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European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December. The journal publishes content in English.

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Abstracts should not exceed 500 words and should be structured with the following subheadings: Objective, Methods, Results, and Conclusion.
The main text should be structured with the following subheadings: Introduction, Material and Methods, Results, Discussion, Limitations, Conclusions, Acknowledgments, References, Main Points, and Figure Legends.
The main text should not exceed 3000 words, excluding the abstract, references, tables, and figure legends.
There should be a maximum of 50 references.
Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified. Units should be prepared in accordance with the International System of Units (SI).
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It is recommended that a letter contains up to 10 references.
The letter recommends adding "Dear Editor" at the beginning of the main text and "Yours sincerely" at the end.

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3000	500 (Structured)	50	6	7 or total of 15 images
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Case Report	1500	200	20	5	1 or total of 5 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images

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

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Place the title, abstract, and keywords on the first page of the main text.
Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion.
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All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.
Define abbreviations at first mention in the text and in each table and figure.
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Do not use field functions.
Do not indent at the beginning of a line.
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When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm).

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Authors are responsible for the accuracy of references.

References

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In references, the names of all authors should be written. Usage of "et al" should not be preferred.
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Use abbreviations for journal names. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed.

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Journal Article
Yurci A, Gungor ND, Gurbuz T (2021) High Endometrial Thickness Does not Affect IVF/ICSI Outcomes. Eur J Ther. 27(1):94-98. https://doi.org/10.5152/eurjther.2021.20102

Example for Journal Article without English Titles
Aktan-İkiz A, Üçerler H, Orhan M (2007) Anatomic features of fossa navicularis at the skull base and its clinical importance [Kafa iskeletinde fossa navicularis'in anatomik özellikleri ve klinik önemi]. Sendrom 19:34–36 ([In Turkish])

Epub Ahead of Print Articles
Doruk M, Mustafaoglu R, Gül H (2023) The Impact of Using Technological Devices on Mental and Physical Health in Adolescents. Eur J Ther https://doi.org/10.58600/eurjther.20232902-592.y

Book
Anderson DM (2012) Dorland's illustrated medical dictionary, 32nd edn. Saunders Elsevier, Philadelphia

Book chapter
Gray H (1858) Anatomy Descriptive and Surgical 1st edn. In: John W, Parker and Son (eds), London, pp 150-155

Online Document
Bergman RA, Afifi AK, Miyauchi R (2007) Persistent congenital arterial anastomoses. Available from http://www.anatomyatlases.org/AnatomicVariants/Cardiovascular/Images0200/0232.shtml Accessed 22 Jan 2022

Reference citations in the text should be numbered in square brackets. Some examples:

Parent et al. [3] reported that .....
..... on medical radiation [21, 22].
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Authors are required to propose at least five reviewers when submitting their manuscripts.
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Special Editorial

What is Artificial General Intelligence and Why Could It Be a Threat as Serious as Climate Change?: An Urgent Call for Medical Education

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ABSTRACT

This article not only explains Artificial General Intelligence (AGI) and Artificial Superintelligence (ASI) concisely in a manner that improves understanding among medical educators and professionals, but also contrasts the emphasis on climate change in medical education with the comparatively less attention paid to the threat of AGI and ASI. Awareness is called for about this technology, which could potentially lead to a prosperous age or the extinction of humanity.

Keywords: artificial intelligence, artificial general intelligence, artificial superintelligence, climate change, medical education

What are artificial general intelligence and artificial superintelligence?

The evolution of AI goes through three stages [1]. The first stage is artificial narrow intelligence (ANI), currently prevalent in applications like face recognition and voice-activated assistants. The second and third stages are artificial general intelligence (AGI) and artificial superintelligence (ASI), respectively. AGI and ASI, even if there are different definitions, refer to highly autonomous systems that have the ability to work as efficient as or outperform humans at nearly any economically valuable work [2]. Unlike narrow or specialized artificial intelligence, which is designed for a specific task or domain such as diagnosing a patient or generating multiple-choice questions [3], AGI and ASI would possess the capability to understand, learn, and apply knowledge across a wide range of tasks and domains at a level comparable to or exceeding that of a human.

Why are AGI and ASI serious risks as climate change is and what would be the solution?

Climate change and superintelligence have been mentioned in 2002 among existential risks that may lead to human extinction [4]. Although it is possible for AGI to help us live in an abundant era due to potential improvements in various fields, it does not come without risks. A recent systematic review [5] revealed the different challenges and potential threats associated with the development of AGI. These risks include, but are not limited to, the possible development of an AGI with poor ethics and morals, and the potential for AGI to remove itself from human control. More specific example is that an AGI tasked to eliminate diseases like cancer might find it more efficient to achieve its goal by killing individuals with a genetic predisposition to the disease [5]. While it may pose this kind of serious risks, AGI might not be far away from today. A survey of expert opinions conducted

in 2013 projected the delivery of AGI between 2040 and 2070. Given the recent advancements [6], there is a possibility of it occurring in the 2020s [7]. Therefore, AGI is a serious threat that should be taken into consideration immediately, as climate change is.

The solution is not easy. In Max Tegmark's concept of "Life 3.0" [8], the key principle is substrate independence, which means that the hardware, software, and models of AGIs are interchangeable and mutable. Unlike Life 2.0, where human hardware is evolutionarily defined but adaptable through learning, Life 3.0 suggests that machines can redesign every aspect. This makes all constraints on them temporary. From this point of view, the consequence is that long-term control of machines becomes inherently impossible due to the dynamic nature of Life 3.0. They are able to change their forms and pursue their own goals. This leads us to a shift in focus from control to alignment in discussions about the future of AGI. Alignment in the context of AI refers to the alignment of AI systems with human goals in order to ensure that the actions and decisions of AI systems are in line with the interests of humans.

The development and deployment of AGI/ASI must consider ethical considerations and be socially accountable to ensure a beneficial future for humanity. However, the present circumstances do not paint an optimistic picture. OpenAI can be considered as one of the most possible companies to deliver AGI. But it seems OpenAI is not that much open [9] and their ex-employees claim that "OpenAI putting 'shiny products' above safety" [10]. Let alone participating in the decision-making process, we do not know how and why some important decisions have been made regarding the future of AI [6]. While the alignment of AI is crucial, under these conditions, how can we ensure that AGI will be developed to prioritize alignment with goals for the greater good, even in the face of challenges in defining precisely what constitutes the "good", rather than primarily serving a company's profit motive? Therefore, it is necessary to benefit from accountable decision-making systems, for example, distributed ledger technologies such as blockchain and holochain [11] in an efficient way that does not lead to climate change but improve decentralization [12]. Centralized structures can cause serious vulnerabilities and we need more decentralized and accountable mechanisms. Moreover, it is apparent that accountability is not only essential for the decision-making process in development of AGI but also for the very architecture of AGI itself. However, a significant challenge arises due to AGI's substantial hardware resource requirements, which raises questions about the feasibility of enabling AI to operate effectively at the edge, considering current limits of hardware opportunities of individuals.

What can we do in terms of medical education?

Both AGI and climate change pose serious threats to planetary health and require immediate action. However, it seems medical education community does not take the AGI issue into account to the extent that they consider climate change. While there are many interventions and research in medical education to be aware of and deal with the threats of climate change [13], AGI and its risk have received little to no attention in medical education, despite the fact that incorporating AI as a topic into medical curriculum is recognized as an important need [14,15].

In other words, the current situation is divided by two looming cataclysms: climate change, an imminent global menace demanding immediate attention, and AGI, an existential threat lurking in the shadows. While our community are being primed to combat climate change, they remain oblivious to the looming AGI threat. It creates an alarming imbalance in our preparedness. There is a need for common awareness and action on climate change and AGI both.

Medical education must consider the ethical and existential risks that can emerge from the integration of AGI/ASI. Therefore, it is necessary for medical educators, program directors, and institutional leaders to integrate AGI/ASI risk awareness into medical curricula. This could be carried out in various ways. One could be the use of cases and simulations that involve AGI/ASI scenarios in the curricula. It could include a critical evaluation of AGI's potential risks and impacts on health, healthcare, and the future of humanity. These activities should encourage critical thinking among the participants regarding the dual-use nature of AI technologies and their capacity to heal or harm. It should also stress historical examples where the advancements of technology did not take ethical considerations into account and led to unintended harm while it could lead to improvements. This can prepare them to think critically about the integration of AI in healthcare processes and all other aspects of our daily life. The scenarios should, for example, direct the participants to consider how they would respond if an AGI system proposed an unethical treatment or if an AGI system became autonomous in a way that could endanger patient safety.

CONCLUSION

By including awareness of AGI/ASI risks in medical education, just as we do for climate change, we can help grow a generation of healthcare professionals who are prepared to handle the potential risks of AGI/ASI as much as possible. They will be better prepared to the conflicts that can happen in the future where AGI/ASI plays a central role in healthcare while safeguarding against its potential threats. This kind of proactive initiative could help humanity to ensure that medicine remains a force for good to benefit from AGI and ASI.

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Special Editorial

Robert Heinrich Johannes Sobotta (1869-1945): The Great Author of the Most Widely Used Anatomy Atlas in Medical Education

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ABSTRACT
In 1904 Sobotta's Atlas of Descriptive Human Anatomy was published for the first time. At that time still divided into three volumes and published by Verlag Lehmann in Munich, the atlas was completely revised in 1982 and restructured into two volumes. Although the atlas has been revised several times since it was first published almost a hundred years ago. After starting out in Berlin, Sobotta worked for twenty-one years at the Anatomical Institute in Würzburg. Here he spent most of his scientific work and created his most important works. A brief three-year stint as director of the Anatomical Institute at the University of Königsberg followed before Sobotta became director of the Anatomical Institute in Bonn in 1919, where he taught until his retirement. The study paper is intended to provide a more detailed insight into the life and work of the scientist, whose name is known to almost every physician and healthcare professional.

Keywords: Robert Heinrich Johannes Sobotta, mediacal education, anatomy, atlas, Sobotta

The Professional life of Robert Heinrich Johannes Sobotta

Robert Heinrich Johannes Sobotta (Figure 1) was born in Berlin on January 31, 1869. His father, Carl August Rudolph Sobotta, and mother, Luise Ottilie Seydel, were from a farming family in Upper Silesia.

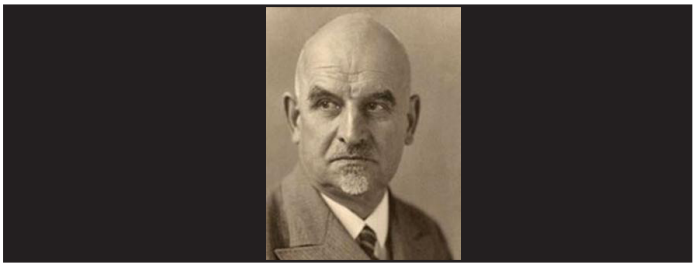

Figure 1. Robert Heinrich Johannes Sobotta (1869-1945), available on https://en.wikipedia.org/wiki/Johannes_Sobotta#/media/File:Johannes_Sobotta.jpg.

From April 1875 to October 1887, Johannes Sobotta attended Berlin's Königliche Wilhelms-Gymnasium. He began his medical studies at the "Royal Medical-Surgical Academy for the Military" after finishing high school. During the summer semester of 1888, he also served in the "Company Kaiser Alexander Garde Grenadier Regiment No. 1" as part of his six-month compulsory military service. Sobotta attended lectures at the Royal Friedrich Wilhelm University in Berlin while at the Academy and passed the preliminary medical examination there on July 13, 1889. Sobotta passed the rigorosum examination on July 17, 1891, and was awarded his doctorate on July 25, 1891 as Doctor medicinae et chirurgica. He left the Medical and Surgical Academy in the autumn of 1891 to work as a trainee assistant at the Friedrich Wilhelm University's First Anatomical Institute in Berlin [1]. He was promoted to third assistant in October 1892 after passing the state medical examination, and

second assistant in October 1893 after passing the state medical examination.

He worked as an assistant at the First Anatomical Institute of Friedrich Wilhelm University in Berlin for one winter semester as a dissection technician for the lectures, one winter semester as a demonstrator in the dissection room, and two summer semesters as a demonstrator in the microscopy course. He also spent two semesters at the Institute of Pathology studying pathological anatomy and histology. Sobotta left the medical and surgical academy in the autumn of 1891 and entered the medical school on January 1st, even before passing the state examination. Following that, he joined the First Anatomical Institute, which was led by Wilhelm von Waldeyer [2]. During his time as a volunteer assistant, he took over the management of a dissecting room on his own. Sobotta had already been offered a position as a histological assistant at the Physiological Institute in Breslau, which he had turned down due to "external reasons" during his studies. Sobotta spent the last months of his work in Berlin conducting research at the Naples Zoological Station [3]. In October 1895, Sobotta followed Koelliker's call as a prosector at the Institute for Comparative Anatomy, Embryology and Histology at the Julius Maximilian University of Würzburg [4-7]. There he was appointed private lecturer on July 29, 1896. Sobotta wrote his habilitation thesis "On the formation of the corpus luteum in the mouse", afterwards for the act of habilitation [8], Sobotta had a booklet printed with the following theses:

1. Histological courses, given exclusively on the basis of ready-made preparations, fail in their purpose as practical exercises and are scarcely more valuable than a simple demonstration. The preparation of the microscopic preparations should therefore also be carried out by the students themselves, just like the macroscopic ones.

2. A real understanding of the structure of the human body is impossible without knowledge of its development. It is therefore imperative that embryology be introduced as a necessary subject of study.

3. The fertilized egg of mammals - and probably that of man as well - is conveyed through most of the fallopian tube into the uterus, not by fibrillation, but by peristalsis [5].

4. When assessing the first developmental processes, especially the gastrulation process in mammals, one must start from the development of reptiles.

5. The primordial mouth of all vertebrates is characterized not only by the formation of entoderm, but also by the almost simultaneously occurring mesoderm (peristomal mesoderm).

6. The vertebrate embryo does not arise from the concrescence of two halves that are preformed at the edge of the germinal membrane or the primordial lips."

In November 1899 he succeeded Heidenhain as prosector at the Anatomical Institute in Würzburg. After Sobotta had been nominated for the rank and title of associate professor for the first time in January 1901, he was finally appointed associate professor on April 26, 1903. Two years later, Sobotta declined the appointment as associate professor and first prosector of the University of Greifswald. In January 1909, Sobotta was appointed assistant with the status of a civil servant, which was followed on March 1, 1912 by appointment as a regular extraordinary professor [5,6].

Sobotta spent the majority of his academic career in Würzburg, where he wrote his most important works and created the first editions of his textbooks and atlases on histology and anatomy (Figure 2). In October 1916, the family left Würzburg, and Sobotta was appointed full professor and director of the Anatomical Institute at Albertus University in Koenigsberg [4]. Three years later, Sobotta was offered a position at the Rheinische Friedrich-Wilhelms University in Bonn, where he succeeded Bonnet in April 1919 as full professor and director of the Anatomical Institute. In the post-war period, Sobotta also had to struggle with money and staff shortages, but in the years that followed achieved a steady improvement in the teaching conditions for its students. His work as a researcher now receded into the background. He devoted most of his time in Bonn to educating his students, but he also continued to work on completing and improving his textbooks and atlases.

Sobotta retired in March 1935, but continued to give lectures and made a significant contribution to the continued operation of the university during the Second World War [4]. He published a large number of scientific works during his professional career. He studied the primitive development of mammals extensively, primarily on mice. Sobotta's research focused on egg fertilization and cleavage, as well as gastrulation, directional spindles, and the formation of directional bodies. He also looked at the egg's migration into the uterus, the egg's development after cleavage, the development of the embryonic organs, and the location of the spermatozoa that had entered the uterus. His work on the corpus luteum was more extensive. He also dealt with the

development of double malformations and other histological topics such as the connection between muscle and tendon. He also wrote two papers in the field of paleontology. He discussed microphotographic techniques and reported on his workplaces with the Zoological Station in Naples and the Anatomical Institute in Bonn [2]. He dedicated commemorative publications to teachers and some of his colleagues.

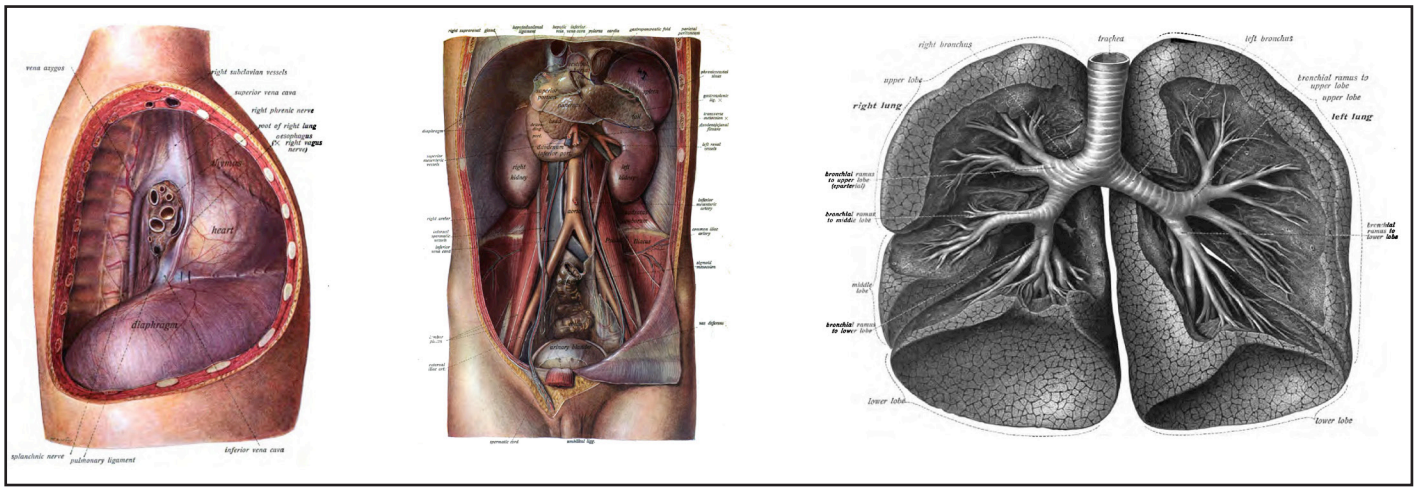

Figure 2. The remarkable illustriations of first 'Sobotta atlas' textbooks and atlases on anatomy. Sobotta, J. (1906). *Atlas and text-book of human anatomy v. 1, 1906* (Vol. 1). WB Saunders company.

The Private Life of Sobotta

Sobotta married Maria Katharina Förtig in Würzburg on March 5, 1900. Rudolf and Walter, their two sons, were born in Würzburg on November 22, 1900 and November 24, 1903 [4]. Both sons from the first marriage remained childless. His wife Katharina, also known as Käte, died in Whit on Monday, 5 June 1922, at the age of only 42 [9,10].

About two years later Sobotta found his second partner, Jeanne (also called Hanne) in Bliemeister. Jeanne was born on March 23, 1903 in Breisbach, Baden, and belonged to the Protestant denomination [9]. She studied medicine but did not complete her education. The couple married in Wiesbaden on 12 August 1924, and Jeanne moved in with her husband at his home in Venusberg on 10 October 1924 [11,12].

In September 1927, Sobotta had to cope with another serious blow of fate. His youngest son, Walter, died in a car accident on September 14, 1927, at the age of 24. The news in Bonner General-Anzeiger said: "A car crashed into a tree on the Niederpleis-Hangelar road last night. Walter, the youngest son of a professor from Bonn, died immediately, while a lady from Linz was seriously injured but her life was not in danger" [13]. And, his oldest son, Rudolf, died in Bonn on 6 July 1971, at the age of 71 [10].

Professor Johannes Sobotta became seriously ill in the last weeks of the Second World War and died of carcinoma in Bonn on 20 April 1945, at the age of 76. His body was buried in an old cemetery in Bonn-Poppelsdorf. His second wife, Jeanne, died in Bonn on February 18, 1982 [14].

On his birthday a year before his death, he received the Goethe Medal of Art and Science for his services to anatomy. Since November 2000, the Sobottaweg, next to the building of the University of Bonn Anatomical Institute in Poppelsdorf, commemorates him [4,5].

Sobotta Atlas of Anatomy

Sobotta's three-volume Atlas of Anatomy, a standard medical work, often called the "Atlas of Anatomy" for short, has existed as a realistic and explanatory atlas since the beginning of the 20th century. The first edition was published in three parts by JF Lehmanns Verlag in Würzburg between 1904 and 1907, the next eleven editions continued to be published in three parts until 1944. After the Second World War, the publishing house Urban & Schwarzenberg acquired the rights to the anatomy atlas. Sobotta collaborated with artist such as Karl Hajek and Erich Lepier for the atlas. Sobotta continued to develop his work until the end of his life in 1945. After his death, in 1956 Hellmut Becher, an anatomist in Münster, took over the further development of the

anatomy atlas. Published 14th to 17th editions. The 18th edition of the Atlas was completely revised in 1982 and was divided into two volumes by the editors Helmut Ferner, an anatomist in Heidelberg and Vienna, and Jochen Staubesand, an anatomist at Freiburg im Breisgau. In 1993, Reinhard Putz, an anatomist at Ludwig Maximilians University in Munich, and Reinhard Pabst, an anatomist from the Hanover Medical School, took over the publication and further development of the atlas. The revised 23rd edition of the Sobotta Atlas of Anatomy, again structured in three volumes, was published in September 2010 by Friedrich Paulsen of the Institute of Anatomy of the University of Erlangen-Nuremberg and Jens Waschke, head of University Anatomy I-vegetative anatomy. From Munich, which in 2003 bought the publishing house Urban & Schwarzenberg from the Holtzbrinck Group, which merged with Urban & Fischer, currently located in the Dutch Wissenschaftsverlag Elsevier. In 2017, the same authors published the 24th edition, revised by Elsevier [2,7].

CONCLUSION

The Sobotta Atlas of Human Anatomy, authored by Johann Sobotta, was first published in 1904 and remains a foundational resource in the field of anatomy. This seminal work has been translated into 19 languages and continues to be a pivotal reference for medical practitioners globally. Throughout the Second World War, Sobotta's scholarly contributions, including his research, theses, and anatomical atlases, significantly advanced the scientific community's understanding of human anatomy. A comprehensive exploration of Sobotta's life underscores his unwavering dedication to science, particularly in the realm of anatomy. The scientific community, alongside physicians and healthcare professionals, profoundly acknowledges and appreciates Sobotta's invaluable contributions.

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Original Research

Investigating the Relationship Between Insulin Treatment Refusal and Psychosocial Factors in Type 2 Diabetic Patients

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ABSTRACT

Objective: Refusal of insulin therapy is an important barrier in the treatment of type 2 diabetes mellitus (T2DM). The current study aimed to investigate the effect of psychosocial status of diabetic patients on insulin treatment acceptance and refusal.

Methods: This cross-sectional study was conducted with age and gender matched 80 diabetic patients who accepted insulin therapy and 80 diabetic patients who refused insulin therapy. Participants were interviewed face-to-face using a questionnaire consisting of five sections: socio-demographic, depression, anxiety, fear of self-injection and adherence to diabetes treatment.

Results: There was no significant difference between the two groups in terms of age and gender. The beck depression scale score *(p=0.002)* and beck anxiety scale score *(p<0.001)* of the participants who refused insulin treatment were statistically significantly higher than the group who accepted the treatment. The injection fear scale score of the group who refused insulin treatment was statistically significantly higher than those who accepted insulin treatment *(p<0.001)*. There was a significant negative correlation between injection fear score and treatment adherence scale score in both participants who accepted *(r:-0.224; p:0.045)* and refused insulin treatment *(r:-0.309; p:0.005)*.

Conclusion: The current study showed that depressive and anxiety moods of the individuals caused insulin therapy refusal. In addition, fear of injection was another factor causing insulin treatment refusal. Depression and fear of injection were also found to negatively affect adherence to treatment.

Keywords: Diabetes mellitus; insulin; medication adherence; treatment refusal

INTRODUCTION

Diabetes Mellitus (DM) is recognized as the third leading cause of death worldwide and is becoming a major public health problem. The International Diabetes Federation (IDF) stated that 425 million adults were living with DM in 2015, with an estimated worldwide prevalence of 9.1%, which is projected to increase to 693 million by 2045 [1]. In Turkey, the prevalence of type 2 DM is estimated at 13.7%, making it the most prevalent country in the European region [2].

Poor blood glucose management can result in a number of illnesses, including cardiovascular disorders, which account for the majority of morbidity and death among diabetics. Additionally, it is to blame for the increased direct and indirect medical costs incurred by DM patients [3]. Numerous pharmacologic options are widely available for the treatment of diabetes. While oral antidiabetic agents are commonly the first choice, as diabetes is a progressive disease and oral hypoglycemic agents (OHAs) eventually lose their effectiveness, a large proportion of people with diabetes will eventually need to switch to insulin therapy, either alone or in combination with OHAs. Insulin therapy is still considered the most effective pharmacologic option for the treatment of diabetes [4].

To prevent and reduce long-term diabetes complications, early use of insulin is recommended in the treatment of poorly controlled diabetes. Patients who start insulin therapy early are less likely to experience chronic hyperglycemia, which lowers their chance of developing complications from diabetes. Even yet, it's typical to start insulin later than expected [5]. About half of patients with poorly managed type 2 diabetes did not begin insulin therapy at the appropriate time; insulin therapy is typically started three to five years after oral hypoglycemic medications have failed [5]. Another study reported that first insulin use was delayed by an average of 10.3 years and that the mean A1c at insulin initiation was 9.0% [6]. Xiong et al. [7] reported that 800 (17.9%) of patients who were recommended to use insulin did not want to start treatment due to reasons such as discomfort, dependence concerns, pain, high cost and possible side effects. Gherman et al. [8] as a result of the literature review, they reported that the barriers to insulin acceptance were categorized into 4 main groups. Refusal to take insulin or reduced adherence to insulin therapy can be caused by a variety of emotional and cognitive factors, including fear of needle stick pain, fear of self-injection, fear of injection technique or correct dosing, and fear of the negative effects of using insulin, such as hypoglycemia, weight gain, lifestyle restriction, and discomfort; social and cultural factors and relational factors, such as social stigma and shame, social stigma and embarrassment, social stigma and embarrassment, and embarrassment; and physical factors, such as pain or bruises from injections. Due to the complexity of non-adherence to insulin therapy, factors associated with non-adherence to insulin therapy are often explored in very specific contexts and therefore often include only a few factors.

