endocrine disorders, and other illnesses is not entirely understood. According to some research, these diseases may develop because of inflammation caused by abnormalities in the enzyme system that creates the blood group antigens expressed in tissues (25-27). A study examining the relationship between adrenal gland tumors and ABO/Rh blood groups has not yet been conducted. In this study, it has been shown that ABO and Rh blood groups are not a risk factor in patients with AI. No correlation was found between the distribution of ABO and Rh blood groups and clinical, radiological, and biochemical features in patients with AI.

Study Limitations

This study had some limitations due to its retrospective nature. The patient group included in the study was heterogeneous, and some patient data was missing. The number of patients was relatively limited. Despite these limitations, to the best of our knowledge, this is the first study in the literature to show that ABO and Rh blood groups are not a risk factor for the development of AI. This study is important in this respect and contributes to the literature.

Conclusion

In this study, the general characteristics of patients with AI and the distribution of ABO and Rh blood groups in these patients were shown. The ABO/Rh/Rhood group distribution in patients with AI was found to be similar to that in the healthy population. In addition, according to the ABO/Rh blood group distribution, the radiological features and functional hormone status of patients with AI were found to be similar at the time of diagnosis. With future clinical and molecular studies, the development mechanisms of AI will be better understood.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval no: 60-2023, date: 29.03.2023).

Informed Consent: The study was conducted as a retrospective case-control study.

Peer-review: Externally peer-reviewed.

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Original Article

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Factors Affecting Recurrent Choledocholithiasis After Endoscopic Biliary Sphincterotomy: A Cross-Sectional Study

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Abstract

Aim: The purpose of this study was to identify and analyze factors associated with the recurrence of common bile duct stones (CBDS) following endoscopic interventions, aiming to provide insights into predictors and characteristics of CBDS recurrence after endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) procedures.

Methods: The study was designed as a single-center, cross-sectional study. Clinical data were collected from 271 patients with CBDS who underwent ERCP between June 2019 and December 2022. According to the diagnostic criteria for CBDS recurrence, patients were categorized into recurrence and non-recurrence groups. The assessment of predisposing risk factors for recurrent bile duct stones included various variables such as age, sex, gallbladder status, presence of periampullary diverticulum (PAD), number and diameter of bile duct stones, bile duct diameter, pre-cutting, and early complications.

Results: A total of 271 patients were included in the study. CBDS recurrence occurred in 25 patients (9.2%), with a median of 18 months after ERCP and EST. Notable findings included that patients with recurrent CBDS had larger common bile duct diameters (7.5±4.5 mm vs 13±1.7 mm, p=0.037). Choledocholithiasis was more common in patients with a choledochal duct diameter ≥1.5 cm (3% vs 48%, p=0.00001). Recurrent choledocholithiasis was frequent in patients with larger stone sizes (7.3±6.5 mm vs 13.5±4.3 mm, p=0.04). The presence of PAD was correlated with a higher recurrence risk (23% vs 44%, p=0.013). The time to stone recurrence after the index ERCP and EST was 18.273±2.021 months. There was no significant difference in recurrence between patients with ≥2 CBDS and those with a single stone (41% vs 44%, p=0.35).

Conclusion: Larger bile duct diameter, choledochal stone size, initial stone size, and the presence of PAD emerged as crucial indicators of recurrence risk. These findings contribute to our understanding of the prediction and management of CBDS recurrence after ERCP and EST procedures.

Keywords: Endoscopic retrograde cholangiopancreatography, endoscopic biliary sphincterotomy, common bile duct stone, recurrence, periampullary diverticulum

Introduction

Gallstones represent a prevalent issue within the digestive system (1). Approximately 10-20% of individuals with gallstones also exhibit common bile duct stones (CBDS), whereas a staggering 95% of patients diagnosed with CBDS concurrently possess gallstones (2). Following the pioneering work of Kawai in 1974, endoscopic sphincterotomy (EST) has emerged as the foremost technique for eradicating CBDS through endoscopic retrograde cholangiopancreatography (ERCP). The success rate of ERCP hovers around 98%, coupled with a clearance rate of up to 95% (3). Reports suggest that the recurrence rate of CBDS following endoscopic treatment ranges from 4% to 25% (4).