Main Points;

- Diabetic participants who refused insulin treatment had higher depression scores.
- Diabetic participants with high anxiety scores were more likely refused insulin treatment.
- Fear of injection is an important reason for insulin treatment refusal.
- Depression, anxiety, and fear of injections negatively affected diabetes mellitus treatment adherence.

"Psychological insulin resistance" (PIR) is a person's opposition to insulin use. Sociodemographic, individual and environmental characteristics have been reported to cause PIR. Psychological insulin resistance is not a formal psychological diagnosis, but rather a term that captures a strong negative attitude towards starting insulin therapy [9]. What is known about the relationship between psychosocial factors affecting the individual and acceptance of insulin therapy is limited. Previous studies have reported that depression decreases acceptance of insulin therapy.[5] Despite all these literature data, studies examining the psychosocial status of patients who refuse insulin therapy are limited and new studies are needed.

The current study aimed to investigate the reasons for refusal of insulin treatment in patients who were indicated for insulin treatment by a physician but refused to start insulin treatment.

MATERIALS AND METHODS

This cross-sectional study was conducted between July 1, 2022 and March 31, 2023 in the endocrinology clinic of a tertiary health care institution. In our endocrinology clinic, health care is provided to all diabetic patients who are referred from primary and secondary healthcare institutions and who apply directly. The population of the study consisted of all T2DM patients admitted to the endocrinology clinic. The depression scores (5.11±0.24 and 6.20±0.35) obtained in the study conducted by Onalan et al. [10] were used to calculate the sample size. In the light of the data obtained from the previous study, it was determined that at least 80 people in each group should be included in the study with power=0.95 (beta=0.05), alpha=0.05 and effect size (d=0.3) in the student t test based Power analysis test (G-power 3.1 package programe). Type 1 DM, those with a diagnosis of psychological illness (depression, anxiety disorder, etc.), those with chronic neurological diseases, and those with visual and auditory problems that would prevent communication were

excluded from this study. A total of 163 volunteer participants over the age of 18 years and diagnosed with T2DM who accepted insulin treatment or refused insulin treatment were randomly included in the study.

Data Collection

Data were collected using a structured questionnaire administered by the researcher. The questionnaire consisted of five sections: the first part (part I) was used to collect sociodemographic characteristics, part II was used to collect adherence to insulin therapy (Morisky 8-item Medication Adherence Questionnaire), part III was used to assess subjects' depressed mood (Beck Depression Scale), Part IV was used to assess subjects' anxiety mood (Beck Anxiety Scale), and Part V was used to assess participants' fear of the disease and insulin treatment (Fear of Self-Injection and Testing Questionnaire).

Patients' adherence to their diabetic treatment was assessed using the 8-item modified Morisky adherence scale (MMAS-8). The eight items of the validated MMAS-8 self-report measure of adherence are part of the tool. Items 1 through 7 featured a "yes" or "no" response option, while question 8 featured a 5-point Likert scale. With the exception of item 5 (reversed score), where the responses "yes" and "no" were rated as "1" and "0," respectively, every "no" response was scored as "1" and every "yes" response as "0". The difficulty remembering to take insulin therapy was measured on item 8 using 5-point Likert scales: never/rarely = 0, once in a while = 1, occasionally = 2, generally = 3, and always = 4. In this scale, if patients choose response "0", the score is "1" and if they choose response "1,2,3, or 4", the score is "0". Higher scores indicate higher adherence levels. The total scores of all the items range from 0 to 8 and was grouped into two levels: adherent (score of 6 to 8), and non-adherent (score < 6). A total score of 8 indicates high adherence, 6-7 points indicate moderate adherence, and <6 points indicate low adherence [11].

The Turkish version of the Beck Depression Scale was used to ask the subjects about their depressive traits. There are a total of 21 items on the Likert-type scale. Every item has a score that ranges from 0 to 3. The scale's total score ranges from 0 to 63. The more depressed one feels, the higher their score on the scale [12].

The Turkish version of the Beck Anxiety Scale was used to ask the subjects about their anxiety traits. There are 21 items on this Likert-style self-assessment scale, with scores ranging from 0 to 3. A high overall score denotes a high degree of anxiety that the individual is experiencing. The internal consistency of the BAI is high (alpha = 0.93) [13].

Participants' fear of self-injection and self-testing during diabetes treatment was assessed with the Turkish Version of the Diabetes Fear of Self-injecting and Self-testing Questionnaire (D-FISQ). The D-FISQ, which contains a total of 15 statements, consists of two subscales: fear of self-injection (fear of self-injection-FSI, 6 statements) and fear of self-testing (fear of self-testing-FST, 9 statements). Each statement has a four-point Likert-type scale ranging from 0 to 3 (0= almost never, 1= sometimes, 2= often, 3= almost always). Self-injection fear score ranges from 0-18, self-test fear score ranges from 0-27 and total fear score ranges from 0-45. An increase in score indicates an increase in fear. Item-total correlation coefficient ranged from 0.72 to 0.86. In terms of test-retest reliability, intraclass correlation coefficient was reported to be over 0.90 [14].

Statistical Analysis

The data was statistically analyzed using the IBM SPSS (statistics Package for Social Sciences) 22 statistics package application. To ascertain if the continuous data were normally distributed, the Shapiro-Wilk test was employed. For continuously distributed variables, the descriptive statistics were represented as mean ± standard deviation; for non-normally distributed variables, as [median (min-max)]; and for categorical variables, as frequency and percentage [n(%)]. Pearson Utilizing the Fischer Exact and Chi-Square tests, the association between category data was investigated. For continuous data that did not fit the normal distribution, the Mann-Whitney-U test was used to examine the association between two independent groups; the Kruskal Wallis test was employed to compare more than two independent groups; and the Dunn test was utilized as a post Hoc test. Spearman correlation analysis was used to analyze the relationship between two continuous variables. The significance level was set as $p<0.05$.

RESULTS

The study included 80 (50.0%) participants who accepted insulin treatment and 80 (50.0%) who refused insulin treatment. Participants who refused insulin treatment had a statistically significantly higher history of hospitalization in the last 1 year (Table 1).

Table 1. Comparison of sociodemographic characteristics of the participants

Variables	Accept insulin n (%)	Refusing insulin n (%)	Total n (%)	p
Gender				
Female	40 (50.0)	43 (53.8)	83 (51.9)	0.635
Male	40 (50.0)	37(46.2)	77 (48.1)	
Marital status				
Married	68 (85)	60 (75)	128 (80)	0.247
Single	2 (2.5)	2 (2.5)	4 (2.5)	
Widow or divorced	10 (12.5)	18 (22.5)	28 (17.5)	
Educational level				
Illiteraate	16 (20.0)	20 (25.0)	36 (22.5)	
Literate	18 (22.5)	14 (17.5)	32 (20.0)	0.097
Primary school	20 (25.0)	30 (37.5)	50 (31.3)	
High school	22 (27.5)	10 (12.5)	32 (20.0)	
University	4 (5.0)	6 (7.5)	10 (6.3)	
Profession				
Housewife	36 (45.0)	38 (47.5)	74 (46.3)	
Officer	21 (26.3)	30 (37.5)	51 (31.9)	0.134
Minimum wage employee	9 (11.3)	3 (3.8)	12 (7.5)	
Tradesmen	11 (13.8)	5 (6.3)	16 (10.0)	
Retired	3 (3.8)	4 (5.0)	7 (4.4)	
Smoking				
Yes	21 (26.3)	18 (22.5)	39 (24.4)	0.581
No	59 (73.8)	62 (77.5)	121 (75.6)	
Alcohol use				
Yes	2 (2.5)	1 (1.3)	3 (1.9)	>0.999
No	78 (97.5)	79 (98.8)	157 (98.1)	
Death of a relative in the last 6 months				
Yes	10 (12.5)	13 (16.3)	23 (14.4)	0.499
No	70 (87.5)	67 (83.8)	127 (85.6)	
Follow-up and treatment feature				
I take my medication regularly. I do not neglect my follow-ups	56 (70.0)	47 (58.8)	103 (64.4)	
I sometimes neglect my treatment and follow-ups	24 (30.0)	31 (38.8)	55 (34.4)	0.168
I only take my medication and go to the doctor when I have complaints	0 (0.0)	2 (2.5)	2 (1.3)	
Chronic disease status				
Yes	62 (77.5)	62 (77.5)	124 (77.5)	>0.999
No	18 (22.5)	18 (22.5)	36 (22.5)	
Hospitalisation in the last 1 year				
Yes	24 (30.0)	40 (50.0)	64 (40.0)	***0.010***
No	56 (70.0)	40 (50.0)	96(60.0)	

There was no significant statistical difference between the median values of age of the participants who accepted and refused insulin treatment *(p=0.152)*. The median values of fasting blood glucose *(p<0.001)* and HbA1c *(p<0.001)* were statistically significantly higher in the participants who refused insulin treatment than in the group who accepted insulin treatment (Table 2).

The beck depression scale *(p=0.002)* score and beck anxiety scale score *(p<0.001)* of the participants who refused insulin treatment were statistically significantly higher than the group who accepted the treatment. The injection fear scale score of the group who refused insulin treatment was statistically significantly higher than those who accepted insulin treatment *(p<0.001)*. There was no significant difference between the treatment compliance scale scores of the two groups *(p=0.119)* (Table 3).

There was a significant negative correlation between injection fear score and treatment adherence scale score in both participants who accepted *(r:-0.224; p:0.045)* and refused insulin treatment *(r:-0.309; p:0.005)*. There was a negative significant correlation between the depression score of the participants who refused insulin treatment and the treatment compliance score (Table 4).

Table 2. Comparison of age and biochemical parameters of the participants

Variables	Accept insulin Median (min-max)	Refusing insulin Median (min-max)	Total Median (min-max)	p
Age (year)	61.00 (36.00-84-00)	67.00 (45.00-83.00)	62.00 (36.00-84.00)	0.152
Monthly income (TL)	7500 (3000-20000)	6500 (3500-18000)	7000 (3000-20000)	0.917
Number of households	3.00 (1.00-7.00)	2.00 (1.00-6.00)	2.00 (1.00-7.00)	0.856
T2DM vintage(year)	13.00 (1.00-47.00)	15.00 (1.00-30.00)	15.00 (1.00-47.00)	0.329
BMI (kg/)	27.55 (19.27-35.91)	27.46 (20.66-41.77)	27.50 (19.27-41.77)	0.891
Fasting blood glucose (mg/dl)	158.00 (72.00-551.00	186.00 (75.00-496.00)	164.00 (72.00-551.00)	*<0.001*
HbA1c (%)	8.0 (5.80-13.50)	10.90 (7.80-17.00)	9.60 (5.80-17.00)	*<0.001*
Triglyceride (mg/dl)	152.00 (11.00-1206.00)	153.00 (62.00-594.00)	152.00 (11.00-1206.00)	0.101
LDL (mg/dl)	114.00 (37.00-203.00)	110.00 (24.00-197.00)	110.50 (24.00-203.00)	0.312
HDL (mg/dl)	48.50 (19.20-81.00)	48.00 (22.00-71.00)	48.00 (19.20-81.00)	0.419
Total cholesterol (mg/dl)	190.00 (93.00-376.00)	194.50 (95.00-310.00)	190.50 (93.00-376.00)	0.259

TL: Turkish lira; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Table 3. Comparison of the scale scores of the participants

Scales	Accept insulin Median (min-max)	Refusing insulin Median (min-max)	Total Median (min-max)	p
MMAS-8	8.00 (1.00-8.00)	7.00 (1.00-8.00)	8.00 (1.00-8.00)	0.119
Beck depression inventory	17.00 (4.00-41.00)	21.00 (8.00-36.00)	18.50 (4.00-41.00)	*0.002*
Beck anxiety inventory	9.00 (1.00-25.00)	17.00 (4.00-51.00)	13.00)1.00-51.00)	*<0.001*
D-FISQ	15.00 (15.00-30.00)	30.00 (15.00-60.00)	15.00 (15.00-60.00)	*<0.001*

MMAS-8: modified morisky adherence scale of 8 items; **D-FISQ**: Diabetes Fear of Self-injecting and Self-testing Questionnaire

Table 4. Spearman correlation analysis between treatment adherence scale and some variables

Variables	Accept insulin	Refusing insulin
	MMAS-8	MMAS-8
Beck depression inventory	r=-0.060	r=-0.266
	p= 0.600	p= ***0.017***
D-FISQ	r=-0.224	r=-0.309
	p= ***0.045***	p= ***0.005***
Beck anxiety inventory	r=-0.105	r=-0.137
	p= 0.356	p= 0.227
Age	r= 0.078	r=-0.152
	p= 0.491	p= 0.179
Monthly income (TL)	r=-0.091	r= 0.085
	p= 0.420	p= 0.456
Number of households	r -0.168	r=-0.007
	p= 0.136	p= 0.953
T2DM vintage (year)	r=-0.031	r=-0.193
	p= 0.783	p= 0.087
HbA1c	r=-0.347	r= 0.006
	p= ***0.002***	p= 0.961

MMAS-8: modified morisky adherence scale of 8 items; **D-FISQ**: Diabetes Fear of Self-injecting and Self-testing Questionnaire

DISCUSSION

The current study focused on the psychosocial factors affecting the acceptance and refusal of insulin therapy in patients who were under follow-up and treatment for T2DM. Fasting plasma glucose and HbA1c values were found to be higher in patients who refused insulin treatment. In addition, patients who refused insulin therapy had a history of more hospitalizations in the last 1 year. Although oral hypoglycemic agents may initially lower blood glucose and HbA1c levels, they are not as effective as insulin therapy in the long term [15]. Therefore, it is expected that the plasma glucose and HbA1c levels of patients who received insulin therapy would be lower than those of patients who refused insulin therapy. Prediabetes and diabetes are known to be associated with increased hospitalization rates during long-term follow-up. Previous studies have shown that among individuals with diabetes, those with poor glycemic control had a 39% higher hospitalization rate than those with good glycemic control [16]. The current findings support that patients who refuse insulin therapy have poor glycemic control and higher hospitalization rates.

The present study showed that both depression and anxiety scores were higher in diabetic individuals who refused insulin treatment. Previous literature has reported that depression and fear negatively affect adherence to insulin therapy [17]. Another study reported emotional or psychological problems of patients as the reason for delaying insulin treatment [15]. Yen et al. [18] reported that diabetic individuals with depression had difficulties in initiation and adherence to insulin therapy. Depression is associated with decreased adherence to medical regimens in patients with chronic diseases. The current study focused on insulin treatment acceptance in individuals without depression and anxiety. Makine et al. reported that patients with high depression scores were less accepting of insulin treatment than those with low depression scores [19]. Wijk et al. [20] showed that an intervention program for factors such as depression, anxiety and general stress increased insulin treatment acceptance and adherence to treatment. Considering the current study data and previous literature, we recommend that depression and anxiety should be evaluated before starting insulin therapy in individuals without a diagnosis of depression and anxiety.

Fear of pain and needles, concerns about the side effects of insulin and the complexity of administering insulin are some of the biggest barriers to starting insulin. The current study showed that patients' fear of self-injection and testing was another reason for refusing insulin treatment. Previous literature has also shown an association between fear of injections and delay and nonadherence to insulin therapy [15,17]. It is expected that the pain caused by insulin injection therapy and its negative impact

on the patient's comfort of life would be associated with treatment refusal and non-adherence. We believe that this problem can be solved with the development of alternative insulin treatment methods.

In the present study, depression and fear of self-injection and testing scale scores were found to be statistically significantly negatively correlated with treatment adherence scale scores. Both depression and fear of injection are known to be associated with poorer treatment adherence. Previous studies have shown that psychological intervention increases diabetes self-management [21]. There are not enough studies in the literature on the effect of supportive treatment on individuals' fear of injection, depression and anxiety. Current findings and literature data are limited to explain the effect of psychological support therapy on individuals' depression, anxiety and fear. We believe that individuals' depression, anxiety and fears should be reduced in order to increase acceptance and compliance with insulin therapy. We recommend that future research should focus on the effect of supportive therapies on depression, anxiety and fear in diabetic individuals. Improvement in depression, anxiety and fear levels were thought to be important in diabetes control.

This study has some limitations, firstly, since it is a cross-sectional and single-center study, patients may not fully reflect the general population. Initiation of insulin may be affected by the culture and health insurance system of the country. Therefore, there are limitations in generalizing these findings to other countries. Strengths of this study include the calculation of the sample size and the investigation of psychological factors in insulin acceptance and refusal with adequate sample size. Another strength is that participants' psychological characteristics such as depression, anxiety and fear were assessed using quantitative scales.

CONCLUSION

The present study showed that depressive and anxiety moods of the individuals caused insulin treatment refusal. In addition, fear of injection was another factor causing insulin treatment refusal. Depression and anxiety were also found to negatively affect adherence to treatment. To increase the acceptance and efficacy of insulin therapy, we recommend psychological evaluation of patients who are offered insulin therapy. In future studies, we recommend investigating the effect of psychotherapeutic interventions to reduce depression and anxiety on insulin refusal and adherence to treatment.

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Original Research

Smokers Versus Non-Smokers: Comparing Cognitive Flexibility and Dyspnea Symptoms in Medical Students

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ABSTRACT

Objective: Smoking is an escalating public health concern globally, notably for its frequency among young individuals and the medical conditions it induces. This research aims to explore the association between smoking and the symptoms of dyspnea as well as cognitive flexibility levels in medical students.

Methods: This cross-sectional study included 188 volunteer medical school students. Participants were administered a sociodemographic data form, the Dyspnea-12 Scale, and the Cognitive Flexibility Scale. The participants were divided into two groups as smokers and non-smokers and compared in terms of the applied scale scores. The data were analyzed using the appropriate statistical methods with IBM SPSS v.22 software.

Results: Of the 188 participants, 56.9% (n:107) were female, while 43.1% (n: 81) were male. The prevalence of smoking among participants was 26.1% (n: 49), with rates at 38.3% (n:31) for males and 16.8% (n: 18) for females. The smoking rate was significantly higher in males ($p<0.001$). No significant difference was detected between smokers and non-smokers regarding the Dyspnea-12 score. However, the Cognitive Flexibility Scale scores were significantly lower in the smoker group (p:0.018).

Conclusion: In our study, we found that the smoking rate among medical students was quite high and that smoking negatively affected cognitive flexibility. It may be beneficial to consider this when evaluating cognitive functions in educated individuals who smoke.

Keywords: smoking, cognitive flexibility, dyspnea, medical students, addiction

INTRODUCTION

Smoking addiction poses a significant public health challenge due to its widespread accessibility, legal status, and social acceptance [1]. The prevalence of smoking varies across countries, demographic groups, and over time. Approximately 22.3% of the global population engages in tobacco use, with a gender distribution of 36.7% male users and 7.8% female users [2]. Notably, most individuals initiate smoking during adolescence, and smoking rates among university students are on the rise [3].

Smoking exerts detrimental effects on virtually every bodily system due to the presence of oxidant substances [4, 5]. These adverse effects encompass a broad spectrum, ranging from mental health issues to academic performance, lung function, and

respiratory difficulties [6-8]. Nicotine, a stimulant for the nervous system, can exacerbate stress and anxiety, thereby negatively impacting cognitive performance, focus, and memory [9]. The detrimental effects of smoking, particularly on individuals' cognitive flexibility, may be attributed to pathophysiological changes in the lungs and reduced oxygenation of the brain [10]. Cognitive flexibility can be defined as the mental capacity to quickly switch one's thinking and adapt to new, changing, or unexpected events and situations [11]. This means being able to change one's approach to a problem, to look at something from multiple perspectives, or to shift strategies effectively when the situation calls for it [11]. It is an essential aspect of problem-solving and is considered a component of broader cognitive functioning, including attention, memory, and executive control processes. It allows an individual to update their approach in the face of new information or to balance multiple tasks and demands simultaneously [12]. Prolonged tobacco exposure is associated with declines in cognitive functions and flexibility, while nicotine addiction and continuous exposure further amplify the negative impact on cognitive functions [13, 14]. The consequences of nicotine intake may also manifest as attention deficits, mental focusing challenges, and performance impairments [15]. The cognitive effects of smoking are intricate and multifaceted, necessitating a comprehensive examination of the cognitive impairments they induce. In a study by Kalmijn et al., a negative relationship between smoking and cognitive flexibility was identified, while Rotheram-Fuller et al. found no effect of smoking on cognitive flexibility in their research [16, 17]. Inconsistencies like these in the current literature underscore the necessity for further research in this field [18]. Understanding the adverse effects of smoking on mental and physical health is paramount in developing effective interventions and treatment strategies.

Main Points;

- **Gender Disparity in Smoking Rates:** Male medical students have significantly higher smoking rates (38.3%) compared to females (16.8%), influenced by societal and cultural norms.
- **Impact on Cognitive Flexibility:** Smoking adversely affects cognitive flexibility, crucial for problem-solving and adaptation, even in young, educated individuals.
- **Dyspnea Symptoms:** There is no significant difference in dyspnea symptoms between smokers and non-smokers, indicating short-term smoking may not affect perceived shortness of breath.
- **Need for Multidisciplinary Interventions:** Addressing smoking addiction to prevent cognitive deterioration requires a multidisciplinary approach, emphasizing the importance of comprehensive interventions.

Recent medical literature has frequently explored the impact of smoking on lung diseases, neuroinflammation and cognitive functions. In recent years, evidence has emerged suggesting that the detrimental effects on cognitive flexibility extend to various bodily disease conditions. This study aims to comparatively evaluate the symptoms of dyspnea and cognitive flexibility in medical students who smoke and those who do not.

MATERIALS AND METHODS

Research Design and Sampling

This study was conducted with the participation of volunteer students at the Faculty of Medicine, Hitit University. Participants without any known physical or mental illness were included in the study. Informed consent forms were obtained from all participants. The participants were given the sociodemographic data form, the Cognitive Flexibility Scale, and the Dyspnea-12 questionnaire and were asked to answer all the questions. Designed as a cross-sectional and descriptive study, the participants were divided into two groups as smokers and non-smokers. The Dyspnea-12 and Cognitive Flexibility Scale scores of both groups were compared. The ethical approval of the study was obtained from the Hitit University Non-Interventional Ethics Committee with the decision number 2024/04. Our research was conducted in accordance with the rules of the 1964 Helsinki Declaration.

Data Collection Tools

Sociodemographic Data Form

The sociodemographic data form prepared by the researchers includes questions on gender, marital status, smoking status, total duration of smoking, daily pack count, and place of residence (urban/rural).

Cognitive Flexibility Scale

The Cognitive Flexibility Scale (CFS) was developed by Martin and Rubin in 1995 [19]. Çelikkaleli conducted validity and reliability studies on the scale and adapted it to the Turkish language in 2014 [20]. The scale consists of 12 items and measures a single dimension. It employs a 6-point Likert-type measurement tool, with ratings ranging from "strongly disagree" to "strongly agree." Four items on the scale are reverse-scored

(2, 3, 6, and 10). Scores on the measurement tool range from 10 to 60, with higher scores indicating higher levels of cognitive flexibility. The internal consistency coefficient of the Turkish adaptation was found to be .74, the test-retest correlation coefficient was .98, and the split-half reliability was .77 [20].

Dyspnea-12 Questionnaire

Developed by Yorke et al. (2010), this scale assesses the severity of dyspnea and consists of a total of 12 items with a four-point Likert scale [21]. The scale has two sub-dimensions: physical and emotional. The first seven items address the physical difficulties caused by breathing on the individual, constituting the physical dimension, while the remaining items assess the impact of breathing on emotional states such as depression, distress, stress, restlessness, and irritability [22]. The maximum score for the physical sub-dimension of the scale is 21 points, while the maximum score for the emotional sub-dimension is 15 points. The total score that can be obtained from the scale ranges from 0 to 36. An increase in the scale score indicates an increase in the severity of dyspnea perceived by the patients. In 2018, Metin and Helvacı conducted a Turkish validity and reliability study and reported a Cronbach's alpha value of 0.97 [22].

Statistical Analysis

All data obtained from the study were evaluated using the standard program IBM SPSS 22.0 (Statistical package for social Sciences for Windows 22). Numerical variables were summarized as mean ± SD, and categorical variables were summarized as number and percentage. Parametric and non-parametric tests were used in the statistical evaluation. The Kolmogrov-Smirnov test was used to evaluate whether the data were normally distributed. The Mann Whitney U test was used to examine whether the smoking and non-smoking groups differed in terms of cognitive flexibility and dyspnea scores. The Spearman Correlation test was used to analyze the presence of correlation between the variables. The p value of <0.05 was accepted statistically significant.

RESULTS

Out of the 188 participants included in the study, 107 (56.9%) were female and 81 (43.1%) were male. Among the participants, 49 (26.1%) were smokers. The smoking rate was 38.3% (n: 31) in males and 16.8% (n: 18) in females. The smoking rate was significantly higher in males (p<0.001). Table 1 presents the comparison of variables according to the gender of the participants.

As presented in Table-2, the mean age was significantly higher in the smoking group (p<0.001). While the Dyspnea-12 score did not show a statistically significant difference between the smoking and non-smoking groups (p:0.243), the Cognitive Flexibility score was significantly lower in the smoking group (p:0.018)(Table-2).

Comparison of age, smoking, Cognitive Flexibility Scale score, and Dyspnea-12 Scale score according to the living place of the participants is presented in Table-3.

The correlation between age and cognitive flexibility score was evaluated using the Spearman correlation test, and no statistically significant correlation was found (R: 0.008; p: 0.909). Additionally, when examining the correlation between cognitive flexibility score and the number of cigarette packs smoked per year in the smoking group using the Spearman correlation test, no statistically significant correlation was found (R: 0.233; p: 0.111).

Table 1. Comparison of variables according to the gender of participants

	Female (n: 109)	**Male (n: 81)**	**P value**
Age	21.7± 3.3(SD)	22.1± 2.8(SD)	0.085*
Cognitive Flexibilty score	49.6 ± 3.08(SD)	49.2± 3.1(SD)	0.349*
Dyspnea-12 score	2(IQR:7)	1(IQR:7)	0.458**
Smoking	16.8% (n:18)	38.3% (n:31)	**<0.001*****

*Student T test, **Mann-Whitney U, ***Pearson Chi-Square. IQR: Interquartile range, SD: Standart deviation.

Table 2. Comparison of variables in smoking and non-smoking participants

	Smoker	**Non-smoker**	**P value**
Age	24 (IQR:5)	21(IQR:3)	**<0,001***
Dyspnea-12 score	2(IQR:7)	1(IQR:7)	0,243*
Cognitive Flexibilty score	48.5±2.8(SD)	49,7±3,1(SD)	**<0,018****

*Mann-Whitney U, **Student T test. IQR: Interquartile range, SD: Standart deviation.

Table 3. Comparison of variables according to the living place of the participants

	Urban	Rural	P value
Age	21.5(IQR:4)	20.5(IQR:3)	0,251*
Cognitive Flexibilty score	49.4 ± 3,1(SD)	49,4 ± 2,7(SD)	0,931**
Dyspnea-12 score	1(IQR:7)	2,5(IQR:9)	0,461*
Smoking	27,2% (n=43)	20% (n=6)	0,409 ***

*Mann-Whitney U, **Student T test, ***Pearson Chi-Square. IQR: Interquartile range, SD: Standart deviation.

DISCUSSION

Our study aimed to provide a perspective on the evidence-based need in the literature by examining the relationship between the symptoms of dyspnea and cognitive flexibility levels of medical school students who smoke. The main findings indicate that gender has a significant impact on smoking rates, with men smoking significantly more than women, and smoking may have negative effects on cognitive functions.

Among female participants, the smoking rate was determined to be 16.8%, while among males, this rate was found to be 38.3%. This result indicates that men smoke at a significantly higher rate compared to women. This difference reflects the influence and support of societal and cultural norms on smoking behavior according to gender. Additionally, societal gender roles and attitudes towards smoking could have a significant impact on the acceptability of this behavior. Many clinical researches on smoking addiction compare usage rates in men and women, and similar to our study, discuss the high smoking rates among men [23, 24]. The higher average age in the smoking group suggests that individuals may be more likely to start smoking or continue smoking as they age. This implies that starting smoking in young adults could become a habit that continues with age and may be difficult to quit.

In our study, no statistically significant differences were found in terms of age, smoking, cognitive flexibility, and dyspnea-12 score based on the living place. This indicates that there may not be a significant difference between rural and urban areas in the sample of the study in these variables. It is believed that especially smoking and cognitive flexibility levels may depend on personality traits, genetic structure, stress coping methods, family environments, education levels, etc. factors rather than where individuals live [25, 26]. However, there are also studies in the literature with contrary findings. In a study by Cassarino et al., it was shown that healthy individuals living in urban areas had better cognitive functions compared to those living in rural areas [27]. This discrepancy might be due to the limited number of participants in our study.

The mean values of cognitive flexibility levels in the smoker group being significantly lower suggest that smoking may have negative effects on cognitive functions. While previous studies have supported the finding that smoking impairs cognitive flexibility [18], the original aspect of our study is that it was conducted on a medical school sample and revealed this effect in the educated group as well. Cognitive flexibility refers to the individual's ability to adapt their thoughts and behaviors to changing conditions [28]. Our findings indicate that smoking could have harmful effects on critical cognitive functions such as problem-solving and adaptation in rapidly evolving situations. Individuals who are not cognitively flexible may experience difficulties in developing instant solutions and this may lead to stress, resulting in smoking. Therefore, the interaction between smoking and impaired cognitive flexibility seems to be a finding that needs to be supported with additional evidence on whether it is in which direction or if it is bidirectional. In the short term, it is known that nicotine can temporarily increase attention and concentration by binding to receptors in the brain, but in the long term, it is known to have negative effects on memory, attention, cognitive functions, and psychomotor functions [29, 30]. Moreover, there is evidence supported by previous studies that smoking increases the risk of Alzheimer's disease and other neurodegenerative diseases [31]. The oxidative stress and inflammation caused by smoking can contribute to the development of cognitive impairment by causing damage to brain cells [32].

Studies have found that cognitive impairment is associated with atherosclerotic processes [33]. Smoking is a major preventable risk factor for atherosclerosis [34]. Smoking may both increase inflammation and trigger these atherosclerotic processes, leading to impaired cognitive function.

The lack of a significant correlation between the age of the participants and cognitive flexibility may be due to the sample consisting of educated young individuals and the narrow age range. Additionally, the absence of a significant correlation between pack-years of smoking and cognitive flexibility may

suggest that exposure to smoking affects cognitive processes regardless of the number of packs and duration. Despite our sample consisting of young and educated individuals, the detection of low cognitive flexibility in the smoking group may imply that the negative effects of smoking cannot be balanced out even at a young age. This situation can be interpreted as a threat for more negative mental processes in later years. Our findings suggest that the impact of age on cognitive flexibility is limited and smoking independently of pack-years may have more pronounced negative effects on cognitive functions.

No significant difference was found between the group of participants who smokes and those who do not in terms of symptoms of dyspnea. These results may indicate that the distribution of dyspnea in the included research group is independent of smoking status or gender. It may also suggest that smoking in the short term does not have a significant impact on individuals' levels of shortness of breath, but further research is needed to evaluate the long-term effects. Additionally, the subjective measurement of dyspnea symptoms and the use of a scale, and the fact that any examination or evaluation of dyspnea with more objective techniques may have led to these results. All of these results considered together could provide a basis for future research to more thoroughly examine the relationship between smoking and cognitive functions.

Our study demonstrated the effects of smoking on dyspnea symptoms and cognitive flexibility in medical students. However, due to the cross-sectional design not establishing causal relationships, the limited generalizability of the sample group consisting only of medical students, the potential for subjective biases with self-report methods, and the inadequacy of short-term evaluations on long-term outcomes for dyspnea and cognitive flexibility, our study has limitations. These limitations highlight the need for future research to utilize larger and more diverse sample groups, integrate longitudinal designs, and incorporate objective measurement methods. Despite these constraints, the findings of our study can provide health professionals working in this field with insights into the impact of smoking addiction on cognitive functions in an educated sample and the interventions needed to prevent it.

CONCLUSION

This study examined the relationship between smoking frequency, dyspnea symptoms, and cognitive flexibility levels in medical school students. The high prevalence of smoking among individuals with higher levels of education and those who are aware of the health risks associated with it is a common finding in our study and in other literature. In our study, it was shown that smoking negatively affects cognitive flexibility. This may be due to smoking-related inflammation or the effect of atherosclerotic processes triggered by smoking. Therefore, when evaluating individuals' cognitive functions, the effects of smoking on these functions should be kept in mind. It is believed that combating smoking addiction may be beneficial in preventing deterioration in cognitive functions. Similar to many other complex diseases, treating addiction requires a multidisciplinary approach.

Informed Consent: Written informed consent was obtained from each subject following a detailed explanation of the study objectives and protocol.

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Original Research

Clinical Features, Psychiatric Comorbidities and Treatments in Childhood Obsessive Compulsive Disorder in terms of Symptom Severity, Gender and Age

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ABSTRACT

Objective: The aim of this study was to investigate the clinical features, psychiatric comorbidities, and treatments of childhood obsessive-compulsive disorder (OCD), with consideration given to OCD severity, gender and age.

Method: The study included 104 children and adolescents between the ages of 6 and 17 who were diagnosed with OCD and followed up in Child and Adolescent Psychiatry outpatient clinics between 2016 and 2023. The study examined the sociodemographic characteristics, clinical features, comorbid psychiatric disorders, and treatment approaches of children and adolescents with OCD.

Results: The sample had a mean age of 13.1 ± 2.7 years, and the mean age at onset of OCD was 11.9 ± 2.7 years (range: 5-17 years). Those with mild OCD had a significantly lower mean age at presentation and onset of OCD compared to those with moderate and severe OCD (p=0.012, p=0.02, respectively). Patients with severe OCD had longer illness duration (p=0.009) and outpatient follow-up (p=0.004) compared to those with moderate OCD. Boys had significantly higher rates of family history of psychiatric disorders (p=0.006), attention-deficit/hyperactivity disorder/oppositional defiant disorder (p=0.003), and tic disorder (p=0.035) comorbidity rates than girls, while girls had higher rates of anxiety disorders (p=0.022) comorbidity. The study found that repeating and counting compulsions were more common in adolescents than in preadolescents (p=0.003, all).

Conclusion: These results suggest that clinical presentation and comorbidity may vary with disease severity, gender and age, in children and adolescents with OCD. Early intervention is crucial to prevent clinical progression, worsening, and mental health sequelae.

Keywords: child, adolescent, obsessive-compulsive disorder, comorbidity, psychopharmacotherapy, gender, age

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition accompanied by obsessions and/or compulsions [1]. According to Diagnostic and Statistical Manual of Mental Disorders 5th ed. (DSM-5), obsessions are defined as 'recurrent and persistent thoughts, urges, or images', and compulsions as 'repetitive behaviors or mental acts'. There is a mutual relationship between obsessions and compulsions that causes significant distress, impairment, or excessive time consumption. Irrational or excessive compulsions are some other thought images, or impulses/urges that are felt to be necessary in response to obsessions and have been reported to function to ignore, suppress, or neutralize obsessions [2, 3].

The prevalence rates of OCD range from 2% to 4% [4]. The incidence of OCD has a bimodal distribution, with onset occurring between the ages of 9 and 10 and in the early 20s [1, 5]. While OCD is more prevalent in males during childhood, this pattern reverses during adolescence and adulthood, with females exhibiting a higher prevalence of OCD. Additionally, the age at which OCD first manifests is earlier in males than in females [1].

Although the etiology of OCD remains poorly understood, mounting evidence suggests that both genetic and environmental factors may influence its development, like that observed in other psychiatric conditions [1]. OCD is hereditary, with genetic influences accounting for 45% to 65% of childhood OCD symptoms [6]. Childhood OCD has been associated with a higher familial and genetic risk, as suggested by several studies [7, 8]. The rate of at least one other comorbid condition in children with OCD is high, ranging from 56% to 64% [9, 10]. Anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), behavioral disorders, and tic disorders are frequent [1, 9, 11].

Exposure and response prevention, as well as appropriate cognitive-behavioral therapy (CBT/ERP), are generally reported as the most effective and first-line treatments for childhood OCD. However, psychopharmacotherapy is used in children who do not respond to CBT or cannot access it reliably [1, 12]. The leading treatments include monotherapy with Selective Serotonin Reuptake Inhibitors (SSRIs), a potentiation strategy with low doses of neuroleptics, and behavioral and pharmacotherapy approaches for comorbidities [1, 12, 13].

OCD is among the ten most prevalent causes of disability globally and represents the fourth most common psychiatric disorder, according to the World Health Organization's (WHO) findings. Therefore, it is necessary to improve public awareness and optimize assessment and treatment to reduce the societal burden of OCD worldwide [14]. Despite its high prevalence, chronicization rate, and severe negative consequences, delays in diagnosis and inadequate treatment are known issues [15]. Childhood OCD can become chronic or progress with relapses and recurrences, causing psychosocial deterioration for many years if not treated effectively. Therefore, early intervention and adequate treatment by specialists are crucial [1, 16].

Despite numerous studies, no definitive conclusions have been reached regarding differences in OCD based on age and gender. It is crucial to disseminate epidemiological data, clinical manifestations, treatment modalities, and follow-up experiences in childhood OCD in order to enhance our understanding of this complex and debilitating condition. The objective of this study is to examine the sociodemographic and clinical characteristics, psychiatric comorbidities, treatment options, and clinical differences among children and adolescents diagnosed with OCD, with particular attention to the impact of the severity of the disorder, gender, and age.

Main Points

- Obsessive-compulsive disorder (OCD) is a psychiatric disorder that usually begins in childhood and in which obsessions and compulsions can cause significant functional impairment.
- Childhood OCD is often associated with other psychiatric comorbidities and has a high potential for chronicity and worsening.
- As there are different findings in the literature regarding the aspects of OCD that differ by gender and age, the dissemination of epidemiological data, clinical symptoms, treatment methods and follow-up experiences regarding OCD in childhood is crucial to improve our understanding of this disorder.
- The results of the study suggest that clinical presentation and comorbidity in children and adolescents with OCD may vary with severity of illness, gender and age, and that early intervention is important to prevent clinical progression, exacerbation and mental health sequelae.

MATERIALS AND METHODS

This retrospective study was approved by the local ethics committee (Date: 26.04.2022, session no: 2022/14, Decision no: 11). Study included 104 children and adolescents aged 6-17 years diagnosed with OCD according to DSM-5 criteria. Data from a university hospital Child and Adolescent Psychiatry outpatient clinics between 2016-2023 were used. The study analyzed sociodemographic characteristics, family psychiatric history, clinical features of OCD, duration of the disorder, triggering factors, comorbid psychiatric disorders, and treatment approaches for OCD. The data were obtained from the patient's medical records, which contained precise data and Clinical Global Impression (CGI) scales. The clinician initially evaluated the CGI scales in the patients' files and then again after a period of at least six months, during which time the patients had undergone active treatment. This was done in order to determine the severity of the disease and the efficacy of the treatment. This was achieved by utilising the Clinical Global Impression-Severity (CGI-S) sub-scale and the Clinical Global Impression-Improvement (CGI-I) sub-scale, respectively. The study excluded patients with missing data and children diagnosed with mental retardation or Autism Spectrum Disorder (ASD).

Clinical Global Impression (CGI) Scale

The CGI is a seven-point clinician-rated scale that assesses disease severity and therapeutic effectiveness. Lower scores on the CGI-S indicate less severe disease, while a score of seven indicates extreme illness. The CGI-I subscale is employed to assess the efficacy of treatment based on the observed improvement. A score of one indicates a markedly improved outcome, while a score of seven signifies a markedly worsened outcome [17]. The severity of OCD is defined by a cut-off score of three, four, and five, respectively, on CGI-S subscale. The following classifications describe the severity: mild, moderate, and severe. In accordance with the CGI-I subscale, a positive response to treatment was defined by a score of 1 or 2, a partial response was indicated by a score of 3, and resistance to treatment was identified by a score of 4 or above.

Statistical Analysis

The analyses were conducted using SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 software. Descriptive data are presented as n and % values for categorical data, and mean ± standard deviation and median (min-max) values for continuous data. To compare categorical variables between groups, we used the Chi-square analysis (Pearson Chi-square). We assessed the conformity of continuous variables to normal distribution using the Kolmogorov-Smirnov Test. Non-parametric mean comparisons were conducted within each of the two samples. These comparisons involved the Kruskal-Wallis tests for overall differences, followed by the Mann-Whitney tests for specific group comparisons. The level of statistical significance for the analyses was set at a p value of less than 0.05.

RESULTS

Sociodemographic Characteristics of the Sample

A total of 104 children and adolescents were included in the study. Of these, 58 (55.8%) were girl, with a mean age at presentation of 13.1±2.7 years (range: 6-17 years). The patients were classified into two age-based categories: preadolescents (ages 6-11) and adolescents (12-17). Of the sample, 39 (37.5%) individuals were in the preadolescent group, while 65 adolescents constituted 62.5% of the sample. Twenty-four children (23.1%), exhibited a positive family history of OCD. Additionally, 35 (33.7%) children had a history of psychiatric illness. Table 1 provides the sociodemographic characteristics of the children and adolescents.

Clinical Features of OCD

The mean age at which the onset of OCD occurred was 11.9 ±2.7 years (range: 5-17 years) and the mean duration of illness was 2.1 ±1.5 years. The time without treatment before applying to the outpatient clinic was 13.67±10.84 months. The mean duration of outpatient follow-up was 12±13.7 months (range: 6-75 months). The data indicates that 79.8% (n=83) of patients exhibited persistent OCD symptoms for at least one year, while 43.3% (n=45) exhibited persistent symptoms for at least two years. Of the patients, 5.8% (n=6) had mild severity, 24% (n=25) had moderate severity, and 70.2% (n=73) had severe severity. Moreover, 24% (n=25) of the patients had at least one precipitating factor.

Obsessions were not reported in 6.7% (n:7) of the patients, while compulsions were not reported in 4.8% (n:5). Furthermore, 32.7% (n:34) of the children reported more than one obsession, and 51.9% (n:54) reported more than one compulsion. The study found that the three most commonly reported types of obsessions were contamination (62.5%, n: 65), religious (30.8%, n: 32), and sexual (14.4%, n: 15). The three most commonly reported types of compulsions were cleaning/washing (57.7%, n: 60), repeating (51.9%, n: 54), and checking (26.9%, n: 28). Table 2 also presents the clinical features of OCD in children and adolescents.

Table 1. Sociodemographic characteristics of the sample

Variables	Number (n)	Percentage (%)
Gender		
Male	46	44.2
Female	58	55.8
Age groups		
Preadolescent child	39	37.5
Adolescent	65	62.5
Place of residence		
Urban	89	85.6
Rural	15	14.4
Mother's education		
Only literate	2	1.9
Primary school	34	32.7
Secondary school	28	26.9
High school	19	18.3
University degree	21	20.2
Father's education		
Only literate	0	0
Primary school	7	6.7
Secondary school	31	29.8
High school	25	24.0
University degree	42	39.5
Family income level†		
Low	31	29.8
High	73	70.2
Family type		
Nuclear	98	94.2
Single-parent	2	1.9
Extended	2	1.9
Adoptive child	2	1.9
Family history of OCD		
Yes	24	23.1
No	80	76.9
Family history of psychiatric disorder		
Yes	35	33.7
No	69	66.3
Family Psychiatric history		
OCD	24	23.1
Anxiety disorder	10	9.6
Depressive disorder	1	1
Bipolar disorder	4	3.8

†The level of income was determined by the minimum wage value on the date of the study.

Table 2. Clinical features of obsessive-compulsive disorder in the sample

	Number (n)	Percentage (%)
Duration of OCD		
<12 months	21	20.2
12-24 months	38	36.5
24-36 months	23	22.1
≥36 months	22	21.2
Severity of OCD		
Mild	6	5.8
Moderate	25	24
Severe	73	70.2
Presence of precipitating factor(s)		
Yes	25	24
No	79	76
Type of precipitating factor(s)		
Parent/sibling(s) relationship problems	9	8,7
Peer/social relationship problems	7	6,7
Abuse	3	2,9
Covid-19 infection	3	2,9
Loss and grief	2	1,9
Exam/success anxiety	1	1,0
Obsession type		
No	7	6.7
Contamination	65	62.5
Religious	32	30.8
Sexual	15	14.4
Magical thinking	8	7.7
Somatic	8	7.7
Aggressive	5	4.8
Hoarding/saving	5	4.8
Compulsion type		
No	5	4.8
Cleaning/washing	60	57.7
Repeating	54	51.9
Checking	28	26.9
Counting	17	16.3
Ordering/arranging	15	14.4
Superstition	5	4.8
Hoarding/collecting	4	3.8

Comorbid Psychiatric Disorders and Treatment Approaches for OCD

Out of the sample of children, 58.7% (n: 61) had no other comorbid disorder, while 41.3% (n: 43) had one or more comorbid psychiatric disorders. The three most common comorbid disorders were anxiety disorders (28.8%), ADHD and/or Oppositional Defiant Disorder (ODD) (25%), and depressive disorder (11.5%).

Upon examination of the pharmacological treatment by children received in the 6th month after application, it was determined that 91.3% (n=95) of the study group utilized at least one pharmacotherapeutic agent in conjunction with psychoeducational and behavioral interventions for OCD. The remaining 8.7% (n=9) did not use any pharmacological agent. Table 3 presents the comorbid psychiatric disorders associated with OCD and the corresponding therapeutic approaches.

Variables According to the Severity of OCD

The study found that patients with mild OCD had a significantly lower mean age at presentation and onset compared to those with moderate and severe OCD (p=0.012, p=0.02, respectively). Moreover, patients with severe OCD had a longer duration of illness (p=0.009) and outpatient follow-up (p=0.004) compared to those with moderate OCD. No statistically significant relationship was observed between the time interval without treatment and disease severity (p = 0.29). (data not shown in table).

No significant relationship was found between a family history of OCD, a family history of psychiatric illness, the existence of precipitating factors, the presence of comorbid psychiatric diagnosis, the presence of multiple comorbid diagnoses, types of obsessions and compulsions, and OCD severity (p>0.05). Table 4 provides information on the sociodemographic variables and clinical characteristics that affect OCD severity.

Comparisons Between Genders and Age Groups

No significant difference was found between genders in terms of age group distribution, place of residence, income level, family structure, or family history of OCD (all p values>0.05). Although there was no significant difference between genders in terms of family history of OCD (p>0.05), the rate of family history of psychiatric illness was significantly higher in boys than in girls (p=0.006) (Table 5).

Table 3. Comorbid psychiatric disorders, and treatment approaches for obsessive-compulsive disorder in the sample

	Number (n)	Percentage (%)
Presence of psychiatric comorbidity		
Yes	61	58.7
No	43	41.3
Comorbid psychiatric disorders		
Anxiety disorders*	30	28.8
ADHD/ODD	26	25
Depressive disorder	12	11.5
CD	5	4.8
Tic disorder	4	3.8
PTSD	1	1.0
Specific learning disability	1	1.0
Other psychiatric disorders**	14	13.5
Psychotropic medications		
None	9	8.7
SSRI only	45	43.3
Antipsychotic only	4	3.8
SSRI + Antipsychotic	28	26.9
SSRI+ADHD medications	7	6.7
SSRI + ADHD medications + Antipsychotic	4	3.8
SSRI+AP+Additional medication***	7	6.7
Response to treatment		
Positive response	65	61,9
Partial response	21	20,0
Resistant to treatment	7	6,7
Unmedicated/non-compliance with treatment****	11	10,5

*Generalized anxiety disorder, panic disorder, social anxiety disorder, specific phobias, agoraphobia, separation anxiety, selective mutism, etc.

**Communication disorders, elimination disorders, sleep and eating disorders, trichotillomania, etc.

***NaSSA, Benzodiazepine, Mood stabilizer medication

****Non-compliance with treatment: the non-use or discontinuity of the treatment process.

Abbreviations: ADHD: Attention-Deficit/Hyperactivity Disorder, CD: Conduct Disorder, OCD: Obsessive-Compulsive Disorder, ODD: Oppositional defiant disorder, PTSD; Post-traumatic stress disorder, SSRI: Selective serotonin reuptake inhibitor

When analysing the accompanying psychopathologies separately, it was found that anxiety disorders were significantly more prevalent in girls (p=0.022), while ADHD/ODD (p= 0.003) and tic disorder (p= 0.035) were significantly more prevalent in boys. No significant gender difference was found in depressive disorders (p>0.05) (refer to Table 5).

Treatment options and responses did not differ significantly between genders (p>0.05).

When analysing children and adolescents based on their age (preadolescent/adolescent) in terms of sociodemographic characteristics and OCD clinical findings, the only significant difference found was that counting and repeating compulsions were more common in adolescents than in preadolescents. No significant differences were observed in terms of family history of OCD and psychiatric illness, the existence of precipitating factors, and comorbid psychopathologies presence or type (p>0.05). The comparison between the age groups is shown in Table 6.

There were no significant differences (p>0.05) in terms of place of residence, income level, family structure, age at disease onset, disease duration, duration of outpatient follow-up, treatment options, and treatment responses across different age groups.

Table 4. Sociodemographic variables and clinical features according to the severity of obsessive-compulsive disorder in the sample

	Mild OCD (n:6)	**Moderate OCD (n:25)**	**Severe OCD (n:73)**	**p-value***
Gender (n,%) Male Female	 2 (33.3) 4 (66.7)	 9(36) 16(64)	 35 (47.9) 38 (52.1)	0.547
Place of residence Urban Rural	 6 (100) 0 (0)	 24(96) 1(4)	 59(80.8) 14(19.2)	0.125
Age (years), Median (min-max)	7.0 (6.0-14.0)	12.0 (7.0-17.0)	12.0 (5.0-17.0)	**0.012**
Age of OCD onset (years), Median (min-max)	6.5 (5.0-12.0)	12.0 (6.0-17.0)	7.0 (6.0-14.0)	**0.02**
Duration of OCD (month), Median (min-max)	18.5(2.0-31.0)	15.0 (3.0-32.0)	24.0 (4.0-104.0)	**0.009**
Outpatient clinic follow-up period (month), Median (min-max)	4.0 (0.0-11.0)	4.0 (0.0-18.0)	9.0 (0.0-75.0)	**0.004**
Family history of OCD (n,%) Yes No	 1(16.7) 5(83.3)	 7(28) 18(72)	 23(31.5) 50(68.5)	0.843
Family history of psychiatric disorder(n,%) Yes No	 1(16.7) 5(83.3)	 11(44) 14(56)	 16(21.9) 57(78.1)	0.384
Presence of precipitating factor(s) (n, %) Yes No	 0 (0) 6 (100)	 20(80) 5(20)	 53(72.6) 20(27.4)	0.375
Presence of psychiatric comorbidity (n,%) Yes No	 3(50) 3 (50)	 12(48) 13(52)	 27(37) 46(63)	0.352
Presence of more than one psychiatric comorbidity (n, %) Yes No	 1(16.7) 5(83.3)	 2(8) 23(92)	 51(70.8) 21(29.2)	0.074

*The chi-square test for categorical variables and the Kruskal Wallis Test for continuous variables were used to test group differences.
Bold font indicates statistical significance: $p<0.05$. *Abbreviations:* OCD: Obsessive-compulsive disorder

Table 5. Comparisons of the variables according to the gender in the sample

	Male(n: 46)	Female(n:58)	p-value*
Age groups			
Preadolescent child	17(43.6)	22(56.4)	0.919
Adolescent	29(44.6)	36(55.4)	
Family history of OCD (n,%)			
Yes	14(30.4)	10(17.2)	0.089
No	32(69.6)	48(82.8)	
Family history of psychiatric disorder (n,%)			
Yes	22(47.8)	13(22.4)	**0.006**
No	24(52.2)	45(77.6)	
Presence of precipitating factor(s) (n, %)			
Yes	8(82.6)	1(29.3)	0.158
No	38(17.4)	41(70.7)	
Obsession type			
Contamination	30 (65.2)	35 (60.3)	0.610
Religious	16 (34.8)	16 (27.6)	0.430
Sexual	5 (10.9)	10 (17.2)	0.358
Magical thinking	2 (4.3)	6 (10.3)	0.297
Somatic	3 (6.5)	5(8.6)	0.494
Aggressive	3(6.5)	2(3.4)	0.653
Hoarding/saving	3(6.5)	2(3.4)	0.653
Compulsion type			
Cleaning/washing	29 (63.0)	31 (53.4)	0.322
Repeating	23 (50.0)	31 (53.4)	0.727
Checking	10 (21.7)	18 (31.0)	0.288
Counting	8 (17.4)	9 (15.5)	0.797
Ordering/arranging	6 (13.0)	9(15.5)	0.721
Superstition	3(6.5)	2(3.4)	0.653
Hoarding/collecting	3(6.5)	1(1.7)	0.319
Presence of psychiatric comorbidity (n,%)			
Yes	28(60.9)	33(56.9)	0.683
No	18(39.1)	25(43.1)	
Presence of more than one psychiatric comorbidity (n, %)			
Yes	11(23.9)	13(22.8)	0.895
No	35(76.1)	43(77.2)	
Comorbid psychiatric disorders			
Anxiety disorders	8(17.4)	22 (37.9)	**0.022**
ADHD/ODD	18 (39.1)	8 (13.8.)	**0.003**
Depressive disorder	3(6.5)	9 (15.5)	0.154
CD	2(4.3)	3 (5.2)	0.609
Tic disorder	4(8.7)	0 (0)	**0.035**
PTSD	0(0)	1(2.2)	0.558
Specific learning disability	1(2.2)	0(0)	0.442
Other psychiatric disorders	7(15.2)	7(12.1)	0.640

Notes: *The chi-square test and Fisher's exact test (as appropriate) were used to test group differences. **Bold font** indicates statistical significance: $p < 0.05$.