Even after cholecystectomy, stones may recur, with biliary stasis and gallbladder bacteria implicated as the primary culprits for CBDS recurrence. While dilated common bile ducts, large or multiple stones, and the presence of periampullary diverticulum (PAD) have been proposed as predictors of CBDS recurrence after endoscopic stone removal (5,6), consistent definitions remain elusive due to study design variations. Referred

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to as a belated complication after successful ERCP and biliary tract stone extraction, CBDS recurrence has spurred essential research into the identification of its predictors. Several studies (7-9) have consistently underscored specific factors associated with heightened recurrence probabilities. For instance, an enlarged common bile duct increases the risk because of its potential to harbor residual stones or facilitate stone reformation. Larger stones, which are more laborious to completely extract during the initial procedure, can lead to recurrence. Correspondingly, the presence of multiple stones and PAD has been associated with elevated recurrence risk (8-10). These collective findings substantiate the pivotal role of these predictors in shaping CBDS recurrence following endoscopic stone removal procedures.

We aimed to assess the recurrence rate of symptomatic CBDS in patients who have undergone ERCP and EST for CBDS while also examining the associated factors.

Methods

Compliance with Ethical Standards

Our study received authorization from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (protocol no: 166, date: 07.04.2023) and adhered to the Declaration of Helsinki. Informed consent was secured from each participant.

Study Design

This study adopts a cross-sectional design, with data sourced from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital database covering the years 2019 to 2022. EST and stone extraction were performed on 271 patients diagnosed with gallstones and established CBDS. The CBDS diagnosis was validated using magnetic resonance cholangiopancreatography, or ERCP. The inclusion criteria encompassed patients with biliary stones who had not previously undergone ERCP treatment. Stone number, diameter, and CBD diameter were confirmed by fluoroscopic imaging. EST was performed on all 271 patients, and as appropriate, CBD clearance was achieved using a balloon or basket. The confirmation of PAD presence was based on duodenoscopy images. Only patients in whom CBD was entirely and successfully cleared of stones were considered for the study. Patients with CBD strictures, periampullary and biliary tract cancer, intrahepatic duct stones, or CBDS identified via cholangiography were excluded. Recurrent CBDS, defined as occurrences at least 6 months after endoscopic extraction (11,12), were tracked along with symptomatic recurrences and cholecystectomy history during follow-up.

Statistical Analysis

The data obtained were subjected to analysis using SPSS 15.0 (Statistical Package for Social Sciences). Descriptive statistics were employed, expressing the data as the mean and standard deviation. The measurement parameter's normal distribution was verified using the "Kolmogorov-Smirnov test". For group comparisons, the "Independent groups t-test" was used for parametric data, whereas the "Mann-Whitney U test" addressed non-parametric data. Qualitative data comparisons employed the Pearson chi-square test. A p-value of ≤0.05 was deemed significant, with a confidence interval of 95%.

Results

A total of 271 patients who had not undergone any previous procedure and were treated with ERCP + EST because of choledocholithiasis during the study period were included in the study (Table 1). There were 159 female patients (59%) and 112 male patients (41%) with a female-to-male ratio of 1.4:1. The median age of the patients during the first ERCP (index ERCP) was 63.6±17.2 years. CBDS recurrence was observed in 25 patients (9.2%) at least 6 months after endoscopic treatment.

Clinical indicators of CBDS recurrence exhibited variability (Figure 1), encompassing pain (96%), jaundice

Table 1. Parameters associated with recurrent choledocholithiasis

	Non-recurrent CBDS	Recurrent CBDS (%)
Patients	246	25 (9.2)
Gender (male/female)	101/145	11/14
Age (mean ± SD, years)	63.6±17.2	65.2±15.6

CBD: Common bile duct, CBDS: Common bile duct stone, ERCP: Endoscopic retrograde cholangiopancreatography, EST: Endoscopic sphincterotomy, SD: Standard deviation

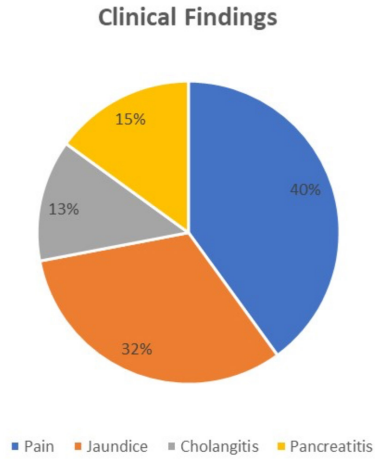

Figure 1. Clinical findings of recurrent choledocholithiasis

(76%), pancreatitis (36%), cholangitis (24%), or a combination thereof. Pain and jaundice were the most frequent clinical manifestations. Parameters linked to recurrent choledocholithiasis were meticulously assessed (Table 2).