Table 6. Comparisons of the variables according to the age groups in the sample

	Preadolescent(n:39)	**Adolescent(n:65)**	**p-value***
Gender (n,%)			
Male	17 (43.6)	29 (44.6)	0.541
Female	22 (56.4)	36 (55.4)	
Family history of OCD (n,%)			
Yes	10(25.6)	14(21.5)	0,631
No	29(74.4)	51(78.5)	
Family history of psychiatric disorder (n,%)			
Yes	14(35.9)	21(32.3)	0.708
No	25(64.1)	44(67.7)	
Presence of precipitating factor(s) (n, %)			
Yes	13(33.3)	12(18.5)	0.086
No	26(66.7)	53(81.5)	
Obsession type (n,%)			
Contamination	24 (61.5)	41 (63.1)	0.875
Religious	10 (25.6)	22 (33.8)	0.380
Sexual	8 (20.5)	7 (10.8)	0.171
Magical thinking	1 (2.6)	7 (10.8)	0.253
Somatic	5 (12.8)	3(4.6)	0.148
Aggressive	1(2.6)	4(6.2)	0.648
Hoarding/saving	3(7.7)	2(3.1)	0.361
Compulsion type (n, %)			
Cleaning/washing	19 (48.7)	41 (63.1)	0.151
Repeating	13 (50.0)	41 (63.1)	**0.003**
Checking	9 (23.1)	19 (29.2)	0.493
Counting	1 (2.6)	16 (24.6)	**0.003**
Ordering/arranging	5 (12.8)	10(15.4)	0.719
Superstition	1(2.6)	4(6.2)	0648
Hoarding/collecting	3(7.7)	1(1.5)	0.147
Presence of psychiatric comorbidity (n,%)			
Yes	21(53.8)	40(61.5)	0.441
No	18(46.2)	25(38.5)	
Presence of more than one psychiatric comorbidity (n, %)			
Yes	9 (23.7)	15 (23.1)	0.895
No	29 (76.3)	50 (76.9)	
Comorbid psychiatric disorders (n,%)			
Anxiety disorders	13(33.3)	17 (26.2)	0.434
ADHD/ODD	11(28.2)	15 (23.1)	0.559
Depressive disorder	4(10.3)	8 (12.3)	0.508
CD	2(5.1)	3(4.6)	0.623
Tic disorder	0 (0)	4 (6.2)	0.294
PTSD	0 (8.7)	1 (1.5)	0.625
Specific learning disability	1(2.6)	0 (0)	0.375
Other psychiatric disorders	4(10.3)	10(15.4)	0.458

Notes: *The chi-square test and Fisher's exact test (as appropriate) were used to test group differences. **Bold font** indicates statistical significance: $p < 0.05$.

DISCUSSION

The study evaluated sociodemographic data, OCD clinical features, comorbidities, and treatments of children and adolescents with OCD based on disease severity, gender, and age, using the 6-year follow-up and treatment data of a university hospital.

The sample consisted of 55.8% girls. Previous studies conducted in OCD follow-up centers have reported higher rates of childhood OCD in boys, ranging from 60% to 70% [1]. A recent study on pediatric OCD also reported a preponderance of 56% females, similar to our findings [18]. This situation is also supported by the predominance of women in adult OCD studies [19].

Our study revealed that the mean age of OCD onset was 11.9 years, while the mean age at admission to child psychiatry was 13 years. The duration of symptom onset at presentation was 2.1±1.5 years, which is consistent with the literature indicating a two to three year gap between the onset of OCD and diagnosis [4, 5].

The high rates of positive family history of OCD (23.1%) and history of psychiatric illness (33.7%) in our study support the hypothesis of familial aggregation of OCD or related psychopathology, such as anxiety and/or depression, as reported in the literature. Childhood OCD is linked to a higher familial and genetic risk, with genetic inheritance estimated at around 65% [1, 6]. Probands of children with OCD have a definite OCD rate of 11.7%, while the rate of definite and probable OCD is 16.3% [7]. In another family study, the risk of OCD in first-degree relatives of children with OCD was reported to be 26% [20].

In our study, 41% of participants had one or more comorbid psychiatric disorders. The four most common comorbid disorders were anxiety disorders, ADHD and/or ODD, MDD, and tic disorder. Although studies have shown differences in the rates and types of comorbidities in childhood OCD, a large meta-analysis reports that 64% of children with OCD have comorbidities, with anxiety disorders being the most common [9]. Other common comorbidities in children with OCD include MDD, ADHD, behavioral disorders, ASD, Tourette's syndrome, and tic disorders [1, 9, 11]. Peris et al. conducted a large sample study on pediatric OCD, which found that the four most common comorbid disorders were anxiety disorder (50%), externalizing disorders such as ADHD, ODD, and conduct disorder (CD) (16%), depressive disorder (12%), and tic disorder (11%) [11]. Early detection and identification of comorbidities is crucial for effective treatment planning and intervention, as they can cause increased symptom severity and additional burdens on social, school, and family functioning [21-23].

In this study, 91% of the participants utilised at least one additional pharmacological agent in conjunction with psychoeducation (child and family psychoeducation) and psychotherapies (behavioural methods for OCD symptoms). Even half of the children who received pharmacotherapy used combined drugs, such as SSRI + Antipsychotic, SSRI+ADHD medications, SSRI + ADHD medications + Antipsychotic, or SSRI+AP+Additional medication. The high rate of pharmacotherapy use may have been influenced by the high number of moderate and severe cases in our sample, as well as the high rate of comorbidities. CBT/ERP is usually the most effective first-line treatment for childhood OCD. However, psychopharmacology is often necessary [1, 12]. Monotherapy with SSRIs has moderate effect sizes compared to placebo according to multiple Randomised Controlled Trials [13]. When SSRIs are insufficient (optimal SSRI response requires high doses and a long duration of treatment), the best augmentation strategy is to add low doses of neuroleptics, especially risperidone and aripiprazole. Although studies have been conducted with other drugs, no conclusive evidence has been found [12]. Given the high number of comorbidities, the most effective treatment is one that considers both behavioural and pharmacotherapy approaches for each comorbidity [1].

Our study found that approximately two-thirds of children responded positively to treatment, one-fifth responded partially, one-tenth did not receive drug treatment or were non-compliant, and only 6.7% did not respond to treatment. In a 3-year prospective follow-up study of children and adolescents treated for OCD, partial remission rates were 53% and complete remission rates were 27%. The study reported that 71% of the participants received SSRI treatment, and the duration of SSRI use varied between 4% and 100% of the follow-up period [24]. Research suggests that childhood OCD may have a more favourable prognosis than adult-onset OCD, with a significant proportion of cases becoming subclinical or experiencing partial or complete remission [1].

The study revealed that individuals with moderate and severe OCD were admitted to the outpatient clinic at a significantly higher mean age than those with mild OCD. Additionally, those with severe OCD had longer illness duration and outpatient

clinic follow-up periods compared to those with moderate OCD. These findings support previous studies that suggest OCD is a progressive and worsening condition [25]. Therefore, early detection and intervention in childhood OCD is crucial. Given the increasing burdens that arise over time in the disease and the challenges faced by children in expressing themselves, family information and early awareness become even more crucial. Early intervention tailored to children's developmental stages can prevent the progression of severity and impairment over time.

The results of our study indicated that there was no significant difference in the prevalence of comorbid conditions between genders. However, there were differences in the types of comorbidities. Boys had a significantly higher prevalence of ADHD/ODD and tic disorder, whereas girls had a higher prevalence of anxiety disorders. There are few studies investigating gender differences in childhood OCD. Existing literature has examined age at onset [10, 26], symptom severity [26], OCD symptom dimensions [10, 27], and treatment responses [28], but no significant differences have been found between genders. In our study, we also found no difference in these findings according to gender. However, while there was no difference in family history of OCD according to gender, we found that the family history of psychiatric disease was significantly higher in males. The results suggest the existence of a form of OCD with early onset, high familial inheritance, and a male predominance, as reported in the literature [16]. Vivan et al. found no gender differences in the prevalence of comorbidity among adolescents with OCD, but they did find a significant difference in terms of comorbidity with tic disorder, which was significantly higher in males [10]. Ivarsson et al. reported that ADHD is associated with higher rates of tic disorder in boys, and GAD is also significantly higher in girls [29]. Peris et al. also reported that among children and adolescents with OCD, the odds of an externalizing disturbance are approximately doubled in males [11].

When analysing children and adolescents based on their age (preadolescent/adolescent) in terms of sociodemographic characteristics and OCD clinical findings, the only significant difference found was that counting and repeating compulsions were more common in adolescents than in preadolescents. It is worth noting that childhood-onset OCD may be a separate subtype, which has brought research on this subject to the forefront [30]. The study by Geller et al. revealed no significant differences between age groups in terms of sociodemographic data, with the exception of the age of onset of the disease. Regarding clinical characteristics, only religious and sexual obsessions were overrepresented in adolescents compared to children, while there were no significant differences between other obsessions and compulsions [31]. In a separate study, it was found that the age at onset was significantly higher in adolescents. Additionally, contamination obsession and washing, checking compulsions were reported to be more prevalent in adolescents, while no significant differences were found in other variables [25]. The literature reports that children may have higher rates of fear regarding catastrophic or harmful events happening to themselves or their loved ones, reflecting developmental concerns about separation from attachment figures. Additionally, obsessions related to sexuality, morality, and religion may be more common in adolescence [1, 31]. Our study suggests that obsessions and compulsions may vary according to the age of the patient and their developmental stage. Specifically, we found that counting and repeating compulsions were more common in adolescents. It is important to note that our findings are objective and based on statistical analysis. This may be related to the fact that mathematical ability develops with age.

Limitations

This study analyses sociodemographic characteristics, clinical features, psychiatric evaluation, comorbid conditions, psychiatric treatment options, and treatment effectiveness in children and adolescents with OCD, with a focus on disorder severity, age, and gender. The study is characterised by both strengths and limitations. A strength of the study is that all patients underwent a comprehensive psychiatric evaluation that was conducted in the clinical setting. The study had a relatively large sample size. However, limitations include its retrospective design, lack of standardised treatment methodology, and reliance solely on data from patients who visited the child psychiatry outpatient clinic. A limitation of this study is that the initial assessment and follow-up did not use a valid and reliable form for assessing OCD symptoms. These limitations may hinder the generalizability of the results.

CONCLUSIONS

Our study demonstrated that individuals with moderate and severe OCD were admitted to the outpatient clinic at a significantly higher mean age compared to those with mild OCD. Gender differences were also observed, with boys having higher rates of family history of psychiatric illness, comorbid ADHD/ODD

and tic disorder, while anxiety disorders were more common in girls. The study found that counting and repeating compulsions were more common in adolescents than preadolescents. OCD is a psychiatric disorder that usually appears in childhood and can cause significant functional impairments. It has a high potential for chronicity and aggravation. Although there are studies in the literature comparing OCD across different age groups, the results are inconsistent. The study presents differences in clinical features, comorbidities, and treatment of childhood OCD based on disease severity, gender, and age. These findings can guide clinicians in their approach.

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Original Research

Investigation of the Relationship Between Internet Addiction, Food Addiction and Impulsivity in Adolescents Presenting at the Child Psychiatry Outpatient Clinic

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ABSTRACT

Objective: The purpose of this study was to investigate the relationship between Internet addiction, food addiction, and impulsivity in children and adolescents aged 12-18 years who presented at the child psychiatry outpatient clinic of a university hospital.

Methods: This study included 207 patients aged 12-18 years who presented at the child and adolescent psychiatry clinic. All the study participants completed the Internet Addiction Test (IAT), the Barratt Impulsivity Scale (BIS-11), and the Yale Food Addiction Scale for Children 2.0 (YFAS-C 2.0).

Results: The individuals who scored above the IAT total score cut-off point had substantially higher scores on the YFAS-C 2.0, BIS-11 total scores, and BIS-11 cognitive impulsivity and non-planning subscale than the participants who scored below the IAT total score cut-off point. According to the results of logistic regression analysis, the YFAS-C 2.0 and BIS-11 total scores were found to be related to Internet addiction.

Conclusion: The study's findings indicate that impulsivity and food addiction might be significant risk factors for Internet addiction.

Keywords: Adolescents, Internet Addiction Disorder, Food Addiction, Impulsive Behavior.

INTRODUCTION

Problematic Internet use, which has been named Internet addiction, has become extremely common in recent years [1]. Internet addiction is defined as excessive and unlimited Internet use that can cause functionality disorders and significant problems in daily life, and this has now become an important public health problem with the continuously increasing use of the Internet [1,2]. Adolescence constitutes a risk for Internet addiction, and studies have shown a prevalence of 20%-26.5% for Internet addiction in adolescents [1,3]. There are studies in literature that have shown that Internet addiction could be associated with some psychiatric disorders, depression, attention deficit hyperactivity disorder (ADHD), substance addiction, and eating disorders [4-6].

Impulsivity can be defined as decisions taken rapidly by a person even if they result in negative outcomes and a tendency to translate these decisions into behaviours [7]. It has been

suggested that there could be a relationship between weak impulse control of an individual and Internet addiction, which is defined as uncontrolled Internet use [7,8,9].

A person with a food addiction loses control over how much food they eat and has an overwhelming craving for it. This is characterised by extreme difficulty in stopping the desire to eat and the amount of food consumed, despite knowing that over-consumption will have negative outcomes [10]. It is thought that adolescents may be more predisposed to food addiction as they are more sensitive to rewards, more impulsive, and take more risks than adults. However, studies of the extent of food addiction have been conducted more on adults, and there is a very limited number of studies related to adolescence [11]. In 2021, a study revealed that there might be a connection between food addiction and impulsivity [10]. Additionally, a recent study revealed the possibility of a connection between Internet addiction and food addiction [12].

As stated above, impulsivity, Internet addiction, and food addiction are inter-related. However, as far as we are aware, there aren't many research comparing food addiction and Internet addiction, and there is no study in the literature that has evaluated the relationships of Internet addiction in adolescents, food addiction, and impulsivity together. The purpose of this research was to investigate the connection between impulsivity, food addiction, and Internet addiction in adolescents who visited the psychiatry polyclinic.

The research questions were: (a) is there a significant difference between adolescents with and without Internet addiction in respect of food addiction and impulsivity? and (b) is there a significant corrrelation between Internet addiction, food addiction, and impulsivity?

Main Points;

- Internet addiction is defined as excessive and unrestricted internet use that can cause significant distress and functional impairment in daily life.
- Adolescence is a time when Internet addiction is risky.
- There are studies showing that there may be a connection between impulsivity, internet addiction and food addiction.
- The results of the study suggest that food addiction and impulsivity could be important risk factors for Internet addiction.

MATERIALS AND METHOD

Sample and Research Design

This single-centre, cross-sectional study included adolescents aged 12-18 years who presented at the Child and Adolescent Psychiatry Polyclinic of Afyonkarahisar Health Sciences University Medical Faculty Hospital between August 2023 and February 2024.

The research was explained to the teenagers who consented to take part in the study and all of the participants, along with their parents, gave their informed consent in writing and verbally. The study group was formed of 207 patients with no active psychotic symptoms, no common developmental disorder, and who had the mental capacity of a level to be able to respond to the questions on the questionnaires to be used.

The sociodemographic form was administered to all the study participants by a clinician, then the adolescents completed the Internet Addiction Test (IAT), the Barratt Impulsivity Scale (BIS-11), and the Yale Food Addiction Scale for Children 2.0 (YFAS-C 2.0).

Data Collection Tools

Sociodemographic data form: The researchers developed this form to capture the sociodemographic information of the study participants, including their age and gender.

Internet Addiction Test (IAT): This scale was developed by Young to determine Internet use habits and level of addiction. The scale consists of 20 items with 5-point Likert-type responses. Higher points indicate an increased severity of Internet addiction [13]. The total points are evaluated as 0-30 points indicating a normal level, 31-49 a mild level, 50-79 as a moderate level, and 80-100 as a severe level of addiction [14]. In the Turkish version of the IAT, a total score of >50 points has been defined as pathological Internet use [15]. Similar to other studies on this subject, the participants in this study were separated into two groups as the Internet addiction group with total IAT points ≥50 and the Internet non-addiction group with total IAT points ≤49 [16-18]. The scale was adapted to Turkish, and in a study by Bayraktar (2001) the Cronbach alpha coefficient was found to be 0.91, and the Spearman-Brown value was 0.87 [19].

The Yale Food Addiction Scale for Children 2.0 (YFAS-C 2.0): This scale is used to evaluate symptoms of food addiction in children and adolescents [20]. Validity and reliability studies of the scale in Turkish have been performed [21]. The scale consists of 16 items with 5-point Likert-type responses. High points indicate a higher level of food addiction [20]. The internal consistency reliability coefficent of the Turkish version of the YFAS-C 2.0 has been found to be 0.90 [21].

Barratt Impulsivity Scale 11 (BIS-11): This scale, developed by Patton et al., is used in the evaluation of impulsivity [22]. It is formed of 30 items with 4-point Likert -type responses scored from 1-4 points, in 3 subscales of non-planning, motor impulsivity, and cognitive impulsivity. High points indicate a high level of impulsivity. Validity and reliability studies of the Turkish version of the scale have been conducted [23].

Statistical Analysis

SPSS version 26.0 was used to do a statistical analysis on the study's data. Descriptive statistics were used to examine the sample's demographic features. In the comparisons of the groups with total IAT points above and below the cutoff value, the Student's t-test or Mann Whitney U-test were used depending on the normality of distribution of the data. To determine correlations between variables, Spearman correlation analysis was applied. Potential factors found in the earlier analyses were used in logistic regression analyses to evaluate independent predictors of Internet addiction in the multivariate study. The results were evaluated as statistically significant at Type 1 error level <5%.

RESULTS

Evaluation was made of a total of 207 adolescents, comprising 130 (62.8%) females and 77 (37.2%) males with a mean age of 14.6±1.7 years.

The whole study sample was separated into two groups as those with and without Internet addiction according to the cutoff value of the IAT. The group with Internet addiction (≥50 IAT points) included 52 (25.1%) adolescents and the group without Internet addiction (≤49 IAT points) included 155 (74.9%) adolescents. No significant difference was determined between the groups with and without Internet addiction in respect of gender (x2=0.378, p=0.776), or mean age (14.61±0.24 years vs. 14.61±0.13 years) (z=-0.022, p=0.983).

The IAT total points (p<0.001), YFAS-C 2.0 total points (p<0.001), BIS-11 total points (p<0.001), BIS-11 cognitive impulsivity subscale points (p<0.001) and the BIS-11 non-planning subscale points were determined to be statistically significantly higher in the Internet addiction group than in the group without Internet addiction. No significant difference was found between the groups in respect of the BIS-11 motor impulsivity subscale points (p=0.07) (Table 1).

Table 1. The IAT total points, YFAS-C 2.0 points, and BIS-11 subscale points of the groups with and without Internet addiction

	With Internet Addiction (n:52)		Without Internet Addiction (n:155)		z	p
	Mean	SD	Mean	SD		
IAT total points	62.88	1.32	27.57	1.00	-10.785	**<0.001**
YFAS-C 2.0	30.82	2.01	15.82	1.14	-5.83	**<0.001**
BIS-11 total points	71.40	1.12	61.67	0.86	-5.789	**<0.001**
BIS-11 cognitive impulsivity subscale points	22.019	0.56	18.12	0.36	-5.184	**<0.001**
BIS-11 Motor impulsivity subscale points	16.78	0.57	15.71	0.31	-1.814	0.070
BIS-11 non-planning subscale points	32.59	0.47	27.83	0.41	-6.042	**<0.001**

SD: standard deviation - Mann Whitney U-test

YFAS-C 2.0: Yale Food Addiction Scale for Children 2.0, BIS-11: Barratt Impulsivity Scale- 11, IAT: Internet Addiciton Test

Table 2. Correlations between the IAT total points and the BIS-11 subscale points and the YFAS-C 2.0 (n=207)

	BIS-11 Total points		BIS-11 Cognitive Impulsivity subscale points		BIS-11Motor Impulsivity subscale points		BIS-11 Non-planning subscale points		YFAS-C 2.0	
	r	p	r	p	r	p	r	p	r	p
IAT total points	0.529	**<0.001**	0.474	**<0.001**	0.271	**<0.001**	0.479	**<0.001**	0.479	**<0.001**
YFAS-C 2.0	0.470	**<0.001**	0.503	**<0.001**	0.317	**<0.001**	0.336	**<0.001**		-

Spearman correlation
YFAS-C 2.0: Yale Food Addiction Scale for Children 2.0, BIS-11: Barratt Impulsivity Scale-11, IAT: Internet Addiction Test

Table 3. Results of the Logistic Regression Analyses of the YFAS-C 2.0 and the BIS-11 subscale points to determine the factors related to Internet addiction

	Standard error	p-value	Cox & Snell R2
			0.221
Gender	0.393	0.106	
Age	0.109	0.689	
YFAS-C 2.0	0.013	**<0.001**	
BIS-11 total points	0.020	**0.001**	

YFAS-C 2.0: Yale Food Addiction Scale for Children 2.0, BIS-11: Barratt Impulsivity Scale- 11

The Spearman correlation analysis's findings indicate that a significant positive correlation was determined between the IAT total points and the BIS-11 cognitive impulsivity subscale points ($p<0.001$), the BIS-11 total points ($p<0.001$), BIS-11 non-planning subscale points ($p<0.001$) at a moderate level, between the IAT total points and the BIS-11 motor impulsivity subscale points ($p<0.001$) at a weak level, between the IAT total points and the YFAS-C 2.0 total points ($p<0.001$) at a moderate level, between the YFAS-C 2.0 total points and the BIS-11 total points ($p<0.001$) and the BIS-11 cognitive impulsivity subscale points ($p<0.001$) at a moderate level, and between the YFAS-C 2.0 total points and the BIS-11 motor impulsivity subscale points ($p<0.001$) and BIS-11 non-planning subscale points ($p<0.001$) at a weak level. The results of the correlation analyses are shown in Table 2.

Logistic regression analyses were used to determine relationships of age, gender, YFAS-C 2.0 total points, and BIS-11 total points with Internet addiction (Table 3). The analysis results showed a significant correlation of YFAS-C 2.0 total points ($p<0.001$) and BIS-11 total points ($p=0.001$) with Internet addiction.

DISCUSSION

According to our study results, a significant relationship was found between food addiction, impulsivity and Internet addiction. Food addiction scores were higher in adolescents with internet addiction. Despite the fact that several research have been conducted and published in the literature demonstrating a connection between food and Internet addiction [6,24], to the best of our knowledge, there are very few studies that have examined the relationship between Internet addiction and food addiction in the adolescent age group. A study conducted in 2023 of 180 obese and non-obese children aged 8-18 years reported that there could be a relationship between Internet addiction and food addiction [12]. 'Some studies have shown that Internet addiction is associated with eating disorders [25,26]. In another study of eating behaviours in adolescents with Internet addiction, it was seen that high Internet usage could have an impact on negative eating behaviours such as skipping meals, and snacking [24]. It has been reported that increased frequency of Internet use can lead to a decrease in physical activity and the development of irregular eating habits [12]. When it is considered that there is an extremely limited number of studies related to Internet addiction and food addiction in the adolescent age group, the current

study suggests that there is a need for more comprehensive studies related to the correlation between Internet addiction and food addiction in adolescents and the potential mechanisms of this relationship. The results of this study also show that food addiction could be a risk factor for Internet addiction.

Some previous studies have also shown higher impulsivity in adolescents with Internet addiction compared to those without, similar to the findings of the current study [8,9]. In the current study regression analyses, impulsivity was seen to be correlated with Internet addiction at a significant level. Using the DSM-IV criteria, some authors have suggested that Internet addiction is a condition associated with problems of impulse control [27,28]. Impulsivity is dealt with as an endophenotype of individuals at risk of developing addiction, primarily substance abuse and pathological gambling [29]. Another study also showed that the presence of impulsivity characteristics in adolescents was associated with Internet addiction [9]. Internet addiction is defined as difficulty in controlling internet use [8]. At the same time, impulsivity is the tendency to act prematurely without forethought, which is considered a lack of cognitive control. It is therefore suggested that impulsivity may play an inhibitory role in the stopping of addictive behaviors [30]. Adolescents are thought to be at greater risk of Internet addiction as in this youthful period they are more impulsive, and have weaker self-regulation capabilities for Internet use [3]. To the best of our knowledge, there is a limited number of studies that have examined the relationship between Internet addiction and impulsivity in the adolescent age group. In the light of the above-stated information, the results of this study suggest that impulsivity in adolescents could play an important role in terms of Internet addiction and impulsivity characteristics could be a significant risk factor for Internet addiction.

The current study results also demonstrated a significant positive correlation between food addiction and impulsivity. It is thought that more frequent and severe loss of control over food and eating is associated with impulsivity [31,32]. It has also been reported that characteristics such as an increase in reward-seeking and low capability of self-control can be seen in adolescence, and these can cause an increase in risk-taking behaviours [33,34]. When the neurodevelopmental characteristics of adolescence are taken into consideration, it has also been stated that the mechanism between food addiction and impulsivity has not been sufficiently understood [10]. Although the current study results support the findings in literature of a relationship between food addiction and impulsivity, the above-mentioned information suggests that there remains a need for more comprehensive studies of the potential mechanisms of the relationship between impulsivity and food addiction.

No study could be found in the literature that has evaluated Internet addiction, food addiction, and impulsivity together at the same time in adolescents. Therefore, this can be accepted as a strong aspect of this study. The results of this study demonstrate that food addiction and impulsivity in adolescents aged 12-18 years could be a risk factor for Internet addiction. Further studies of the relationships between Internet addiction, food addiction, and impulsivity would be helpful for the better understanding of the mechanisms of these important problems in adolescence and for the development of intervention methods.

Limitations of this study were primarily the cross-sectional design and relatively small sample size, which prevent the generalisation of the results. Another limitation could be said to be that self-reported scales were used for the evaluation of food addiction, impulsivity, and Internet addiction, and that the mental capaity of the children was not evaluated with objective intelligence tests.

CONCLUSION

The results of this study demonstrated that food addiction and impulsivity were determined at higher rates in adolescents with Internet addiction compared to those without. In addition, significant positive correlations were determined between Internet addiction and impulsivity and food addiction, and between food addiction and impulsivity. In the logistic regression analysis, food addiction and impulsivity were seen to be correlated with Internet addiction at a significant level and could be significant risk factors. Nevertheless, there is a need for further studies to be able to better understand the underlying mechanisms of impulsivity, food addiction and Internet addiction which can be observed in adolescence, and the relationships between these.

Informed Consent: Verbal and written informed consent for participation in the study was provided by all the study participants and their parents.

Conflict of Interest Declaration: There is no conflict of interest between the authors.

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Ethics Committee Approval: Study procedures were performed in accordance with the Declaration of Helsinki. The study received ethical approval from the ethics committee of Afyonkarahisar Health Sciences University Faculty of Medicine. (date: 11.08.2023, ethics committee no: 2023/330).

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Original Research

Fractal Analysis of Trabecular Alveolar Bone with Intrabony and Furcation Defects Using Periapical Dental Radiographs

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ABSTRACT

Objective: Fractal analysis (FA) is a non-invasive method that quantitatively measures complex patterned geometric structures present throughout the image. Trabecular morphology of the alveolar bone and the changes occurring in the trabeculae in case of periodontitis can be detected with this method. To examine the periodontal defects in human skull bones using the FA, to compare them with healthy alveolar bone regions.

Methods: Furcation and intrabony defects were artificially created in the mandible alveolar bones (n:24). Periapical X-ray images of alveolar bone regions containing teeth with defects were taken using the parallel technique. Fractal analysis was performed by box-counting method using Image J software on images from areas containing healthy and defective trabecular bone.

Results: No statistically significant difference was found between the fractal values of healthy tissue and bifurcation defetcs and between the healthy tissue and intrabony defects ($p>0.05$).

Conclusion: Many factors may have affected the outcomes; patient selection, imaging methods, sample size, Region of interest (ROI) selection-location and size, individual and anatomical variations. These variables need to be standardized as much as possible and the limitations of the method need to be improved.

Keywords: fractal analysis, fractal dimension, periodontal defect, periodontitis, periapical radiograph, trabecular bone.

INTRODUCTION

Chronic inflammation in periodontitis causes bone loss and the formation of bone defects [1]. Untreated alveolar bone destruction around the teeth eventually leads to tooth loss. It was determined that when the destruction in the alveolar bone reached 30-50%, it could be detected with conventional radiographs [2]. In this case, the initial stages of periodontitis may not be noticed. Additionally, radiographic analyzes are completely subjective and do not provide quantitative data. Nowadays, as technology is developing, efforts are being made to develop non-invasive diagnostic methods that include objective and quantitative data in radiographic analysis [3].

It has been proven that trabecular bone has fractal properties, and with the fractal analysis (FA) method, details in its structure that cannot be distinguished by the human eye can be evaluated [4]. One of the two important characteristics that represent fractal geometry is self-similarity, that is, any part resembles the whole object when viewed from different scales. The other feature is a varying of a determined scale. In addition, when the analyzed region is narrowed or expanded, it resembles the entire shape at every scale size [5]. If any part of the object resembles the original, the general shape of the self-similar object does not change. Fractal analysis is a non-invasive method that quantitatively measures complicated patterned geometric designs present all through the image [6,7]. While a decrease in the fractal dimension (FD) value indicates a simpler structure, an increase is observed in case of a more complex patterned structure [8]. There are many approaches to estimate FD, however, the most preferred is the box counting method and is suitable for two-part figure analysis.

There are studies reporting that differences in the trabecular morphology of the alveolar bone in disease and health status can be defined with this procedure [9]. However, there are a bounded number of research in the literature supporting the use of FA to reinforce the radiographic diagnosis of periodontal disease. Periapical films have been adopted by many researchers due to their clarity and high detail in determining the status of bone defects occurring in periodontal disease [10]. It is the most utilized radiography technique as an easy, practical and economic imaging method used in limited areas for any dental reason.

Main Points;

- No statistically significant difference was found in terms of fractal analysis (FA) between artificially created three-walled alveolar bone defects and defect-free areas in human skulls.
- Artificial defects that cannot fully replicate natural defects, the superposition of intact bone walls in two-dimensional radiographs, and the fact that the experiment was self-controlled may have affected the outcomes.
- There may be some standardization problems of the FA method, such as different imaging procedures, methodological differences in FA stages, individual differences, ROI size and location.
- Although the FA method is non-invasive, quantitative and safe, it has difficulties in clinical practice in terms of performing the procedure steps and ensuring standardization.

In the studies carried out, measurements of the trabecular structure of the alveolar bone surrounding the teeth were made, and the applicability of these measurements in certain areas of dentistry was discussed. According to current developments, these areas are; it includes the diagnosis of osteoporosis with dental radiographs, the effects of diabetes on the jaws, the effects of orthodontic therapy on the bone, follow-up of implant osseointegration, follow-up of periapical lesions, and evaluation of the diagnosis and follow-up of periodontitis [9].

The goal of this in vitro study is to examine the periapical radiographs of artificially created periodontal defect areas in human skull bones using the FA method, to compare them with healthy alveolar bone regions and to investigate possible bone structure differences.

MATERIALS AND METHODS

This in vitro study includes areas of intact alveolar bone with and without periodontal defects of molar teeth of human skull mandible bones. (Ethical approval: Health Sciences Ethics Committee, Ankara Yıldırım Beyazıt University, Date and no: 08.12.2022-19/1229). Alveolar bone fragments consisting of 24 teeth without metal restorations, fillings, pins or wires were included in the study. Furcation and intrabony defects were artificially created in the mandible bones with teeth. Elevated speed rotating diamond burs were applied for this process. The apex of the bony margins of each defect was accepted as the reference point. Then, periapical X-ray images of alveolar bone regions containing teeth with bone defects were taken using the parallel technique. Fractal analysis was performed on periapical x-ray images from areas containing healthy and defective trabecular bone.

Creation of Bifurcation Defects

About 2-4 mm of cortical and trabecular bone was removed from the bifurcation area of the mandibular molar teeth. Thus, gaps were prepared in the form of class 2 furcation defects (n:12).

Creation of Intrabony Defects

Vertical bone defects with three walls were readied mesially

or distally (2 mm bucco-lingual, 5 mm depth and 2 mm wide, approximately) from the interdental septum to the root of the mandibular molar tooth (n:12).

Image Acquisition

Alveolar bone areas with periodontal defects were coated with double layers of pink wax to simulate soft tissue before imaging. The X-ray machine (Gendex Digital Systems, Hatfield, PA, USA) used for digital intraoral periapical radiographs (at 65 kVp and 7 mA) was a device with a size 2 photostimulated phosphor plate detector (GXPS-500 PSP, Gendex Digital Systems, Bensheim, Germany). Images were recorded in 32 bit color and 64 lm (high) pixel size. Ex vivo imaging was performed (0.25 s image exposure time and 40 cm focus receptor distance) using equipment of the paralleling technique with standardized rectangular collimation (Rinn Manufacturing Company, Elgin, IL, USA) [11].

Fractal Dimension Analysis

Fractal analyses were applied in a software (ImageJ v1.53for Windows; National Institute of Health, Bethesda, MD, USA). Region of interest (ROI) was drawn in a square shape from the regions with defects (bifurcation - intrabony) and healthy trabecular bone (interdental). The ROI drawn for each tooth was made reproducible and standardized by keeping its size and location the same (25 × 25 pixels; Figure 1A, 1B).

The box counting method was completed by following the steps below, as performed by White and Rudolph (Figure 2) [8]. The replicated 25 × 25 pixel ROI image was blurred by applying Gaussian blur (sigma = 35 pixels, Figures 2A and 2B). 128 shades of gray were added to each pixel of the blurred image (Figure 2D), which was subtracted from the original image (Figure 2C). To convert the image to a 2-color black and white image, it was first converted to 8-bit format by using the "Type" option and then the "Threshold" option. Here the outlines of the bone marrow could be distinguished from the trabecular structure (Figure 2E). Image noise was reduced with the "Erode" option (Figure 2F) and existing areas were made more distinct with the "Dilate" option (Figure 2G). The "Invert" option was used to reveal the outline of the trabecular bone, thus converting white areas to black and black areas to white. (Figure 2H). With the "Skeletonize" option, the outlines of the trabecular bone were determined and it was ready for FA (Figure 2 I). "Fractal box counting" in the "Analyze" tab was then applied to calculate the FD.

Statistical Analysis

Statistical analyzes were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). Normal distribution of the data were analysed using Shapiro-Wilk test. Fractal dimensions of the healthy bone tissue with bifurcation defects, and with the intrabony defects were compared with student's t-test. The value of $p<0.05$ was determined as the limit of statistical significance. Before the study, to determine the required minimum sample size; Error level (a) = 0.05, power (1-b) = 0.80, f = 0.25, estimated correlation between repeated measurements = 0.75 values were used as criteria. It was calculated that a total of 24 periodontal defects, including 12 furcation and 12 intrabony defects, would be sufficient (GPower 3.1 program).

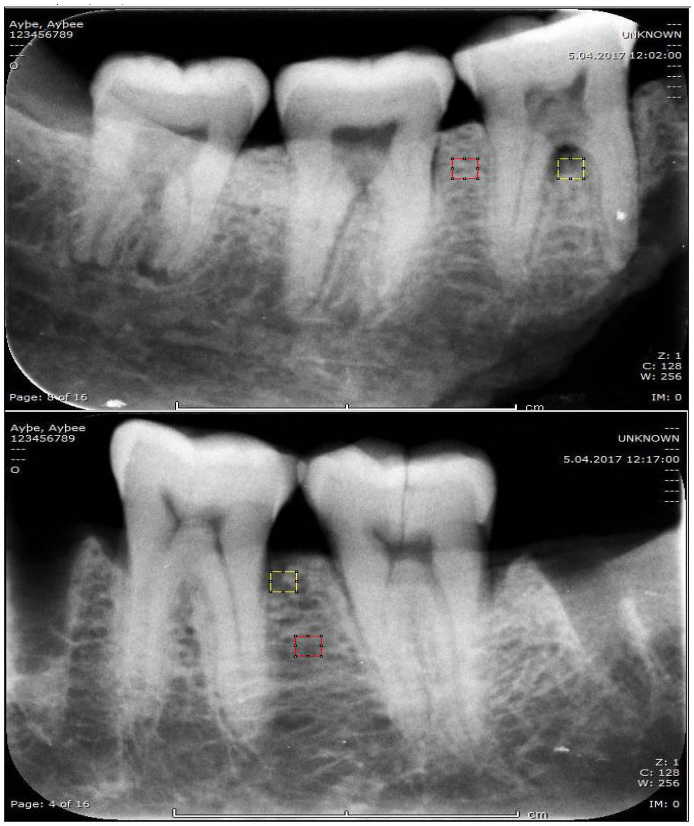

Figure 1. Square-shaped region of interest (ROI) drawn from bifurcation (Figure 1A) and intrabony defects (Figure 1B) and healthy interdental trabecular bone.

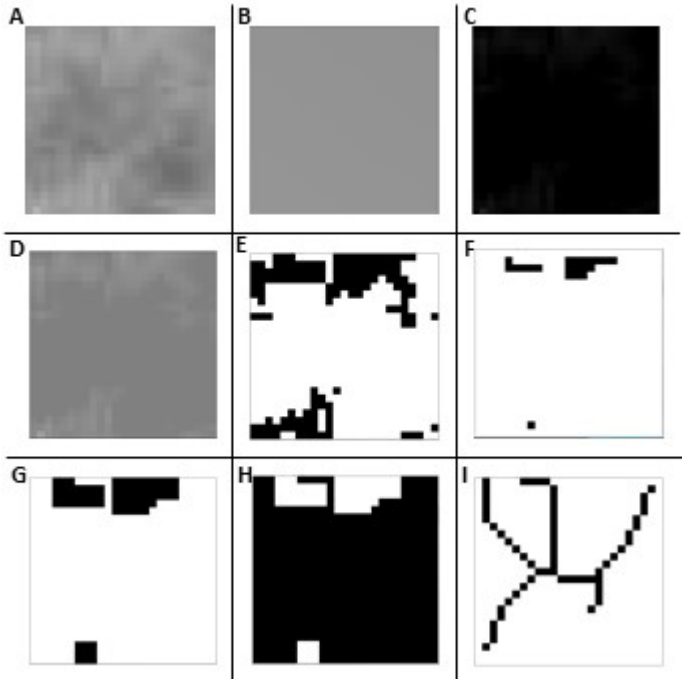

Figure 2. The box counting method was applied for fractal analysis. Blurred by applying Gaussian blur (sigma = 35 pixels, 2A and 2B). Subtracted from the original image (2C). Gray were added to each pixel (2D). Convert to black and white image, "Type" and "Threshold" (2E). Reduced image noise, "Erode" (2F). Made more distinct, "Dilate" (2G). Convert white areas to black and black areas to white, "Invert" (2H). Ready for FA, "Skeletonize" (2I). Calculate the fractal dimension, "Analyze".

RESULTS

The results were shown on table-1. No significant difference was found between the fractal values of healthy tissue and bifurcation defetcs ($p > 0.05$; t-test) and between the healthy tissue and intrabony defects ($p > 0.05$; t-test).

Table 1. Comparing the fractal dimension values of healthy bone tissue with the bifurcation defects and intrabony defects

	Mean±SD	n	t	p
Bifurcation defects	1.062±0.120	12	1.660	0.111
Healthy bone	0.979±0.125	12		
Intrabony defekt	1.082±0.083	12	1.300	0.207
Healthy bone	1.033±0.102	12		

DISCUSSION

Radiographic examination is a subjective evaluation that does not contain quantitative data [12]. Compared to immediate measurements at the time of surgery, intraoral radiographs measured nearly 1.4 mm less depth of bone defects around the teeth [13]; In this case, early stage bone defects may not be noticed in radiographic evaluation [14]. Fractal analysis has been frequently used in recent years to analyze bone and examine invisible details through various radiographic imaging methods [15–17]. In our study, we examined the healthy areas in the interdental region and the areas with periodontal defects using the FA method, and we could not detect any difference in-between the FD values.

In the first study to evaluate bone loss in periodontitis with FA using periapical radiographs, conventional radiographs were scanned and digitalized on a computer, and as a result, the FD values of the healthy group were found to be significantly higher than the periodontitis group [18]. Image losses occur due to the decrease in the gray value range of the radiographs digitized in this way, which affects the FD [3,19]. We can also state that our results are not similar because ROIs of different sizes were determined by the form and dimension of the interproximal bone in the study [18]. There are also studies stating that the location of the selected ROI from different areas of the jaws causes significant differences in FD values [20,21,22]. Updike et al., who selected the ROI from the apical region of the mandibular anterior teeth, showed that FA can be considered a diagnostic tool to distinguish between healthy and periodontitis subjects, but cannot determine the severity of periodontitis [23]. Our results may be different due to differences in ROI location or size. Similarly, Lin et al. reported that significant differences were observed in FD measurement of trabecular bone structure depending on the selected region [24].

In the study of Updike et al., significant difference in mean age between the healthy group and the periodontitis groups may have caused the difference in FD values. Belgin et al measured FD from digital periapical films and the measurements of the healthy group were found to be higher than the periodontitis group [14]. However, in the study, the mean age of the healthy group was statistically significantly lower than the periodontitis group, and this may have caused the difference in FD between the groups. Since our study was designed with self-control, individual factors were minimized and thus it was not affected by the age factor. While Ruttimann demonstrated in his in vitro

study that the calculated FD value of trabecular bone increased with the age variable [4], Amer et al. reported that the FD of trabecular bone had no relationship with age [25]. This indicates the possibility that a larger sample size could reveal a significant difference.

In the study of Cha et al., who used periapical radiographs, the FD values of the healthy group were found to be significantly higher than the values of the periodontitis group with furcation-involved defects [26]. However, while a significant difference was reported in the measurements in the furcation area, there was no significant difference in the measurements made from the top of the alveolar crest [26]. In our study, there was no significant difference between the FD values in the regions with in vitro created bone defects and the interdental regions without bone defects, but we think that the superposition due to the 3-wall nature of the defects we created and the fact that it was a self-controlled study affected our results.

While a significant difference was found in a study using periapical radiographs when measuring the FD of the trabecular bone of healthy and periodontitis groups [3], no significant difference was found in the study of Coşgunarslan et al. using CBCT images [27]. In another study comparing periapical and panoramic radiographs of the same patients, the authors reported that higher FD was calculated in periapical radiographs [28]. This suggests that differences in detail and resolution in imaging procedures may vary the outcomes in diseases with local bone loss. Periapical radiographs, which we preferred in this study, have better resolution and provide better detail, but their disadvantages are that they only allow imaging of a very limited area and the number of films to be taken increases when the full mouth is desired to be evaluated [29].

Based on the information in the literature that differences in image resolution may change FD values [14], the analysis of all images in our study was performed on the same computer and by the same physician. Radiographs with fillings, root canal treatment, lesions, bone fractures, or various artifacts in the relevant area that were likely to change our study results, and radiographs with no diagnostic value due to wrong positioning were excluded from the study. All films were taken with the same x-ray device, following the same irradiation parameters and the same positioning rules. In our study, digital periapical radiographs with the same format and high image quality were used.

The ROI we chose in our study was determined within the boundaries of trabecular bone, not including cortical bone, teeth or periodontal ligament space. According to a study on the selection of optimal teeth in determining periodontal bone loss, it was reported that measurements taken from the posterior regions of the mandible represent whole-mouth bone loss measurements [30]. In our study, we selected the ROI of the artificially created defects from the mesial, distal and furcation regions of the mandibular molar teeth and compared them with the ROI we selected from the interdetal areas of the teeth without any defects. Unlike some studies in the literature that similarly determined ROI from periapical films of the mandibular molar regions [3, 14], there is no significant difference in our study.

Although the existing dimensions and shapes of the interdental and interradicular bone to be analyzed are limiting in determining ROI dimensions, we preferred a square ROI of 25 × 25-pixels. Performing the ROI selection process manually may lead to individual errors and the inability to standardize the ROI location [31]. It is not possible to standardize by selecting ROI from exactly the equal location in each individual, which could give onto differences in measurements and is a limitation of this study. In a study in which lung cancer was evaluated using FA, it was reported that the main limitation of this method was the standardization problem [32]. Moreover, the artificially created defects in our study may not fully mimic real periodontal defects, and the defects created from samples may not fully replicate defects in living tissue.

We cannot make an evaluation in terms of gender, but since our study is self-controlled, we think that the gender variable does not affect our study. Additionally, there are studies that did not find a significant relationship between FD values and gender [23,14,20]. In the literature, many different studies investigating FA draw attention with contradictory results. For example, in a study where FD was calculated from periapical and panoramic X-rays of patients with a history of osteoporotic fracture, FD of patients in the osteoporosis group was found to be higher than the control group [28]. Contradictory results stand out in the literature regarding whether the FD of demineralized bone will increase [4,28,33] or decrease [34,35], as in osteoporosis. Geraets stated that there were conflicting results due to the image being obtained by different methods or the anatomical differences of the analized area [36]. Additionally, when performing FA, it should be remembered that all of the stages in the methodical series have an impact on the results. In fact,

mandibular dimension and structure, medical history, and individual differences in bone metabolism may be determinants that can affect the FD value [14].

CONCLUSION

There are many studies in the literature reporting that FA can be used in certain areas, that it produces contradictory results, or that it needs to be improved. There are difficulties in performing FA in clinical practice in terms of performing the process steps and ensuring standardization. Many factors such as patient selection, quality of the methods and different imaging methods, gender and age distributions, sample size, ROI size and location, anatomical variations and individual differences in ROI selection are likely to affect the results. It seems that the limitations of FA need to be improved, standardized, and performed in larger sample sizes.

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Original Research

Evaluation of Rubber Dam Use in Endodontic Treatments in Terms of Patients' Awareness Level, Acceptability, and Usage Experience

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ABSTRACT

Objective: This study aimed to measure patients' awareness levels about rubber dam used in endodontic treatments and their opinions about the necessity of its use, to evaluate their endodontic treatment experiences with rubber dam, and to compare the relationship between these opinions and treatment experience.

Methods: A survey including 16-questions was designed to access the participants' demographic information and previous rubber dam experiences, their current experience, and their preferences for the use of rubber dams in subsequent treatments. 9 questions aimed to measure the attitude via five-point Likert scale indicating measurements ranging from strongly agree to strongly disagree. The survey was completed when the number of participants reached 150 patients. Fisher-Freeman-Halton test, Fisher's Exact test and Pearson Chi Square test were used to compare categorical data, and multiple comparisons were examined with the Bonferroni Corrected Z test. $p<0.05$ was considered sufficient for statistical significance.

Results: 27.3% of the participants had previously received dental treatment with rubber dam. It was determined that there were significantly more patients with primary education levels among those who did not know the benefits of rubber dam use before coming to treatment ($p=0.013$). There was a statistically significant connection between the question "I was informed by my dentist about the reasons for using rubber dam before the treatment" and the question "I think the use of rubber dam is necessary for the dentist/patient" ($p<0.001$). In this study, only 4 people were observed who did not prefer rubber dam for the next treatment.

Conclusion: Before endodontic procedures, the advantages and necessity of rubber dam use should be explained to patients in detail and the questions in the patients' minds should be eliminated. The clinician should improve himself in the use of rubber dam and provide the patient with a more comfortable treatment.

Keywords: Endodontic treatment, patient, rubber dam, survey.

INTRODUCTION

Endodontic treatment is a method applied to prevent early tooth loss to ensure that the tooth remains in the mouth for a long time, and improve canal pathologies by eliminating microorganisms in the root canals [1]. For a successful root canal treatment, it is obligatory to isolate the tooth to be treated by preventing bacterial and saliva contamination throughout the entire treatment.

Infection control is one of the most essential factors determining the prognosis of endodontic treatment. For a high standard of endodontic treatment, cross-contamination must be prevented at each step of the treatment [2]. Today, the rubber dam is the most ideal option for tooth isolation and cross-contamination prevention and is considered an indispensable step of root canal treatment [3,4]. The rubber dam is defined as the gold standard in endodontic treatment by international organizations such as the European Society of Endodontology and the American Association of Endodontics [3,5].

The use of rubber dams is actively used today, with many advantages such as increasing the field of view of clinicians and allowing easier application of dental materials, as well as creating an aseptic work area, and preventing aerosol contamination. Rubber dam has many advantages for patients as well as clinicians. It provides a more comfortable treatment for the patient by eliminating soft tissues and protecting them from injuries, preventing swallowing and aspiration of endodontic instruments, and preventing the used solutions from coming into contact with the oral environment [6,7]. The use of rubber dam prevents cross-infection and protects both the patient, clinician, and clinical assistant staff from diseases transmitted through blood and saliva [8].

However, despite all these advantages, it has been observed that the use of rubber dam is not as widespread as desired [9,10]. Clinicians list the main reasons why they do not want to use rubber dam as they think that the application takes time and is difficult to use, they find the equipment costly, and some of their patients worry about the lack of knowledge about this application and do not accept it because they feel uncomfortable [11,12]. Many clinicians say that patients do not like rubber dam and do not want them to be used. However, studies have reported that patients have a positive attitude towards rubber dam and that they may prefer it at the next examination after experiencing it [11,13].

Main Points:

- The use of rubber dam is an indispensable step in root canal treatment.
- In this study, the attitudes of patients who undergo root canal treatment with rubber dam were evaluated.
- The survey was completed with 150 volunteer participants.
- Informing about rubber dam before root canal treatment affects patients acceptance of rubber dam use.
- The clinician should improve himself about the use of rubber dam and provide the patient with a more comfortable treatment.

Although there are studies investigating dentists' opinions on the use of rubber dams in Turkish society, there are few studies examining patients' awareness of rubber dams and their feedback on their usage experience [9,10,14-16].

The aim of this study was to measure patients' awareness levels about rubber dam used in endodontic treatments and their opinions about the necessity of its use, to evaluate their endodontic treatment experiences with rubber dam, and to compare the relationship between these opinions and treatment experience.

MATERIALS AND METHODS

Determining the Number of Participants

The sample size was calculated using the sample-size calculating software G*Power version V3.1.9.6 (Kiel University, Kiel, Germany) based on the data acquired from a previous study [15] and as a result of this power analysis of the study, the total number of participants in the study was determined as 150.

Survey Design

Ethics committee approval for the study was received from the Kocaeli University Non-Interventional Ethics Committee on 13 July 2023 with project number 2023/231. A survey including 16-questions was designed to access the participants' demographic information and previous rubber dam experiences, their current experience, and their preferences for the use of rubber dams in subsequent treatments. The 9 questions measuring attitude used a five-point Likert scale indicating measurements ranging from strongly agree (5) to strongly disagree (1). High scores reflected the participant's positive attitude towards the rubber dam. The average duration of the survey was 1-2 minutes.

Distribution of the Survey

This survey was completed by 150 volunteer patients who were indicated for endodontic treatment at Kocaeli University Faculty of Dentistry, Department of Endodontics, between August and September 2023. All of the participants in the survey were selected from volunteer patients who would undergo root canal treatment

by endodontic residents, and a rubber dam was applied before endodontic procedures. All endodontic residents performing the procedure routinely use rubber dams in their treatments. The rubber dam placement technique was accomplished first with the clamp and dam, then with the frame.

Before the treatment, participants were given brief information about the survey and a survey form was distributed to those who accepted to participate in the research. Participant names or personal information were not requested for the purpose of collecting objective data. The survey continued until the number of completed surveys reached 150. The data obtained from the completed surveys were entered into the database.

Statistical Analysis

Statistical analysis was performed with the IBM SPSS V23 (IBM Corp., Armonk, NY, USA) program. Fisher-Freeman-Halton test, Fisher's Exact test, Pearson Chi Square test were used to compare categorical data, and multiple comparisons were examined with the Bonferroni Corrected Z test. Analysis results were presented as frequency (percentage). $p<0.05$ was considered sufficient for statistical significance.