Upon comprehensive evaluation of all patients who underwent ERCP + EST, those with recurrent CBDS showcased a broader common bile duct (7.5±4.5 mm vs 13±1.7 mm, p=0.037). Furthermore, recurrent choledocholithiasis was notably prevalent in individuals with a common bile duct diameter of 1.5 cm or more (3% vs 48%, p=0.00001). A similar pattern was observed with larger choledocholithiasis stone sizes, which correlated with an elevated occurrence of recurrent choledocholithiasis (7.3±6.5 mm vs 13.5±4.3 mm, p=0.04). Patients with PAD exhibited heightened susceptibility to recurrent choledocholithiasis (23% vs 44%, p=0.013). The mean interval between the index ERCP + ES and stone recurrence was 18.273±2.021 months. Notably, the recurrence rate showed no significant difference between patients harboring two or more CBDS and those with a solitary stone (41% vs 44%, p=0.35). Among patients who experienced recurrent stones post-index ERCP + ES, 8% had undergone cholecystectomy.

Discussion

ERCP, in conjunction with EST, is internationally acknowledged as the primary approach for the extraction of CBDS due to its minimally invasive nature. While ERCP is a highly effective and safe non-surgical intervention, complications, whether minor or major, can still manifest. A notable delayed complication of EST is the recurrence of CBDS (13). Recurrence rates following ERCP typically vary between 2-22% (12,14). However, a challenge arises when recurrent CBDS appear six months or more after ERCP, introducing complexities for medical practitioners. Despite diverse reports on the recurrence rate of choledocholithiasis post-ERCP, statistics often oscillate between 4% and 24%. Nevertheless, the connection between these risk factors and optimal therapeutic strategies remains enigmatic. Previous observational studies that evaluated patients post-EST have highlighted risk factors for recurring bile duct stones, yet their association with recommended treatments lacks clarity. These risk factors, such as multiple CBDS, larger stone sizes (exceeding 1 cm), and concurrent balloon dilation or stent insertion during ERCP, can be considered moderate risk predictors for primary CBD stone recurrence (11,15).

Table 2. Parameters associated with recurrent choledocholithiasis

Factors	Non-recurrent CBDS 246 (%)	Recurrent CBDS 25 (%)	P-value
PAD	56 (23)	11 (44)*	0.013ᵗ
CBD Diameter (mean ± SD, mm)	7.5±4.5	13±1.7*	0.037ᵗ
CBD Diameter ³1.5 cm	7 (3)	12 (48)*	0.0000ᵗ
Number of CBDS ³2	100 (41)	11 (44)	0.35ᵗ
Widest diameter of CBDS, mean ± SD (mm)	7.3±6.5	13.5±4.3*	0.04ᵗ
Recurrence time, mean ± SD (months)	-	18.273±2.021	-
Cholecystectomy	-	2 (8)	-

*p≤0.05, ᵗStudent's t-test
CBD: Common bile duct, CBDS: CBD stone, ERCP: Endoscopic retrograde cholangiopancreatography, EST: Endoscopic sphincterotomy, PAD: Periampullary diverticulum, SD: Standard deviation

In line with existing literature, our study revealed a recurrence rate of choledocholithiasis of 9.2% following ERCP and EST. Notably, stone size, CBD dilation, and the presence of a PAD emerged as risk factors for stone recurrence during the initial assessment. Intriguingly, a CBD diameter exceeding 1.5 cm was identified as a risk factor for recurrence. The precise mechanism behind CBD dilation remains uncertain; a reduction in bile hydrostatic force and disruption of normal CBD motility may render patients more susceptible to recurring stone formation (16). While CBD diameter is already acknowledged as a risk factor for CBD stone recurrence, a definitive "cut-off" diameter remains undefined, as various diameters correlate with distinct recurrence rates. For instance, Pereira Lima et al. (17) demonstrated that patients with a CBD diameter of 15 mm or more faced a four-fold higher risk of recurrence compared to those with a diameter of 10 mm or less. Patients with a CBD diameter ≥15 mm exhibited a recurrence risk of 46%, whereas those with a diameter ≤12 mm exhibited a 20% risk (5). Numerous studies underscore the significant correlation between CBD diameter and CBDS recurrence (4,6,18,19). There is consensus that a CBD diameter ≥15 mm signifies a high-risk factor for recurrent CBDS.