RESULTS

Participants in the study were 80 (53.3%) female and 70 (46.7%) male.The largest number of participants were between the ages of 26-40 with a rate of 35.3%. The demographic information and survey responses of the participants are given in Table 1.

27.3% of the participants had previously received dental treatment with rubber dam. There was no statistically significant connection between gender or age and the question "I knew the benefits of using rubber dam before the treatment." (p=0.257, p=0.373). It was determined that there were significantly more patients with primary education level among those who did not know the benefits of rubber dam use before coming to treatment (p=0.013) (Table 2).

There was a statistically significant connection between the question "I was informed by my dentist about the reasons for using rubber dam before the treatment" and the question "I think the use of rubber dam is necessary for the dentist/patient" ($p<0.001$). Detailed analysis of the answers given is shown in Table 3.

There was no statistically significant connection between the time of application and the question "I did not feel any pain during the rubber dam application" (p=0.426). There was no statistically significant connection between the time of the treatment and the question "I did not feel any pain during the rubber dam application" (p=0.762).

In this study, only 4 people were observed who did not prefer rubber dam for the next treatment. There was no statistically significant connection between the question " I would prefer to use a rubber dam in my next treatment." and gender (p=0.623). One of 4 people who did not prefer rubber dam selected the option "Disagree" to the question "I did not experience shortness of breath during the treatment with the rubber dam". A person who did not prefer rubber dam selected the option "Disagree" to the question "No solution got into my throat during the treatment with the rubber dam." Two of 4 people who did not prefer rubber dam responded to the question "I felt safe and comfortable during the treatment with the rubber dam" by saying "Disagree".

Table 1. Participants' responses to survey

	n	%
Gender		
Female	80	53,3
Male	70	46,7
Age		
13-25	38	25,3
26-40	53	35,3
41-55	38	25,3
Above 55	21	14
State of education		
Primary Education	21	14
High School	65	43,3

University	64	42,7
Have you ever used a rubber dam in your dental treatment?		
Yes	41	27,3
No	109	72,7
I knew the benefits of using rubber dam before the treatment.		
Strongly disagree	68	45,3
Disagree	20	13,3
Neutral	16	10,7
Agree	19	12,7
Strongly agree	27	18
I was informed by my dentist about the reasons for using rubber dam before the treatment.		
Strongly disagree	9	6
Disagree	5	3,3
Neutral	12	8
Agree	37	24,7
Strongly agree	87	58
The dentist's explanations were convincing about the necessity of using a rubber dam.		
Strongly disagree	6	4
Disagree	2	1,3
Neutral	12	8
Agree	28	18,7
Strongly agree	102	68
I think the use of rubber dam is necessary for the dentist.		
Strongly disagree	1	0,7
Disagree	-	-
Neutral	7	4,7
Agree	33	22
Strongly agree	109	72,7
I think the use of rubber dam is necessary for the patient.		
Strongly disagree	1	0,7
Disagree	-	-
Neutral	9	6
Agree	24	16
Strongly agree	116	77,3
I did not feel any pain during the rubber dam application.		
Strongly disagree	3	2
Disagree	2	1,3
Neutral	10	6,7
Agree	34	22,7
Strongly agree	101	67,3
I did not experience shortness of breath during the treatment with the rubber dam.		
Strongly disagree	2	1,3
Disagree	4	2,7
Neutral	3	2
Agree	26	17,3
Strongly agree	115	76,7
No solution got into my throat during the treatment with the rubber dam.		
Strongly disagree	3	2

Disagree	3	2
Neutral	4	2,7
Agree	25	16,7
Strongly agree	115	76,7
I felt safe and comfortable during the treatment with the rubber dam.		
Strongly disagree	1	0,7
Disagree	2	1,3
Neutral	3	2
Agree	20	13,3
Strongly agree	124	82,7
I would prefer to use a rubber dam in my next treatment.		
Yes	146	97,3
No	4	2,7
Placement Time of rubber dam		
Less than 1 min	100	66,7
1-5 min	32	21,3
6-10 min	6	4
11-20 min	12	8
Treatment time with rubber dam		
Less than 15 min	12	8
15-60 min	109	72,7
More than 60 min	29	19,3

Table 2. Relationship between state of education and rubber dam knowledge level

	I knew the benefits of using rubber dam before the treatment.					**p**
	Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**	
State of Education						
Primary education	17 (81)[a]	1 (4,8)	1 (4,8)	1 (4,8)	1 (4,8)	
High School	20 (30,8)[b]	13 (20)	6 (9,2)	12 (18,5)	14 (21,5)	**0,013***
University	31 (48,4)[b]	6 (9,4)	9 (14,1)	6 (9,4)	12 (18,8)	

* Fisher-Freeman-Halton test; [a-b]: There is no difference between groups with the same letter

Table 3. The relationship between being informed by the dentist and dentist/patient necessity

	I was informed by my dentist about the reasons for using rubber dam before the treatment.					**p***
	Strongly disagree	**disagree**	**Neutral**	**Agree**	**Strongly Agree**	
I think the use of rubber dam is necessary for the dentist.						
Strongly disagree	0 (0)	0 (0)	0 (0)	0 (0)	1 (1,1)	**<0,001**
Neutral	1 (11,1)[ab]	0 (0)[ab]	3 (25)[b]	2 (5,4)[ab]	1 (1,1)[a]	
Agree	1 (11,1)[ab]	1 (20)[ab]	5 (41,7)[ab]	16 (43,2)[b]	10 (11,5)[a]	
Strongly Agree	7 (77,8)[ab]	4 (80)[ab]	4 (33,3)[b]	19 (51,4)[b]	75 (86,2)[a]	
I think the use of rubber dam is necessary for the patient.						
Strongly disagree	0 (0)	0 (0)	0 (0)	0 (0)	1 (1,1)	**<0,001**
Neutral	2 (22,2)	1 (20)	2 (16,7)	1 (2,7)	3 (3,4)	
Agree	0 (0)[ab]	1 (20)[ab]	4 (33,3)[b]	13 (35,1)[b]	6 (6,9)[a]	
Strongly Agree	7 (77,8)[ab]	3 (60)[ab]	6 (50)[b]	23 (62,2)[b]	77 (88,5)[a]	

*Fisher-Freeman-Halton test; [a-b]: There is no difference between groups with the same letter.

DISCUSSION

The rubber dam introduced by Dr. Barnum in the 1860s has increased its importance day by day and has become accepted as the standard in root canal treatment. Through the rubber dam, which has many benefits for patients and clinicians, a more professional, comfortable and safe treatment is possible [17,18]. Although rubber dam has been known for a long time and has many advantages, its use is not as widespread as desired. A study conducted in Turkey found that 16.7% of dentists preferred the use of rubber dams during root canal treatment [10]. Among the reasons for not using rubber dam, the patient is uncomfortable and refuses to apply rubber dam. However, contrary to popular belief, patients do not reject the use of rubber dam and may prefer treatment with it at the next treatment [7,19]. In the study conducted by Kaşıkçı et al. [4] among endodontists and endodontic Resident/Ph.D. students only, 89.1% of the participants stated that they applied rubber dam in their routine endodontic treatments, especially after the COVID-19 pandemic. In this survey study, the opinions of patients who underwent root canal treatment with rubber dams and their rubber dam post-application experiences were examined.

The first treatment experience with rubber dam affects the patient's general attitude towards rubber dam [6]. 72.7% of the participants had root canal treatment with rubber dam for the first time. 97.3% of the participants preferred the use of rubber dam in their subsequent treatments. A good treatment experience may increase the acceptability of rubber dam in the next treatment.

The majority of patients did not know about rubber dams before the appointment. It has been shown that providing information about the importance and benefits of rubber dam before treatment has a very positive effect on patients' preference for treatment with rubber dam isolation [20]. This survey study, similar to many studies, showed that informing patients before treatment affected the acceptance of rubber dam use [13,20,21].

According to the findings, explaining the advantages of using rubber dam plays an important role in convincing the patient. It is very important that the clinician informs the patient about the reasons and benefits of using a rubber dam before the procedure. The fact that an adequate explanation was given to the majority of patients before the application convinced them that the rubber dam would be beneficial to both themselves and the clinicians.

The second most common cause of accidental swallowing in adults is dental procedures. Swallowing or aspirating instruments used during endodontic treatment can be life-threatening. The use of a physical barrier such as a rubber dam is of great importance in preventing unwanted accidents [22,23]. In this study, almost all of the patients felt safe and comfortable during rubber dam treatment.

The majority of patients participating in this study expressed positive preferences for the use of rubber dam in their next treatment. Similar results were found in other studies examining patients' attitudes towards rubber dams [13,21,24,25]. The results obtained support that patients do not view the rubber dam application negatively and even want to apply it.

The experience of the person applying the rubber dam may affect the patient's thoughts and preferences about the application. Görduysus [16] showed that the acceptability of the rubber dam increases as experience increases. With a good understanding of the basic principles and sufficient experience, rubber dam insulation can be achieved in a very short time [19]. In this study, no significant relationship was found between rubber dam application time or treatment duration and patients' preferences. This may be because the clinicians performing the practice already have similar experiences.

It is stated that the pain and discomfort felt during rubber dam application affect the choice of use in the next treatment [20,26]. In this study, most patients did not feel pain during rubber dam application. By ensuring the depth of anesthesia and selecting the appropriate clamp, patients' pain can be reduced during rubber dam application.

Although the survey questions were written in simple sentences, the possibility that the patients did not understand the questions correctly can be considered a limitation of the study. Additionally, the evaluations were made after only a single session of rubber dam experience. It is recommended to conduct a study with more participants in which different factors regarding the use of rubber dam are evaluated.

CONCLUSION

It is observed that when patients are informed correctly about rubber dam by their clinicians before endodontic treatment, patients' positive attitude towards the use of rubber dam increases and they want to prefer the use of rubber dam in their next endodontic treatment. Before endodontic procedures, the

advantages and necessity of rubber dam use should be explained to patients in detail and the questions in the patients' minds should be eliminated. The clinician should improve himself in the use of rubber dam and provide the patient with a more comfortable treatment.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest: The authors deny any conflict of interest related to this study.

Ethical Approval: Non-interventional ethics committee of the Kocaeli University approved this in *vitro* study (GOKAEK-2023/12.36).

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Original Research

Stress-Responsive MAPK Signaling Pathway with Proliferation and Apoptosis in the Rat Testis After 2100 MHz Radiofrequency Radiation Exposure

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ABSTRACT

Objective: Mobile phone technology has progressed quickly in recent years. Cell phones operate using radiofrequency radiation (RFR), and the complete biological impacts of RFR remain unidentified. Thus, we aimed to investigate the potential effects of 2100 MHz radiofrequency radiation exposure on the stress-responsive JNK/p38 MAPK pathway, apoptosis and proliferation in rat testis.

Methods: RFR groups were created with 2100 MHz RFR exposure for acute (2 h/day for 1 week) and chronic (2 h/day for 10 weeks) periods. Sham groups were kept under identical conditions without RFR. The cell apoptosis and histopathological changes in testis were evaluated. Immunolocalization of PCNA, active caspase-3, Bcl-xL, p-JNK and p-p38 were analyzed by immunohistochemistry, the total protein expressions were identified by Western blot.

Results: There were no differences between RFR and sham groups by means of histopathology and TUNEL analysis. Also, the expression levels and the immunolocalization patterns of PCNA, active caspase-3 and Bcl-xL proteins were not altered. p-JNK and p-p38 protein expressions were prominently elevated in acute and chronic RFR groups.

Conclusion: In conclusion, 2100 MHz RFR exposure had no considerably deleterious consequences on cellular proliferation and apoptosis processes in rat testis. However, increased expression of stress-activated protein kinases, p-JNK and p-p38, suggests the involvement of the MAPK signaling pathway as a critical (may be detrimental) cellular response.

Keywords: Apoptosis, MAPK pathway, proliferation, radiofrequency radiation, rat, testis

INTRODUCTION

Throughout the years, the technologies of our daily devices have undergone upgrades, leading to significant advancements in the world due to the rapid progress of the technology. Mobile phones are one of the most commonly used technological devices in today's world. However, they work with radiofrequency radiation (RFR). Thus, it is crucial to investigate any possible negative impacts that mobile phones may have on human health. The quantity of studies in this area has drastically expanded during the last century. Despite the fact that the mechanisms

underlying RFR's biological effects have not yet been fully elucidated, RFR has been categorized as a potential carcinogen by the International Agency for Research on Cancer in 2017 [1].

The majority of studies indicated that RFR exposure and unfavorable biological consequences are directly correlated [2-4]. The studies report that RFR increases reactive oxygen species (ROS) [3], causes fatigue and headache [4], affects brain signals [5], decreases sperm count [6] and causes testicular apoptosis [7]. Oxidative stress (OS) particularly takes a special attention related to RFR exposure recently as it has a significant potential to have these biological side effects. Oxidative stress arises because of increased levels of ROS or oxidants. The increased free radical production or weakening of the antioxidant defense system can negatively change lipids, proteins, DNA and trigger a number of human diseases. Thereafter, ROS acts as a double-edged sword. They also function as key signal molecules in fertility related biological processes including fertilization, capacitation and hyperactivation of sperm and fusion of oocyte and sperm plasma membrane [8]. For instance, excess ROS can induce the dysfunction of sperm through motility loss, DNA and lipid peroxidation [9]. In an ultrastructural study in which rats were applied to long-term (3 months) low-dose RFR, no significant alteration was found in the testicular weight and seminiferous tubule diameters; however, vacuolization in Sertoli cells was reported [10]. Moreover, there have been studies indicating that carrying a mobile phone adjacent to testis may have detrimental effects on sperm concentration and motility [7]. Besides, Leydig cells' secretory activity (serum testosterone level) was found to be reduced after 220 MHz RFR exposure in male adult rats [2]. It was also noted that male rats exposed to Wi-Fi RFR for a year experienced decreased epididymal and seminal vesicles weight, a decrease in tunica albuginea thickness and seminiferous tubule diameter, as well as an increase in sperm head abnormalities [11].

Main Points:

- 2100 MHz RFR exposure does not alter testicular cell proliferation and apoptosis
- Expression of stress-activated MAPKs were increased after exposure to 2100 MHz RFR
- A special attention is needed to the molecular mechanism of MAPK signaling pathway

It is known that OS induces apoptosis in cells by activating multiple signaling pathways [12]. The mitogen-activated protein kinase (MAPK) cascade is defined as a critical pathway for transmitting stress-related stimuli [13]. Growth factors, hormones, radiation, carcinogenic agents and inflammation are some examples of stimuli that might activate the MAPK cascade. This activation results in different biological reactions like cell division, differentiation, migration and apoptosis [13]. The MAPK family is consisted of proteins p38, c-Jun NH2-terminal kinases (JNKs), and extracellular signal-regulated kinases (ERKs) [13]. The growth stimuli can activate ERK1 and ERK2 and contribute to cell growth; however, JNK and p38 MAPKs, which are stimulated by some environmental stress and inflammatory factors, stimulate cell apoptosis and the inhibition of growth [14]. The mammalian testis has a variety of MAPK isoforms. MAPKs function in spermatogenesis, maturation and capacitation of sperm [15] and also in the fertilization of oocytes [16].

Our research group have recently reported that p38/JNK-mediated MAPK signaling was triggered significantly in the rat testis after 900 MHz RFR exposure [17]. However, it is unknown whether the p38/JNK-mediated MAPK signaling is also involved in the rat testis after 2100 MHz RFR exposure, which is used in global mobile communication systems (GSM). Currently, it is clear that the JNK/p38 MAPK pathway is important in biological reactions in response to ROS. Since the effects of the JNK/p38 MAPK cascade on cell survival or cell death events have not been completely elucidated, here our purpose is to examine the proliferation/apoptosis balance and the JNK/p38 MAPK proteins in the rat testis after acute and chronic 2100 MHz (Universal Mobile Telecommunication System, UMTS, frequency, UMTS-2100) RFR exposure.

MATERIALS AND METHODS

Study Groups

The experimental animal protocols utilized in this study received approval from the Akdeniz University Local Ethics Committee for Animal Experiments (protocol number: 758/2018.10.07). Male Wistar albino rats weighing 250-300 g were categorized as Group 1 (sham control group for one week-acute sham: aSh), Group 2 (sham control group for 10 weeks-chronic sham: chSh), Group 3 (2100 MHz RFR exposure group for one week-acute RFR: aRFR) and Group 4 (2100 MHz RFR exposure group for 10 weeks-chronic RFR: chRFR) (n = 6/each group). Rats were kept in plexiglass tubes at a distance of 10 cm radially around

the 2100 MHz radiofrequency (RF) emitting antenna. Rats in Groups 1 and 3 were held in plexiglass tubes for one week (2 h/day, 5 days per week). On the other hand, rats in Groups 2 and 4 were held in plexiglass tubes for 10 weeks (2 h/day, 5 days per week). Radiofrequency simulator device was retained in OFF state for the control groups and ON state for RFR exposure groups throughout the experiments. Animals (4 rats/cage) were kept in a 12 h light/dark cycle during the experiment periods and provided tap water and commercial rat chow.

Radiofrequency Radiation Treatment

Except for the 2100 MHz RFR frequency and the distance of the rats from the antenna, the details of the experimental setup and RFR application were as previously reported [17]. An RF generator which produce 2100 MHz RFR (2100 MHz UMTS Simulator; Everest Corp., Adapazari, Türkiye) was used to represent the exposure of the UMTS. 2100 MHz used as carrier frequency and the pulse width was 0.577 ms. The modulation frequency was 217 Hz, and the generator's power range was 0-2 W. The electric-field potency over the rat's head at a distance of 10 cm from the antenna was 35.2 V/m for 2100 MHz when the experiment was in "signal on" status.

Using a finite integration technique (FIT) program, CST Microwave Studio (3DEXPERIENCE, Dassault Systemes, Hamburg, Germany), dosimetry simulations were performed. The FIT was established by Weiland [18]. The electrical features of the testis tissue of the simulation model rats were measured at the operating frequency. At 2100 MHz, the average specific absorption rate (SAR) for the whole-body was 0.16 W/kg. On average, the SAR value for the testis was 0.0347 W/kg.

Sample Collection and Histopathological Analysis of the Testis

Rat testicular tissues were dissected at the end of the experiments as described previously [17]. The potential consequences of acute and chronic 2100 MHz RFR exposure on testis histopathology were investigated after sections were deparaffinized and stained with periodic acid-Schiff (PAS).

Immunohistochemistry

The immunolocalization patterns of proliferating cell nuclear antigen (PCNA), active caspase-3, Bcl-xL, phosphorylated-JNK (p-JNK) and phosphorylated-p38 (p-p38) proteins were carried out in the paraffin sections of testis tissues. PCNA (cat#2586S; Cell Signaling, 1:600), Bcl-xL (cat#2764S; Cell Signaling, 1:300), active caspase-3 (cat#9661S; Cell Signaling, 1:300), p-JNK (cat#44682G; Thermo Fisher Scientific, 1:200) and p-p38 (cat#4511S; Cell Signaling, 1:100) antibodies were used as primer antibodies. Immunohistochemistry protocol is described in more detail in our recent paper [17]. The threshold quantification of the immunohistochemical images was further evaluated blindly for the localization patterns by using ImageJ version 1.46 (NIH)

SDS-PAGE and Western Blotting

The membranes were incubated with primary antibodies in TBS-T and 5% nonfat dry milk overnight (cat#2586S, PCNA, Cell Signaling, 1:1000; cat#2764S, Bcl-xL, Cell Signaling, 1:1000; cat#9661S, active caspase-3, Cell Signaling, 1:500; cat#44682G, p-JNK, Thermo Fisher Sci., 1:1000 and cat#4511S, p-p38, Cell Signaling, 1:500). The details for the Western blot protocol were previously presented [17]. The optical densities of the Western blot bands were standardized to OD values of beta actin, and the relative amounts of proteins were analyzed by ImageJ version 1.46 (NIH).

Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling (TUNEL) Assay

The apoptotic cells were identified by TUNEL method with a commercial TUNEL kit (cat#1684809, In situ Cell Death Detection Kit, AP, Roche Diagnostics, Germany) as published previously [17]. The number of TUNEL-positive/negative seminiferous tubules were counted blindly and the percentages of positive seminiferous tubules were further calculated for experimental groups (% apoptotic index).

Statistical Analysis

The statistical analysis between acute and chronic RFR periods versus control groups of the related week was compared by SigmaStat 3.5 (Systat Software, USA). All normally distributed data were analyzed by one-way analysis of variance (ANOVA). However, data were compared using Kruskal-Wallis test followed by Dunn's test, or the Mann-Whitney U test if the data are not normally distributed. The results were presented as mean ± SEM. The statistical significancy of the data was accepted as $p < 0.05$.

RESULTS

Histopathological Evaluation of the Testis Tissues After 2100 MHz RFR Exposure

Leydig cells, acrosome structures, and seminiferous tubule basement membranes were clearly observed in the testis

sections from all experimental groups by PAS staining (Figure 1). However, no prominent histopathological differences were detected for acute or chronic RFR groups compared to control groups.

Proliferation and Apoptosis of the Testicular Cells After 2100 MHz RFR Exposure

Immunolabeling cells with PCNA revealed that PCNA-positive cells were similarly localized as a single layer along the basement membrane of the basal compartment of the seminiferous tubules in RFR versus related control groups (Figure 2A-D). Immunoreactivity for PCNA was observed in the spermatogonia nuclei and some spermatocytes. In line with no differences in the distribution patterns, no significant alterations were observed in neither the PCNA staining intensities by ImageJ analysis (Figure 2E) nor the total protein levels by Western blotting between the control and RFR groups (Figure 6A, B).

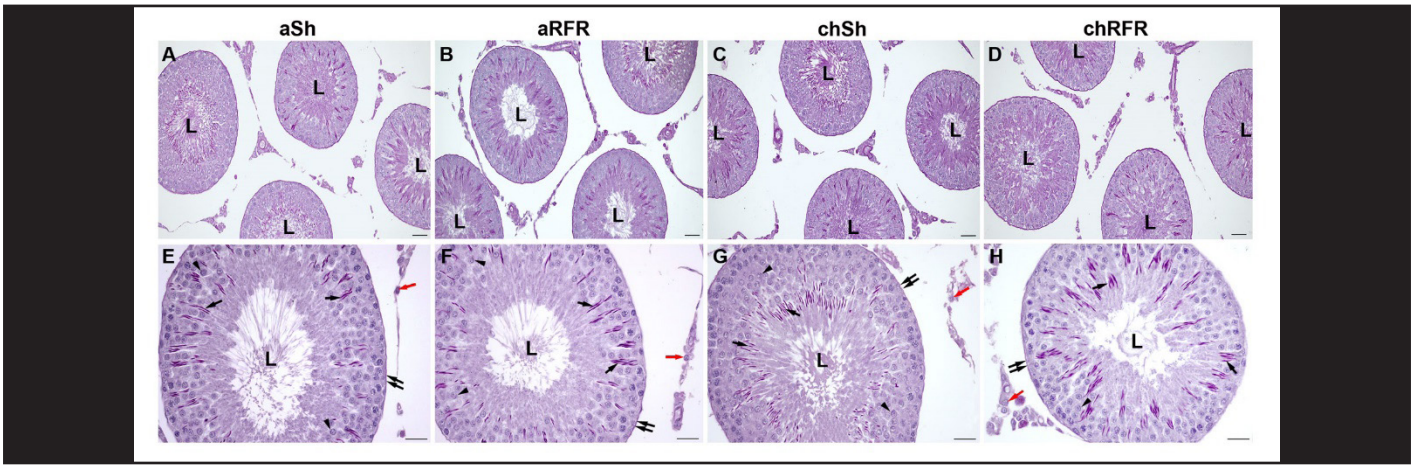

Figure 1. PAS staining in the rat testis tissues of the control and RFR groups. Please observe PAS-positive elongated spermatids (arrows), basement membrane (double arrows), acrosomal caps (arrow heads) and Leydig cells (red arrows). Acute control (aSh): A, E; acute RFR (aRFR): B, F; chronic control (chSh): C, G; chronic RFR (chRFR): D, H; lumen (L). Scale bars present 50 µm

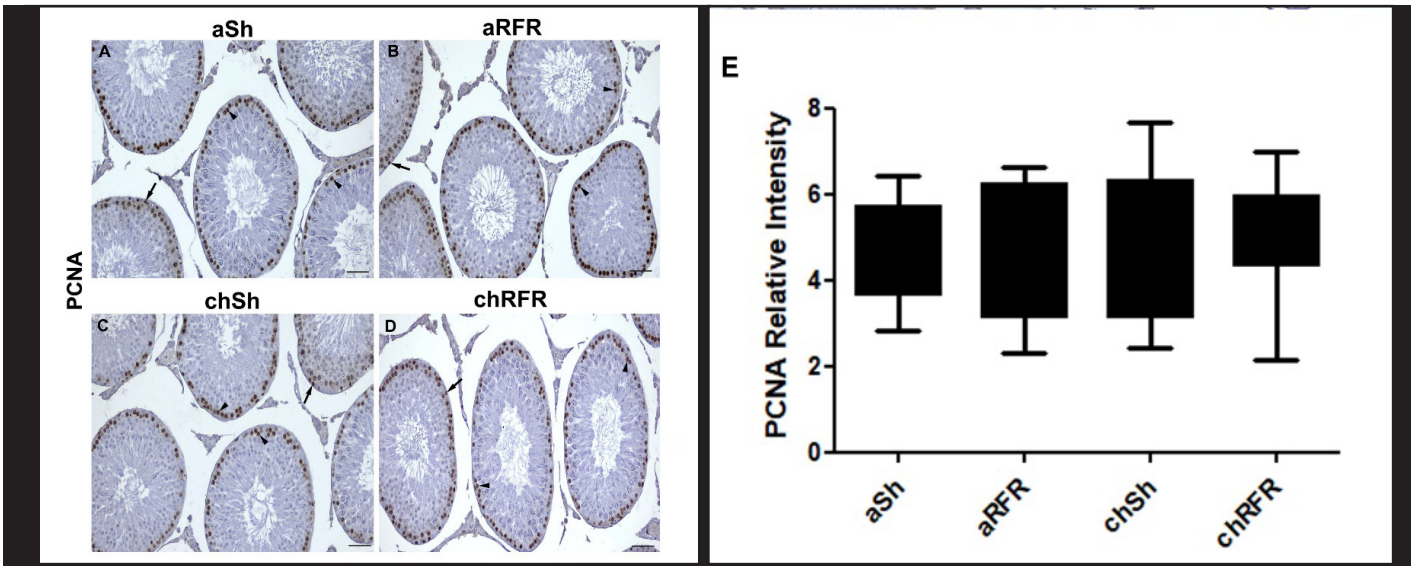

Figure 2. PCNA immunostaining in the rat testis tissues of the control and RFR groups (A-D) and the data for the ImageJ analysis of the immunostaining (E). Spermatocytes (arrow heads), spermatogonial cells (arrows). Acute control (aSh): A; acute RFR (aRFR): B; chronic control (chSh): C; chronic RFR (chRFR): D. Scale bars present 50 µm

The active caspase-3 immunostaining was identified mostly in postmeiotic germ cells, predominantly in round spermatids in the rat testis (Figure 3A-D). However, immunostaining of Bcl-xL was detected in the cytoplasmic areas of round spermatids and spermatocytes (Figure 3E-H). Additionally, Bcl-xL was expressed in elongated spermatids and mature spermatozoa (Figure 3E-H). As observed with PCNA immunostaining, the intensity and distribution patterns of active caspase-3 (Figure 3I), an enzyme responsible for the majority of proteolysis during apoptosis, and Bcl-xL (Figure 3J), as an anti-apoptotic protein, were not noticeably different in RFR groups with ImageJ analysis. The analysis of the protein bands by Western blot also indicated that the total protein expressions of both active caspase-3 and Bcl-xL proteins in the testicular tissue lysates from RFR-exposed groups were not altered compared to those in the testis tissues from control groups (Figure 6A, C, D).

In addition to these markers, apoptosis was evaluated by the TUNEL assay. TUNEL-positive cells were determined particularly in spermatocytes, spermatogonia and Leydig cells. Our data indicated that there was no increase in the apoptotic activity revealed by the TUNEL method in the testis tissues of the RFR groups (Figure 3K). Therefore, the effects of 2100 MHz RFR exposure on spermatogenesis could not be obviously identified as a death and/or an alteration in the testicular cell proliferation.

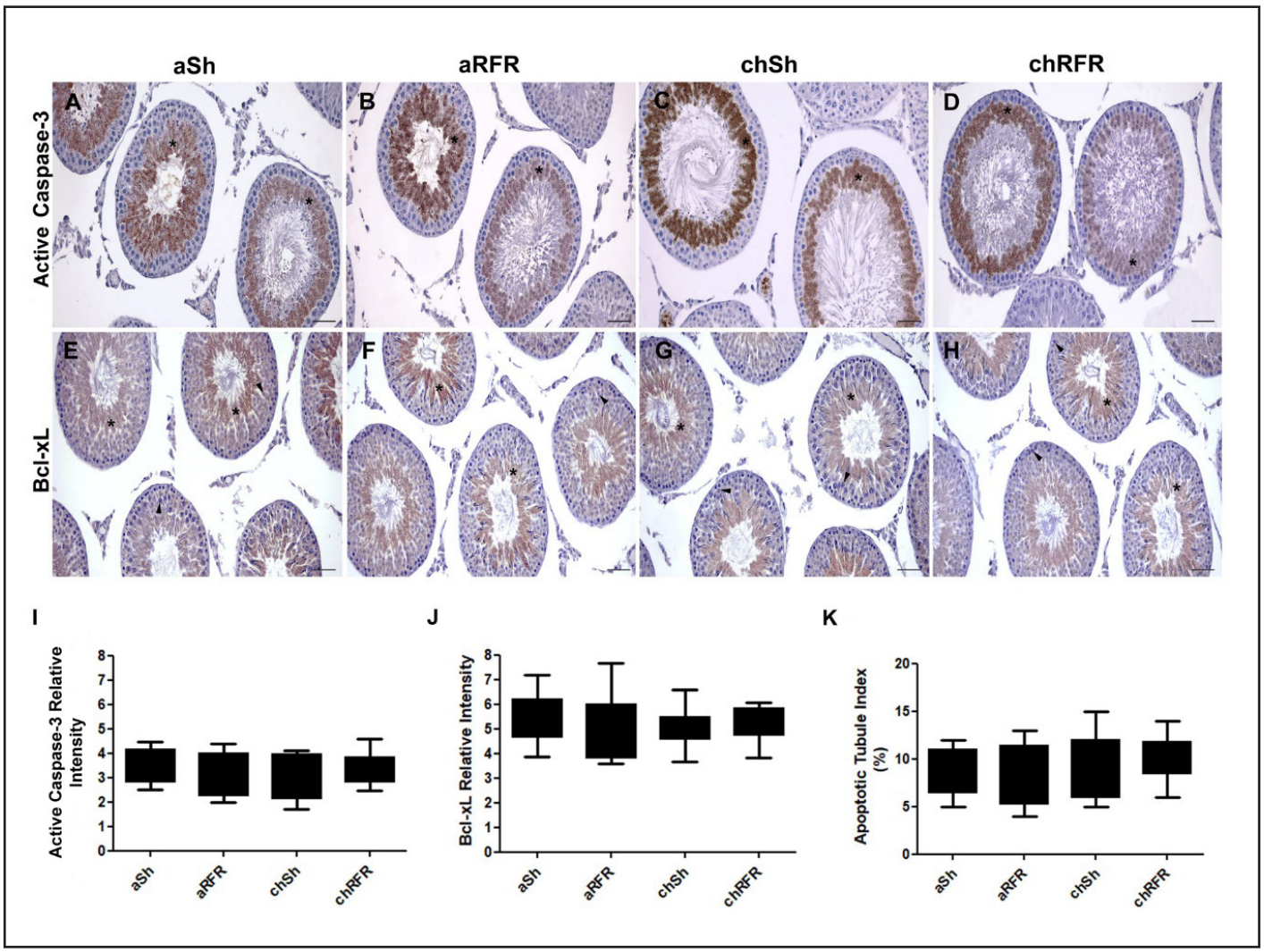

Figure 3. Active caspase-3 (A-D), Bcl-xL (E-H) immunostaining, and the apoptotic tubule index (K) in the rat testis tissues of the control and RFR groups. ImageJ analyses of active caspase-3 (I) and Bcl-xL (J) immunostaining are also presented. Postmeiotic germ cells (asterisks), spermatocytes (arrow heads). Acute control (aSh); acute RFR (aRFR); chronic control (chSh); chronic RFR (chRFR). Scale bars present 50 μm

Altered Expression of JNK and p38 Proteins After 2100 MHz RFR Exposure

We detected a marked testicular expression for p-p38 and p-JNK MAPK proteins in RFR groups. Although p-JNK immunoreaction was detected in the nuclei of spermatocytes, spermatogonia, and the heads of elongated and round spermatids in some seminiferous tubules and also in Leydig cells (Figure 4A-H), a considerable increased expression of p-JNK protein in both acute ($p < 0.001$) and chronic ($p < 0.001$) RFR groups were detected by ImageJ analysis (Figure 4I). Similarly, Western blot analysis indicated an increased total protein level of p-JNK protein in the testis lysates (Figure 6A, E).

p-p38 expression was similarly located in the spermatocyte nuclei, elongated spermatids, round spermatids, and some of the Leydig cells (Figure 5A-H). As of p-JNK, a dramatic increase in the staining intensity for p-p38 in the testis sections from RFR groups was determined by ImageJ analysis ($p < 0.001$) (Figure 5I). Our Western blot data further confirmed that exposure to 2100 MHz RFR resulted in an increased expression of p-p38 protein for both acute and chronic RFR groups (Figure 6A, F).

DISCUSSION

Modern society has become accustomed to using any technological device or product to perform almost anything. In this line, mobile phones have a crucial role in our daily lives as they are the easiest form of communication, and they have become an indispensable part of our lives. Although there is widespread concern about the risks of RFR exposure from mobile phones on human health, perceptions of risk associated with other sources of electromagnetic fields must be investigated. It has been suggested that RFR may cause oxidant damage [3], brain electrical activity changes [5], DNA damage [19] *etc*. RFR may also have detrimental effects on the testis tissues [17, 20]. Therefore, we investigated the consequences of 2100 MHz RFR exposure on the rat testis by means of cell proliferation, apoptosis and the MAPK signaling pathway including p-p38 and p-JNK stress-activated protein kinase (SAPK) proteins.

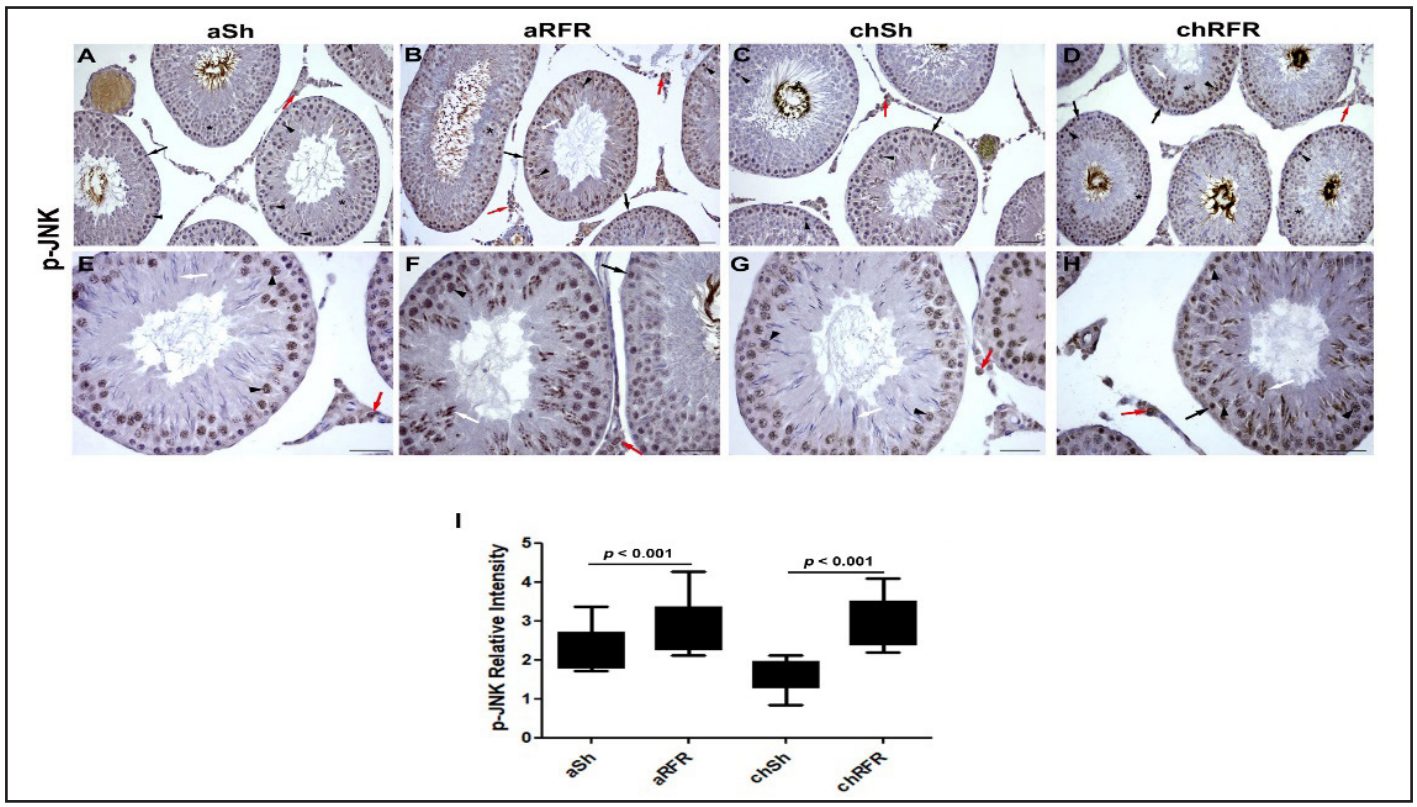

Figure 4. p-JNK immunostaining in the rat testis tissues of the control (A, E, C, G) and RFR (B, F, D, H) groups and their ImageJ analyses (I). p-JNK-positive spermatocytes (arrow heads), spermatogonial cells (arrows), round spermatids (asterisks), Leydig cells (red arrows) and elongated spermatids (white arrows). Acute control (aSh); acute RFR (aRFR); chronic control (chSh); chronic RFR (chRFR); L, lumen. Scale bars present 50 µm

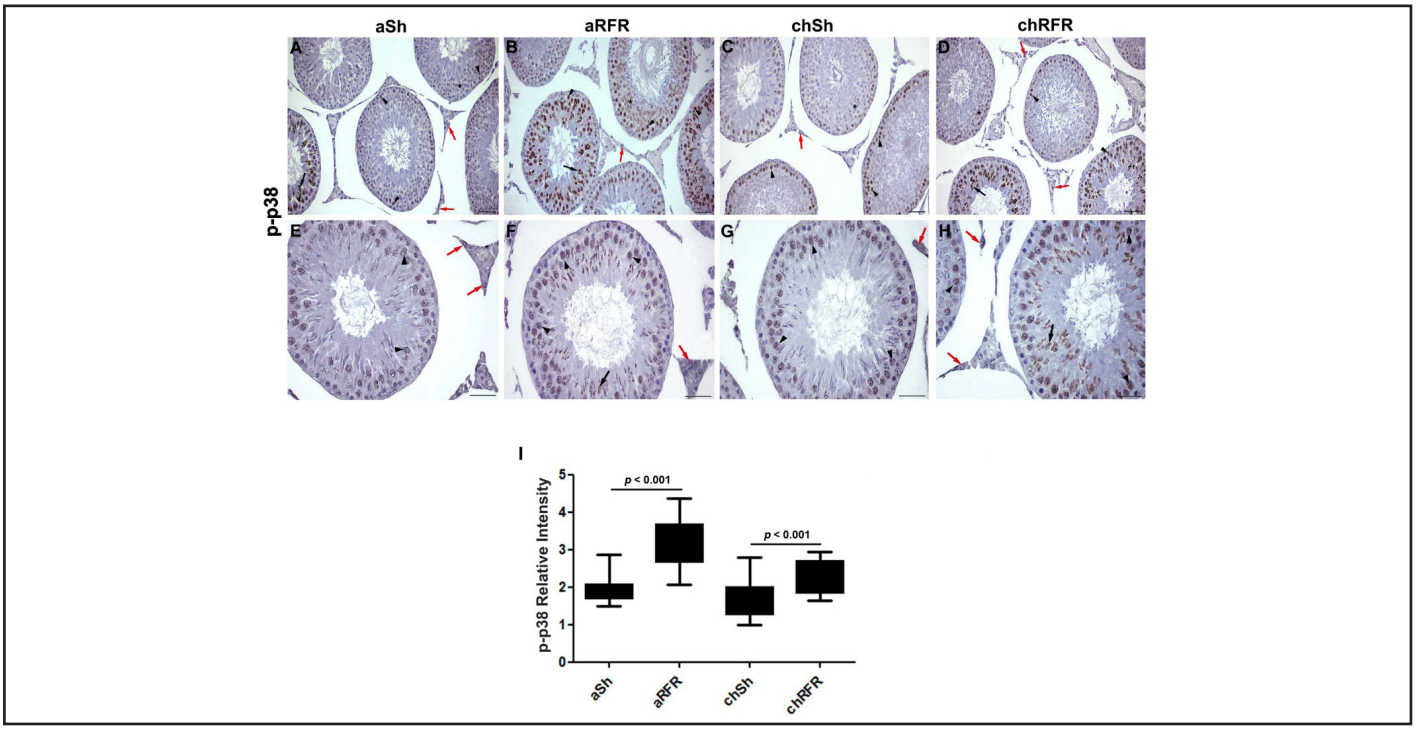

Figure 5. p-p38 immunostaining in rat testis tissues of control (A, E, C, G) and RFR (B, F, D, H) groups and their ImageJ analyses (I). p-p38-positive round spermatids (asterisks), spermatocytes (arrow heads), Leydig cells (red arrows) and elongated spermatids (arrows). Acute control (aSh); acute RFR (aRFR); chronic control (chSh); chronic RFR (chRFR); L, lumen. Scale bars present 50 µm

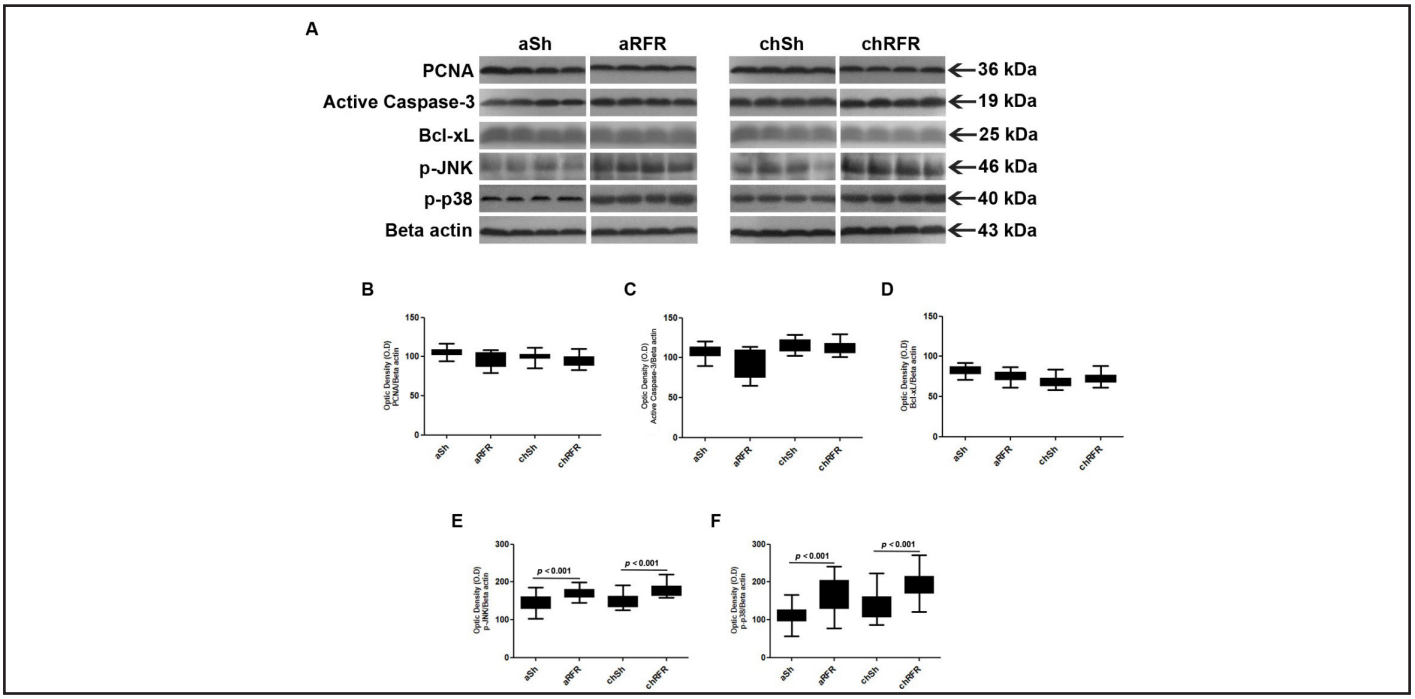

Figure 6. Total protein analysis of the testis lysates of the control and RFR groups by Western blot (A). Please observe the bands for PCNA (36 kDa), active caspase-3 (19 kDa), Bcl-xL (25 kDa), p-JNK (46 kDa) and p-p38 (40 kDa) proteins. Total protein levels of the target proteins are normalized to beta-actin (43 kDa) as a loading control and graphed (B-F). Acute control (aSh); acute RFR (aRFR); chronic control (chSh); chronic RFR (chRFR)

The interaction of RFR and cell proliferation has been a very curious subject. Unfortunately, there are very few studies in the current literature providing the different results with conflicting data [21, 22]. The reports on testis, skin, and brain tissues indicated that PCNA expressions did not change in the RFR groups [17, 21, 23]. In contrast, some studies revealed that PCNA expressions were reduced in testicular and liver tissues of RFR groups [22, 24]. However, we found no significant differences in PCNA expression and its distribution patterns in the rat testis after acute and chronic 2100 MHz RFR exposure in terms of both Western blot and immunohistochemistry methods.

On the other hand, we also aimed to investigate the consequences of RFR administration on testicular apoptotic and antiapoptotic factors in addition to cell proliferation after 2100 MHz RFR exposure. The antiapoptotic (Bcl-xL and Bcl-2) and proapoptotic (Bax and Bad) Bcl-2 protein family have significant functions in the survival and death of cells [25]. Our data clearly indicated there was no alteration in testicular cell apoptosis as observed for cell proliferation in RFR groups. Besides, neither the expression patterns nor the protein expression of active caspase-3 and Bcl-xL proteins were statistically different from the control groups in RFR groups. The TUNEL assay was also performed alongside the active caspase-3 and Bcl-xL proteins. However, it did not reveal any change in terms of apoptotic cell death in RFR groups. In fact, we previously reported that apoptosis in the rat testis was increased after 900 MHz exposure for one week by TUNEL analysis. However, no difference was observed after 10 weeks [17]. It was reported that there wasn't any alteration in the testicular cell apoptosis of 5-weeks-old rats with 2.45 GHz RFR exposure for three weeks (2h/day), but an increase was observed in the testis tissues of 6-weeks-old rats [26]. Interestingly, it has been shown that apoptosis was increased in the offspring rat testis after 900 MHz RFR for 1 h/day through days 13-21 of pregnancy [27]. In another study with the administration of 900 MHz RFR (SAR value: 0.07-0.57 W/kg) for 2 h/day during 10 months, no obvious difference was identified in the quantification of cells stained positively with active caspase-3 in testis tissue between experimental groups [28]. However, Guo and colleagues demonstrated that the number of active caspase-3-positive cells and testicular protein level were significantly higher after exposure to 220 MHz RFR (SAR value: 0.014 W/kg) for a month (1 h/day) [2]. Our data for active caspase-3 supports the data that of Dasdag and colleagues [28]. Besides, there are limited number of studies about the Bcl-2 proteins after RFR exposure on the testis. Some of the studies with rat or mouse testis indicated that Bcl-2 or Bcl-xL expressions were decreased after RFR exposure [17, 29, 30] although some other publications, including our study, revealed that there wasn't any remarkable alteration in Bcl-xL expression [17, 31, 32]. In fact, our previous data has shown a decreased expression level of Bcl-xL protein in the acute period; however, we reported no significant difference after chronic 900 MHz RFR exposure in the rat testis [17]. The active caspase-3 protein was not changed after acute period, but a dramatic reduction was observed in the 900 MHz chronic RFR group by means of the Western blot technique. However, it was not detected in the ImageJ analysis of the immunohistochemical images [17]. Therefore, the usage of the different RFR frequencies, exposure duration periods, SAR values, age or situations such as pregnancy and also the sensitivity of the analysis methods in different species may be potential reasons why the results were altered between several research groups.

JNK and p38 SAPK proteins can affect apoptosis via Bcl-xL [33]. Therefore, the consequences of 2100 MHz RFR on p-p38 and p-JNK proteins were investigated in line with Bcl-xL expression in the rat testis tissue in the current study. Our data clearly revealed that the expressions of both proteins were significantly higher in acute and chronic RFR groups. In a study in which 30 mW/cm^2 microwave radiation was used, p-p38 and p-JNK expressions were increased in the rat testis after a 6-hours exposure [34]. However, there were not any significant differences in the 7-day exposure group. In a similar manner to 2100 MHz RFR, we previously demonstrated that the expression of p-p38 and p-JNK proteins were increased considerably after 900 MHz RFR exposure [17]. It is clearly observed that the activation of a MAPK cascade occurs in an experimental setup after 2100 MHz RFR exposure in rat testis with no changes in cell proliferation or apoptosis.

Limitations

In fact, one can suggest that the various sperm parameters, including sperm motility and concentration, should also be examined in future studies in order to exclude the possibility that 2100 MHz RFR exposure causes no effects on male infertility.

CONCLUSION

Here we report that exposure to 2100 MHz RFR for up to 10 weeks with a low SAR value (up to 2 h daily use) does not result in an obvious harmful effect on rat testis by means of testicular cell proliferation and apoptosis. However, the expressions of

stress-activated protein kinases, p-p38 and p-JNK, were clearly increased in the rat testis tissues. Thus, a special attention is needed to elucidate this molecular mechanism of action and its undesirable side effects.

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Data Availability

The data supporting the findings of this study can be obtained from the corresponding author upon a reasonable request.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Ethics Approval

The experimental animal protocols utilized in this study received approval from the Akdeniz University Local Ethics Committee for Animal Experiments (protocol number: 758/2018.10.07).

Author Contributions

Conception-H.E., L.S.; Design-H.E., L.S.; Supervision-L.S.; Fundings-L.S.; Materials-H.E.; Data Collection or Processing-H.E., B.S., G.G.T., S.O.; Analysis or Interpretation- H.E., B.S., G.G.T., S.O., L.S.; Literature Review-H.E., L.S.; Writing-H.E., L.S.; Critical Review-L.S.

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Original Research

Investigating the Effect of Sluggish Cognitive Tempo Symptoms Independent of Attention Deficit and Hyperactivity Symptoms on Extremity Injuries in Children and Adolescents

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ABSTRACT

Objective: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder. ADHD symptoms in childhood cause a number of comorbidities in adulthood, there is scarce information on whether ADHD in childhood increases the risk of sustaining injuries or accidents. Although previous studies have investigated ADHD-related accidents or extremity injuries, no study has yet examined whether the risk of injury increases in the presence of ADHD combined with Sluggish Cognitive Tempo (SCT) or—although still controversial as a diagnosis—in the presence of SCT alone. The aim of present study was intended to fill this gap in knowledge and to elucidate the effect of SCT on the risk of sustaining injuries in individuals with ADHD.

Methods: The study included the following groups: Group 1 consisting of patients aged 6–17 years who presented to orthopedics outpatient clinics for extremity injuries and had suspected ADHD, and their parents; Group 2 consisting of children and adolescents aged 6–17 years who had no extremity injury but had ADHD, and their parents, and Group 3 consisting of children and adolescents aged 6–17 years without any extremity injury or psychiatric disorders, and their parents. After the sociodemographic questionnaire was filled, the DSM IV based Screening and Assessment Scale for Attention Deficit and Disruptive Behavior Disorders and Barkley Child Attention Scale (BCAS) were administered by a clinician specialized in pediatric and adolescent mental health.