PAD and dilated bile ducts devoid of residual obstruction present challenging risk factors. PAD could potentially contribute to cholangitis and recurrent biliary stone formation (14,20). The presence of a diverticulum in the bile duct is believed to impede the canal or sphincter, leading to slower biliary emptying compared to those without PAD. This delay likely contributes to recurring bile duct stone formation, as evidenced in the literature (20). Our study, akin to prior literature, included patients with PAD, revealing a substantial recurrence rate of typical choledochal stones within the periampullary duodenum. Although the precise mechanism within the diverticulum remains elusive, both stone formation

and CBDS recurrence are evident, establishing PAD as a significant risk factor (21,22).

Literature has long examined the correlation between the number and size of stones in the biliary tract. The prevailing theory suggests an escalated risk of CBDS recurrence with larger stone diameters and increased stone numbers (6,14). For instance, Deng et al. (6) found that a stone diameter below 10 mm is an independent risk factor for recurrence. In congruence with this, our study also underscores that patients with larger stone diameters are more predisposed to recurrent CBDS. However, stone quantity and recurrence didn't exhibit statistical significance. Furthermore, research suggests that having over two stones is a noteworthy risk factor for CBDS recurrence (18).

Recurrence of CBDS may sometimes be asymptomatic, occasionally detected during assessments or radiological evaluations unrelated to the issue. Yet, symptomatic CBDS presents with cholangitis, severe pancreatitis, obstructive jaundice, or biliary colic (23). Our study reveals an escalating prevalence of recurrent choledochal stones associated with discomfort, jaundice, pancreatitis, cholangitis, or a combination of these symptoms. Among these, pain and jaundice were the most frequent. Various studies have established links between endoscopic or surgical treatments for choledocholithiasis and factors like bacterial infection, abnormal biliary anatomy, inflammation, and other related variables.

Study Limitations

Our study has some limitations. The cross-sectional design hinders the establishment of causal relationships between the identified factors and recurrent choledocholithiasis. A single-center study may introduce selection bias and limit generalizability. The relatively short follow-up period may underestimate the true recurrence rate, and retrospective data collection may result in incomplete information. However, the study's substantial sample size, comprehensive assessment of various risk factors, and focus on clinically relevant outcomes enhance its value in elucidating factors influencing choledocholithiasis recurrence after ERCP + ES procedures

Conclusion

The risk factors contributing to recurrent choledocholithiasis remain partially understood and exhibit variation across different studies. Nonetheless, it is theoretically feasible to identify patients at significantly heightened risk of stone recurrence, enabling more vigilant monitoring, early intervention, and potential preventive measures. This strategic approach holds promise for mitigating the occurrence of delayed complications and recurrent stones. Notably, complications, specifically the potential for bile duct stone recurrence following endoscopic stone removal and routine bile duct clearance, may arise. The initial manifestation of stones and anatomical attributes such as choledochal diameter and the presence of PAD appear to correlate with stone characteristics encompassing size and count.

Ethics

Ethics Committee Approval: Our study received authorization from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Ethics Committee (protocol no: 166, date: 07.04.2023) and adhered to the Declaration of Helsinki.

Informed Consent: Informed consent was secured from each participant.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.D., B.Y., Concept: N.D., B.Y., Design: N.D., B.Y., Data Collection or Processing: N.D., Analysis or Interpretation: N.D., B.Y., Literature Search: N.D., B.Y., Writing: N.D., B.Y.

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Case Report

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Two Cases of an Unusual Childhood Aortic Dissection Resulting in Death

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Abstract

Pediatric aortic dissection is an emergency condition that is difficult to diagnose and is associated with high morbidity and mortality. To draw attention to this issue, we present two male cases diagnosed with aortic dissection because of an autopsy. A 16-year-old man with severe new-onset chest pain had an unremarkable physical examination, electrocardiography, and laboratory values. Aortic dissection was not detected on non-contrast computed tomography or echocardiography. Type A aortic dissection was discovered during the patient's autopsy. In the second case, a 10-year-old male patient complained of fever, vomiting, and abdominal pain. The physical examination and biochemical tests were unremarkable. Type B aortic dissection was discovered during the autopsy. Genetic and congenital causes predisposing to aortic dissection and hypertension or a history of trauma were not detected in either patient. Aortic dissection, which is very rare in children, should be considered in cases of persistent chest pain, and rapid diagnosis with contrast-enhanced tomography is vital.

Keywords: Aortic dissection, autopsy, chest pain, child

Introduction

Aortic dissection (AD) is an emergency procedure with high morbidity and mortality. AD occurs as a result of an aortic intimamedia tear, which allows blood flow between the layers. The classical symptoms of AD are the sudden onset of severe chest and back pain. The mortality rate for untreated Type A AD is estimated to be 1% per hour at the beginning, 50% by the third day, and 80% by the end of the second week. Mortality rates are lower in acute type B AD (1).

According to current data, 0.67-3.5% of ADs occur in people under the age of 21. The weakness of the aortic media layer creates predisposition (2). The most common predisposing cause in children is congenital cardiovascular disease. Less frequently, it may also occur due to trauma (3).

We present two male patients, aged 16 and 10 years, who were diagnosed with AD as a result of an autopsy performed in our institution to draw attention to the fact that AD can be rarely seen at a young age and that there may be no findings in echocardiography or non-contrast computed tomography of the thorax and unusual complaints.

Case Presentation

This case presentation was approved by the Council of Forensic Medicine Education and Scientific Research Commission on May 10, 2022, in a decision with the number 407/2022 and the date May 10, 2022.

The first case, a 16-year-old male patient, presented to the emergency department with severe new-onset chest pain. His general condition was moderately good; his body weight was 83 kg (90 percent), his height was 178 centimeters (cm) (72%) and his breathing was comfortable. Vital signs were normal (arterial blood pressure: 134/60 mmHg, heart rate: 99/min, fever: 36 °C, oxygen saturation measured by pulse oximetry: 98%). Examination revealed a systolic, innocent murmur. The electrocardiogram was normal. Laboratory results showed no abnormalities. Serial troponin measurements repeated every 3 hours were normal. No pathology was detected on non-contrast

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thorax computed tomography. He was given symptomatic treatment and discharged with a preliminary diagnosis of myalgia.

The patient, whose chest pain worsened again, was admitted to the emergency unit of a different institution a few hours later. The physical examination was normal except for a 1-2/6 systolic murmur. His heart teleradiogram was normal. Creatine kinase (CK): 680 U/L, CK-MB: 16.7 U/L; C-reactive protein (CRP), 2.45 mg/L; Troponin I: <0.100 ng/mL; white blood cell, 13.130/mm^3; hemoglobin, 15.8 g/dL; platelet count, 212000/mm^3; and the Coronavirus disease-2019 polymerase chain reaction test were negative. The patient was consulted with cardiology. No ischemic electrocardiography (ECG) changes were detected. In addition, no pathological findings were detected in the transthoracic echocardiography except for mild tricuspid regurgitation. While pediatric cardiology control was planned, sudden cardiac arrest developed, and there was no response to cardiopulmonary resuscitation (CPR).

An autopsy was performed. 3500 mL of partially coagulated blood was seen within the right chest cavity. Minimal blood in the pericardial cavity and a 3-cm tear with diffuse hemorrhage around the posterior wall on the upper right of the pericardium were detected. Hemorrhage was observed around the descending and thoracic aortas in the posterior mediastinum. There is a tear in the aortic intima media extending transversely 0.5 cm above the valve (Figure 1a, 1b). Separation in the vessel wall layers and an adventitial defect behind this area, and separation along the thoracic aorta due to AD, pseudolumen formation, and hematoma were observed (Figure 2a, 2b). Histological examination revealed intimomedial separation, fibrin thrombus formation in this area, bleeding, mixed inflammatory cell infiltration in adventitial fatty tissue, and degeneration of elastic fibers in the vessel wall, consistent with AD.

The second case was a 10-year-old male patient weighing 70 kg (99 percentile) who was given ibuprofen by his family after he complained of fever and weakness at 07:00. He was brought to the hospital at 13:00 after he vomited 2-3 times and had abdominal pain. Except for a fever (38 °C), arterial blood pressure of 120/65 mmHg, no other pathological findings were found during his physical examination. He was discharged with a pre-diagnosis of acute gastroenteritis after the administration of intramuscular methaclopropamide and ranitidine.

He was brought back to the hospital at approximately 20:00 because he vomited again at home and his abdominal pain continued. His general condition was good, and there were no abnormal findings on physical examination. The oxygen saturation was 97%, his pulse was 104 bpm, and the fever 36 °C. Except for CRP 11.0

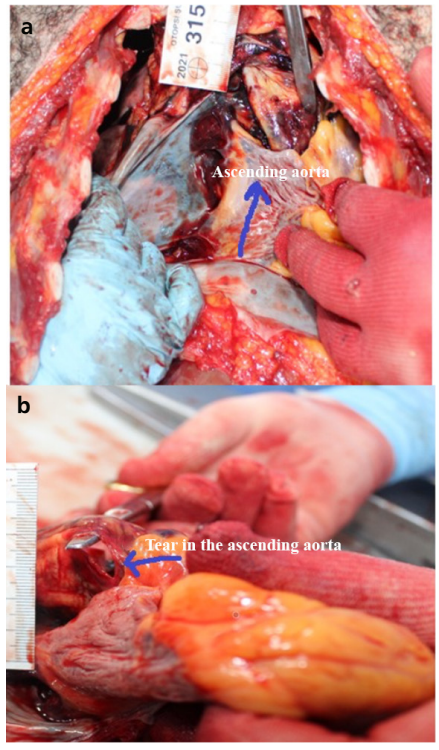

Figure 1. a) Ascending aorta, b) tear in the ascending aorta

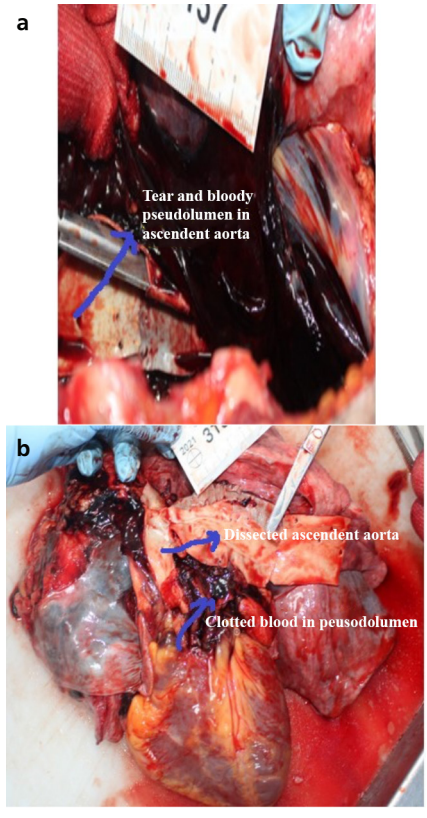

Figure 2. a) Tear and bloody pseudolumen in ascendent aorta, b) dissection and pseudolumen formation in the thoracic aorta

mg/L (ref: <0.5), blood tests were normal. Protein and ketones were positive in the qualitative urine test. At 00:08, a direct abdominal X-ray was taken. Increased gas was seen. General surgery and pediatrics are consulted on the patient. A rectal enema was applied. He was discharged at 3:15. According to his expressions, at 7:30, he said that his stomach hurt a lot and he felt like his heart would stop. He was found lying on the ground, pale yellow, around 7:50. When the emergency aid team arrived, the patient was in cardiopulmonary arrest, and there was no response to CPR.

An autopsy was performed. 100 cc of blood in the right thoracic cavity and 2000 cc of partially coagulated blood in the left thoracic cavity were observed. When the pleura was scraped over the vertebrae, there was a 1.5-cm-long aortic rupture open to the posterior chest wall on the left side. The heart was opened, and rare atheromatous plaques were observed in the aortic lumen and valves. The thoracic aorta was removed from the arch to the level of the diaphragm. There was bleeding around and between the layers. The abdominal aorta appeared intact. When the aorta was opened, it was ruptured at the level of the 7th vertebra of the thoracic spine. There was bleeding between the layers of the aorta downwards and upwards, and there was bleeding to the left side of the chest with a left opening 1.5 cm below the rupture. The aortic diameter was measured at 1.2 cm at the rupture part. In the histopathological examination of the aorta and surrounding connective tissue, medial degeneration in the aorta, laceration forming a cleft in the medial wall, old bleeding areas organizing in this area, hematoma formation in the medial layer, fresh bleeding in the paraaortic soft tissue, an increase in band-type connective tissue, and medial hypertrophy in medium-sized vascular structures were detected. Subendocardial valvular myxoid degeneration was detected in the heart tissue.

Discussion

As in our two cases, 76% of the cases in the literature were male. In addition, risk factors such as trauma, connective tissue diseases, Marfan syndrome, and hypertension were absent in our first case (4). However, in our second case, subendocardial valvular myxoid degeneration and medial degeneration of the aorta were found in postmortem histopathology.

AD is classified according to duration and localization (Stanford Classification). If the elapsed time is less than 14 days, it is acute; if it is more, it is chronic. If the dissection includes both the ascending and descending aorta, it is defined as type A, and if it includes only the ascending aorta, it is defined as type B (1,5). While our two cases were acute dissection, the first case was type A, and our second case was type B dissection. The worldwide incidence of acute AD is approximately 2.6-3.6 cases per 100,000 people per year; however, in China, the rate may reach 5 cases per 100,000 people per year (6). The disease progresses rapidly and is fatal if untreated immediately. Unfortunately, despite recent advances in diagnostic techniques, rapid diagnosis of AD remains challenging, largely because of the heterogeneity of symptoms.

In a series of 1351 ADs for which 9-year data from 12 centers were analyzed, only 9 patients were under 21 years of age. In the projection made, it is predicted that 50 pediatric patients with AD will be seen in the United States between 2005 and 2040, excluding those after trauma (2). In another series, the median age was 19 years (15-21) in 45 patients with AD under the age of 21: 82% were male, 42% were due to trauma, 24% were due to Marfan syndrome, 22% were without predisposition, 8% had aortic valve disease, 6.7% had hypertension, 4.4% had mitral valve disease, 2.2% had Takayasu's arteritis, and 2.2% had fibromuscular dysplasia (7). Strenuous exercise and drug use could cause high blood pressure, a sudden blood pressure increase, and AD (8). In the medical records of both cases, there was no strenuous exercise or drug use. The postmortem weights in both cases were above average. There was also no history of violence or emotional stress. While there was no known predisposing factor in the 16-year-old patient of our two cases, aged 16 and 10 years, medial degeneration of the aorta was detected in the second case.

In cases of traumatic AD, there is a structure that makes dissection easier. Dissections that occur on their own are also common in these patients, and their family members should also be checked for dissection (9). Although Q waves and ST elevation can be seen on the ECG, they may be normal in 25% of patients. Two ECGs taken from our patient were also found to be normal (10). Aortic and mitral regurgitation can be seen on echocardiography, and an increase in aortic diameter can be seen. However, in the first case, echocardiography performed shortly before the patient's death did not reveal any features other than mild tricuspid regurgitation. Again, no pathological features were detected in the non-contrast thorax computed tomography examination performed 8 hours before his death.

Aortography, magnetic resonance imaging, or echocardiography are helpful, but thoracic computed tomography (CT) is the first-choice diagnostic method. Contrast-spiral CT is more sensitive. Transesophageal echocardiography is highly sensitive and is considered a specific imaging modality for detecting intimate flap AD. The gold-standard diagnostic method is angiography (2). In our patient, aortic enlargement was not observed

with non-contrast CT. In our second case, because the symptoms presented as acute gastroenteritis and did not suggest a cardiac cause, AD was not considered in the differential diagnosis, and these tests were not requested.

Although rare, AD can be observed in the pediatric patient group. As in our first case, if there is severe chest pain that cannot be explained by standard diagnostic methods and does not respond to painkillers, it should be referred without delay to an advanced cardiology center, where it should be carefully evaluated in terms of AD and emergency treatment should be performed. Sometimes, AD patients may be masked by accompanying nonspecific findings such as vomiting and abdominal pain, as in our second case, which may cause delays in diagnosis and increase mortality. In severe chest pain that does not respond to painkillers, AD should be considered, and the necessary examinations should be made quickly. Referral to a center where it can be operated may reduce mortality.

Ethics

Informed Consent: Consent was not obtained because the cases were dead and anonymized.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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