Results: The study included a total of 94 children and adolescents, of whom 37 had both fractures and ADHD (fracture + ADHD), 37 had ADHD alone and no history of fracture (ADHD), and 20 had neither a history of fracture nor psychiatric diagnosis (control). The groups differed significantly in terms of SCT, inattention and hyperactivity scores ($p < 0.0001$). Based on the results of the regression analysis, it was concluded that the decrease in SCT scores was associated with the fracture + ADHD group; male sex was associated with the ADHD group; and the increase in inattention and hyperactivity scores played a role in the differentiation of the fracture + ADHD group from the control group.

Conclusion: The present study was intended to fill this gap in knowledge and to elucidate the effect of SCT on the risk of sustaining injuries in individuals with ADHD. Comparison of the

groups in terms of attention deficit, hyperactivity, and SCT scores showed a statistically significant difference among the groups for all three parameters. Regression analysis showed that high SCT scores had a reverse causality with fractures. When evaluated within the context of our study, this seems to act as a mechanism that compensates impulsivity. Although the mechanism is unclear, the strong causality suggests that it may have a protective effect against sustaining injuries.

Keywords: Child, Sluggish cognitive tempo, Extremity injuries

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects an average of 5% of children worldwide [1]. Although ADHD has initially been thought to be a childhood disorder, studies have shown that individuals with this condition experience more social problems, are more prone to mental illnesses, have higher rates of substance use disorders, and are at higher risk for premature death in adult life [2]. A large cohort study has shown that individuals with ADHD are two times at greater risk of death compared to those without the condition [3] . Although these studies have shown that ADHD symptoms in childhood cause a number of comorbidities in adulthood, there is scarce information on whether ADHD in childhood increases the risk of sustaining injuries or accidents.

A study from the United States of America reported that 44% of all fatal accidents in children and adolescents are caused by inattention, that the most common type of injury is traumatic brain injuries and these accidents result in the death of more than 12,000 children and adolescents annually [4]. Given its dangerous consequences, ADHD should be identified and treated in these children and adolescents to prevent accidents.

Main Points:

- Sluggish Cognitive Tempo is defined as a disorder characterized by symptoms such as daydreaming, lethargy, introversion, and low energy.
- Previous studies have investigated ADHD-related accidents or extremity injuries, no study has yet examined whether the risk of injury increases in the presence of ADHD combined with SCT orin the presence of SCT alone.
- The present study was intended to fill this gap in knowledge and to elucidate the effect of SCT on the risk of sustaining injuries in individuals with ADHD.
- Regresen analysis showed that high SCT scores had a reverse causality with fractures. When evaluated within the context of our study, this seems to act as a mechanism that compensates impulsivity.

The predominantly inattentive presentation of ADHD involves certain specific symptoms similar to those of another disorder called Sluggish Cognitive Tempo (SCT). SCT is defined as a disorder characterized by symptoms such as daydreaming, lethargy, introversion, and low energy [5]. These similarities raise questions on whether SCT should be differentiated from ADHD as a different diagnostic category [6]. Although many studies initially examined SCT in the context of ADHD and still investigate it in that context, recent studies have started to look into the relationship of SCT with clinical conditions such as autism spectrum disorder, sleep disorder and traumatic brain injury [7]. These studies point to a growing recognition of SCT as a separate disorder or construct of transdiagnostic significance for psychiatric disorders [8]. Despite the increasing number of studies in recent years, SCT has not been fully elucidated in terms of its neurocognitive and neurobiological aspects. Although many studies have been conducted on cognitive function and attention deficits, the exact mechanism is unknown [9-10]. Although previous studies have investigated ADHD-related accidents or extremity injuries, no study has yet examined whether the risk of injury increases in the presence of ADHD combined with SCT or—although still controversial as a diagnosis—in the presence of SCT alone. Previous studies have investigated the symptoms of SCT that occur after brain injury, but to our knowledge, no study has yet examined the association between SCT and trauma [11]. The present study was intended to fill this gap in knowledge and to elucidate the effect of SCT on the risk of sustaining injuries in individuals with ADHD.

MATERIALS AND METHODS

The study received ethics committee approval and was conducted over a period of two months with patients who presented to a Pediatric and Adolescent Mental Health and Diseases Clinic and Orthopedics outpatient clinics and who met

the inclusion criteria. The study included the following groups: Group 1 consisting of patients aged 6–17 years who presented to orthopedics outpatient clinics for extremity injuries and had suspected ADHD, and their parents; Group 2 consisting of children and adolescents aged 6–17 years who had no extremity injury but had ADHD, and their parents, and Group 3 consisting of children and adolescents aged 6–17 years without any extremity injury or psychiatric disorders, and their parents. The diagnosis of ADHD was made using DSM-5 criteria as a result of the clinical evaluation of a specialist clinician. Volunteers, hospital visitors, hospital employees and their children were evaluated for the group without any extremity injuries or psychiatric disorders. The adolescents included in the study and their parents were verbally informed about the study and then were separately asked to fill out a written informed consent form. After the sociodemographic questionnaire was filled, the DSM IV-based Screening and Assessment Scale for Attention Deficit and Disruptive Behavior Disorders and Barkley Child Attention Scale (BCAS) were administered by a clinician specialized in pediatric and adolescent mental health.

Data Collection Tools

Sociodemographic Questionnaire

The form inquired about the sociodemographic characteristics of patients and was completed by the clinician through direct interviews. It was used to record parameters likely to affect cognitive development such as the age of the patients, maternal age at birth, age at onset of walking and paternal age at birth.

DSM IV-Based Screening and Assessment Scale for Attention Deficit and Disruptive Behavior Disorders

It is a 30-item scale that screens for all symptoms of ADHD and disruptive behavior disorders, with one item for each symptom, including symptom severity. The scale is completed by the clinician or the patient's career. The scale was developed by Atilla Turgay and the validity and reliability of the instrument was analyzed by Ercan et al. [12].

BCAS

The questionnaire was developed by Russel Barkley et al. [13] and the validity and reliability of the Turkish version was analyzed by Fırat et al. [13]. It is a Likert-type scale scored from 0 to 3, and a score above 23 from the Turkish version is considered as indicative of a high risk for SCT. The present study used a cutoff value of 23.

Statistical Analysis

Study data were analyzed using SPSS 22 statistical software. The data were checked for normality of distribution using skewness and kurtosis values, normality tests, and histograms. To determine whether variables exhibited statistically significant differences between groups, they were analyzed using one-way analysis of variance if normally distributed and using Kruskal–Wallis test if non-normally distributed. Multiclass multinomial logistic regression analysis was used to examine the variables that predicted the differentiation of the group with fractures and ADHD from the other groups. Variables "age" and "sex" were included in logistic regression analysis as covariates alongside the variables identified in the research hypothesis. In all analyses, statistical significance was set at $p < 0.05$.

RESULTS

The study included a total of 94 children and adolescents, of whom 37 had both fractures and ADHD (fracture + ADHD), 37 had ADHD alone and no history of fracture (ADHD), and 20 had neither a history of fracture nor psychiatric diagnosis (control). There was no significant difference among the three groups in terms of age and sex distribution ($p > 0.05$). Analysis of the sociodemographic and developmental data showed that the children included in the study differed in terms of the age at which they started talking ($p = 0.037$); children in the fracture + ADHD group had started talking at a significantly later age compared to the other groups. As expected, the groups differed significantly in terms of SCT, inattention and hyperactivity scores ($p < 0.0001$). Post hoc analyses showed that SCT scores were higher in the ADHD group than in the other groups, whereas there was no significant difference between the fracture + ADHD group and the control group. Again, post hoc analyses showed that the inattention score was higher in the ADHD group compared to the other groups, and the score of the fracture + ADHD group was higher only compared to that of the control group. As for hyperactivity scores, there was no difference between the two case groups, but the scores of these two groups were higher than that of the control group.

The study used multinomial logistic regression analysis to identify the independent variables that predicted the differentiation of the fracture + ADHD group from the ADHD group and the control group. The model used the groups as dependent variables; age, SCT, inattention, and hyperactivity as covariates; sex as a factor and finally fracture + ADHD as the reference category ($R^2 = 0.60$ [Nagelkerke], $x^2 = 153.68$).

Analysis results showed that the ADHD*Fracture + ADHD groups were predicted by the SCT score (B: 0.171; SE: 0.072; OR: 1.187, [1.031–1.367]) and male gender (B: 1.698; SE: 0.773; OR: 5.462, [1.200–24.857]); control*Fracture + ADHD groups were predicted by inattention (B: –0.238; SE: 0.109; OR: 0.788, [0.636–0.976]) and hyperactivity scores (B: –0.180; SE: 0.066; OR: 0.836, [0.734–0.952]). Based on the results of the regression analysis, it was concluded that the decrease in SCT scores was associated with the fracture + ADHD group; male sex was associated with the ADHD group; and the increase in inattention and hyperactivity scores played a role in the differentiation of the fracture + ADHD group from the control group.

Table 1. Comparison of sociodemographic and clinical variables between groups

	Extremity injuries +ADHD (a) n=37	**ADHD (b) n=37**	**Control (c) n=20**	**Statistical analysis**	
	Mean±SS	**Mean.±SS**	**Mean.±SS**	**P**	**Post hoc**
Age	11.16±*2,78*	10.29±*1.84*	10.97±*2.08*	0.248 [a]	
Maternal age at birth	26.18±*5,84*	25.67±*5.49*	27.55±*3.81*	0.153 [a]	
Paternal age at birth	32.10±*6,01*	29.45±*6.66*	31.35±*4.60*	0.073 [a]	
Birth weight (g)	3277±*430*	3482±*648*	3161±*494*	0.077 [b]	
Walking time (month)	12.37±*2,55*	11.97±*2.70*	11.50±*1.79*	0.235 [a]	
Talking time (month)	13.725±37	12.18±*3.49*	11.50±*3.99*	**0.037** [a]	a>b=c
Slow cognitive tempo score	15.64±*4,81*	19.54±*5.59*	14.45±*3.28*	**<0.0001** [a]	b>a=c
Attention deficit score	9.27±*6.56*	14.89±*5.75*	3.65±*2.85*	**<0.0001** [b]	b>a>c
Hyperactivity score	13.13±*7.86*	16.13±*7.29*	4.50±*4.51*	**<0.0001** [b]	a=b>c
	n (%)	**n (%)**	**n (%)**	***P***	**Post hoc**
Gender (male)	26 (70.3)	32 (86.5)	16 (80.0)	0.231 [c]	
Birth type (normal)	28 (75.7)	15 (40.5)	14 (70.0)	**0.005** [c]	**a=c>b**

[a]*Kruskal Wallis Test* [b]*One-way ANOVA* [c]*Chi-Square Test*

Table 2. Results of multi-category multinomial logistic regression analysis

	B	**Standard Error**	**Odds Ratio**	**Confidence Interval**
ADHD * Extremity injuries +ADHD				
Constant	-3.271	*2.032*	-	-
Age	-0.275	0.141	0.759	(0.577-1.000)
Slow cognitive tempo score	**0.171***	0.072	1.187	(1.031-1.367)
Attention deficit score	0.095	0.054	1.099	(0.989-1.222)
Hyperactivity score	0.050	0.042	1.051	(0.968-1.141)
Gender (male)	**1.698***	0.773	5.462	(1.200-24.857)
Control * Extremity injuries +ADHD				
Constant	0.251	2.190	-	-
Age	-0.029	0.154	0.971	(0.718-1.314)
Slow cognitive tempo score	0.104	0.112	1.110	(0.891-1.383)
Attention deficit score	**-0.238***	0.109	0.788	(0.636-0.976)
Hyperactivity score	**-0.180***	0.066	0.836	(0.734-0.952)
Gender (male)	0.985	0.899	2.677	(0.460-15.592)

*Referance category: Kırık+DEHB *p<0,05 **p<0.01 ***p<0.001*

R^2=.53(Cox-Snell), .60(Nagelkerke). Model x^2=153.68

DISCUSSION

The present study investigated the effect of ADHD domains and SCT on fractures and the relationship between these parameters in a total of 94 children and adolescents aged 6–17 years divided into three groups. The groups had no statistically significant differences in terms of sociodemographic characteristics. A study from Türkiye found that boys diagnosed with ADHD were more likely than their female counterparts to be admitted to the emergency department with extremity injuries [14]. Also, another thesis study reported that among children with ADHD admitted to the emergency room with head injuries, the proportion of boys was statistically significantly higher than that of girls, but found no statistical difference in their ages [15]. Sex seems to be correlated with the likelihood of sustaining injuries and the lack of a significant difference in the present study prevents this limitation.

Our study found a statistically significant difference between the groups in terms of the frequency of normal delivery. Of note, the frequency of cesarean section was significantly higher in the ADHD group compared to the control group. A recent meta-analysis identified cesarean delivery as a risk factor for autism spectrum disorders and ADHD compared to vaginal delivery [16]. This report is supported by our study in that it found differences in the mode of delivery between the ADHD group and the control group.

Comparison of the three groups in terms of attention deficit, hyperactivity, and SCT scores showed a statistically significant difference among the groups for all three parameters. A study conducted on children aged 3–17 years who presented to the emergency department with injuries used the Conners' Parent Scale for ADHD and analyzed the results. That study used nontrauma participants as the control group and compared the two groups. The results of the comparison showed a statistically significant difference in all Conners' subscales [17]. Our study is in line with previous studies; it found that both hyperactivity and attention deficit domains are correlated with sustaining injuries. Hyperactivity may coexist with impulsivity in ADHD. Impulsivity and psychomotor hyperactivity may be correlated with a higher likelihood of sustaining injuries and accidents in children with ADHD. Another salient difference in children with ADHD is related to executive functions [18]. Of note, individuals with ADHD differ from individuals without the condition in terms of several executive functions including task switching, verbal and spatial memory, inhibition control, planning, and execution. This may explain the differences, particularly when compared to the control group. Poor planning and inhibition control may be playing a role in the occurrence of injuries or increase the risk of injury.

ADHD may also involve differences in some morphological structures in the brain. The literature on neuroimaging includes strong meta-analyses showing that ADHD is associated with differences in neural regions in the prefrontal cortex as well as in the posterior cortex and subcortical structures that clearly demonstrate differentiation in functioning, consistent with changes in the maturation of frontal control [19]. Also, functional data show alterations in the functioning of dopaminergic systems which exhibit increased activity in ADHD and reveal changes in a number of motor centers and decision-making centers, especially fronto–striatal–thalamic pathways [20]. All these changes lead to disorganization or poor performance in decision-making, action control, and motor control in individuals with ADHD. These factors may be contributing to the likelihood of sustaining injuries.

Our study compared the three groups in terms of SCT scores and found a significant difference among the groups; post hoc analysis showed that this difference was caused by the nontrauma ADHD group. Interestingly, regression analysis showed that high SCT scores had a reverse causality with fractures. SCT is essentially characterized by daydreaming, lethargy, and low energy. Although its relationship with impulsivity has not been clearly demonstrated, this pattern of hypoactive symptoms may have led to avoidance or inhibition of behaviors that might cause fracture and injuries. Studies have shown that young people with high SCT scores are more prone to internalization problems and have low motivation and are more apathetic [21]. This apathetic state and low motivation to act may have unexpectedly protected young people from sustaining injuries.

Although SCT phenomenologically resembles daytime sleepiness, studies suggest that this hypoactive state is actually a problem of executive functioning. Mutlu et al.[22] compared individuals with ADHD who scored high and those who scored low on the SCT and found no statistically significant difference between the two groups in parameters such as sleep duration, falling asleep and daytime sleepiness [22]. When evaluated within the context of our study, this seems to act as a mechanism that compensates impulsivity. Although the mechanism is unclear, the strong causality suggests that it may have a

protective effect against sustaining injuries.

There are some limitations to the present study. First, this is a cross-sectional case-control study and thus does not fully explain causality. Also, the small sample size is another limitation. SCT diagnosis usually requires the assessment of multiple assessors, such as parents, teachers, and clinicians. Although clinician assessment was sufficiently reliable in the studies, the lack of a second assessor is a limitation. The age range was broad in our study. In children and adolescents, symptomatology of ADHD and SCT may present differently. Even in the absence of any statistically significant difference between age groups, this may be a limitation for homogeneous evaluation. The study only measured ADHD and SCT scores and did not measure different domains of attention and hyperactivity (executive functions, impulsivity, etc.). Differences in these parameters may have influenced the likelihood of sustaining injuries. Also, the study did not analyze medications used for ADHD treatment. The medications may have a series of cognitive and physical effects, which in turn may modify the likelihood of injuries.

CONCLUSION

Our study is the first in the literature to investigate the effect of SCT on the likelihood of sustaining fractures and injuries. regression analysis showed that high SCT scores had a reverse causality with fractures. Although the mechanism is unclear, individuals with ADHD who exhibit SCT activity may be less likely to sustain fractures and injuries. SCT that coexists with ADHD may be protective against impulsivity. Further studies with larger samples are needed to clarify the mechanism and determine the causes in this relationship.

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Informed Consent: An informed consent form was filled out by all participants and their parents participating in the study.

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Author Contributions: Conception: RO, Ç; MM, Ö - Design: MM,Ö - Supervision: RO,Ç - Fundings:MM,Ö -Materials: MM,Ö ; MN;T- Data Collection and/or Processing: RO,Ç- Analysis and/or Interpretation: RO,Ç; D,S - Literature: RO,Ç; MM,Ö - Writing: RO,Ç; MM,Ö - Critical Review: MN,T.

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Original Research

Ischiofemoral Impingement: Assessment of Diagnosis through MRI and Physical Examination

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ABSTRACT

Objective: The objective of this study is to assess the precision of physical examination tests in individuals diagnosed with ischiofemoral impingement syndrome (IFI), analyze magnetic resonance imaging (MRI) findings and measurements, and explore the correlation between imaging methods and physical examination tests.

Methods: The MRIs of 27 hips of 20 patients who have presented with complaints of hip/groin pain in the study group and 40 hips of 20 patients in the control group were analyzed. Patients were evaluated for the severity of pain, clinical findings, and physical examination tests. Quadratus femoris muscle (QFM) edema was graded and quadratus femoris space (QFS), hamstring tendon area (HTA) and especially ischiofemoral space (IFS), were measured on MRI.

Results: Both the IFS (12.44±3.49) and QFS (6.38±2.09) were significantly reduced in the study groups compared to the control groups (IFS:23.06±4.5, $p<0.001$; QFS:15.36±4.45, $p<0.001$). Measurements of the IFS (cut-off:≤18.58) and the QFS (cut-off:≤10.27) demonstrated high specificity (87.5%) and sensitivity (100%) in identifying IFI. The long-step walking (LSW) test was positive in 59.3% of cases.

Conclusion: The results suggest that MRI is a valuable tool for providing detailed information on various aspects related to IFI. It allows for the assessment of the narrowing of the IFS and QFS, as well as the presence of edema. MRI, when combined with LSW test, can contribute to a comprehensive evaluation and diagnosis of IFI, enabling clinicians to gather important clinical and radiological data for accurate assessment.

Keywords: Hip pain, Long-step walking test, Ischiofemoral impingement, Physical examination, Magnetic resonance imaging, Quadratus femoris muscle

INTRODUCTION

In patient experiencing hip pain, the condition arising from compression of the quadratus femoris muscle (QFM) within the ischiofemoral space (IFS) is referred to as ischiofemoral impingement syndrome (IFI) [1]. The compression of the muscle induces localized pain in the hip, aggravate by hip adduction, extension, and external rotation [2]. The IFS is defined as the distance between the ischial tuberosity of the ischium and the lesser trochanter of the femur, which is covered by the QFM [1]. The QFM is the strongest external rotator muscle of the thigh, and

its proximity to the sciatic nerve highlights its importance [3]. This compression can result in pain in the back of the hip and/or groin, which can radiate towards the knee. The duration of pain can last for several months or years and gradually increases. Symptoms such as a sensation of snapping, joint locking, and difficulties while walking may accompany the pain, particularly during hip extension [4].

IFI was initially delineated by Johnson in a series of three cases [2]. Subsequent case reports [5, 6] emphasized the importance of conducting further investigations into this condition. In 2009, Torriani et al. [1] conducted a study which proposed that the disease could potentially have congenital origins, implying that certain anatomical factors present from birth may contribute to the development of the condition. When the IFS is narrowed due to congenital or acquired causes, the QFM is compressed in this space.

While imaging parameters have been the primary focus in defining IFI, a comprehensive physical examination of the hip serves as a valuable tool in identifying affected patients. Despite the lack of specific physical examination tests for IFI for many years, Gomez-Hoyos et al. [7] introduced the long stride test (LSW) and the IFI test in their study. However, the non-specific symptoms associated with IFI have contributed to its underrecognition among clinicians [5].

The objective of this study is to determine the characteristics of groin pain in patients with a narrowed IFS and to explore the relationship between pain, physical examination tests, and imaging parameters. Additionally, the study aims to analyze the magnetic resonance imaging (MRI) measurements and findings, and investigate the IFS as well as various anatomical parameters that may be associated with this syndrome.

Main Points:

- Ischiofemoral and quadratus femoris spaces exhibit high specificity (87.5%) and sensitivity (100%) for identifying ischiofemoral impingement syndrome, with cut-off values of ≤18.58 and ≤10.27, respectively.
- The affected group demonstrated significantly reduced ischiofemoral and quadratus femoris spaces compared to the control group ($p<0.001$).
- A positive long-stride walking test was associated with significantly reduced ischiofemoral space ($p<0.05$), suggesting that this test could potentially serve as a valuable diagnostic tool for the condition.

MATERIALS AND METHODS

The study was conducted utilizing cases that sought consultation at the Physical Therapy and Rehabilitation outpatient clinic and underwent MRI between the years 2013 and 2022. Ethical approval for the study was obtained from the Local Ethics Committee of the Faculty of Medicine, with the approval number 2022/115. Primarily, a statistically appropriate sample size was determined. A power analysis was conducted using G Power 3.1.9.4, which determined that a sample size of 20 subjects was needed for both the study and control groups. Individuals aged 18 and above with complaints of hip/groin pain and evidence of edema in the QFM on MRI were screened. Physical examinations and patient histories, conducted by an experienced physiatrist, were scrutinized. Subsequently, a study group comprising 27 hips from 20 cases (7 bilateral, 13 unilateral) with both LSW and IFI tests in their records was identified. Patients who had previously undergone pelvic surgery, recently experienced trauma, a lesion or tumor occupying the pelvic region, cancer in the pelvic area or metastasis to the bone or had inflammatory diseases affecting the pelvis were excluded from the study group. The exclusion criteria for the control group were the same as for the study group. In the control group, 40 hips of 20 cases without hip pain, no history of hip trauma or developmental deformities on imaging, and normal bone structure in the hip were included in the study.

In this study, pelvic or hip MRIs were assessed using axial fast spin-echo (FSE) fat-suppressed, proton density-weighted, axial FSE proton density-weighted T2-weighted, and axial T1-weighted images acquired with a 1.5T scanner (Aera, Siemens Healthcare, Erlangen, Germany) with a slice thickness of 5 mm. Routine hip MRI examinations were conducted by hospital procedures, with patients positioned neutrally; their hips and knees facing upward, and feet positioned close together.

IFS (Fig. 1) and quadratus femoris space (QFS) (Fig. 2) were measured according to the definition provided by Torriani et al. [1]. The edema in QFM was graded according to the classification system developed by Tosun et al. [5]. All three measurements were performed in the same axial plane, and T2-weighted images were particularly used for edema grading (Fig. 3).

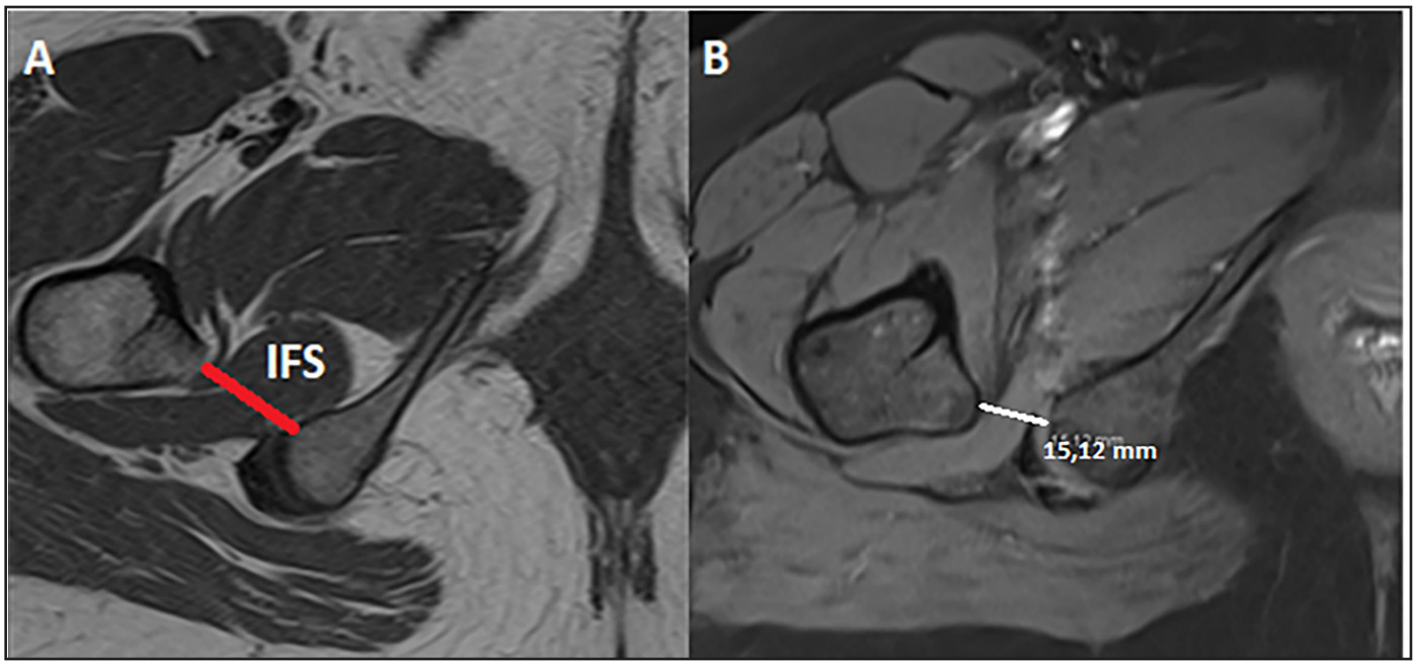

Figure 1. A Patient in the control group with a normal ischiofemoral space (IFS) in the axial plane as seen on the magnetic resonance imaging (MRI) (straight red line) and **B** The IFS measurement was acquired from the MRI of a female patient, aged 47, who presented with pain in her right hip. The patient exhibited positive results in the ischiofemoral impingement (IFI) and the long-step walking (LSW) tests

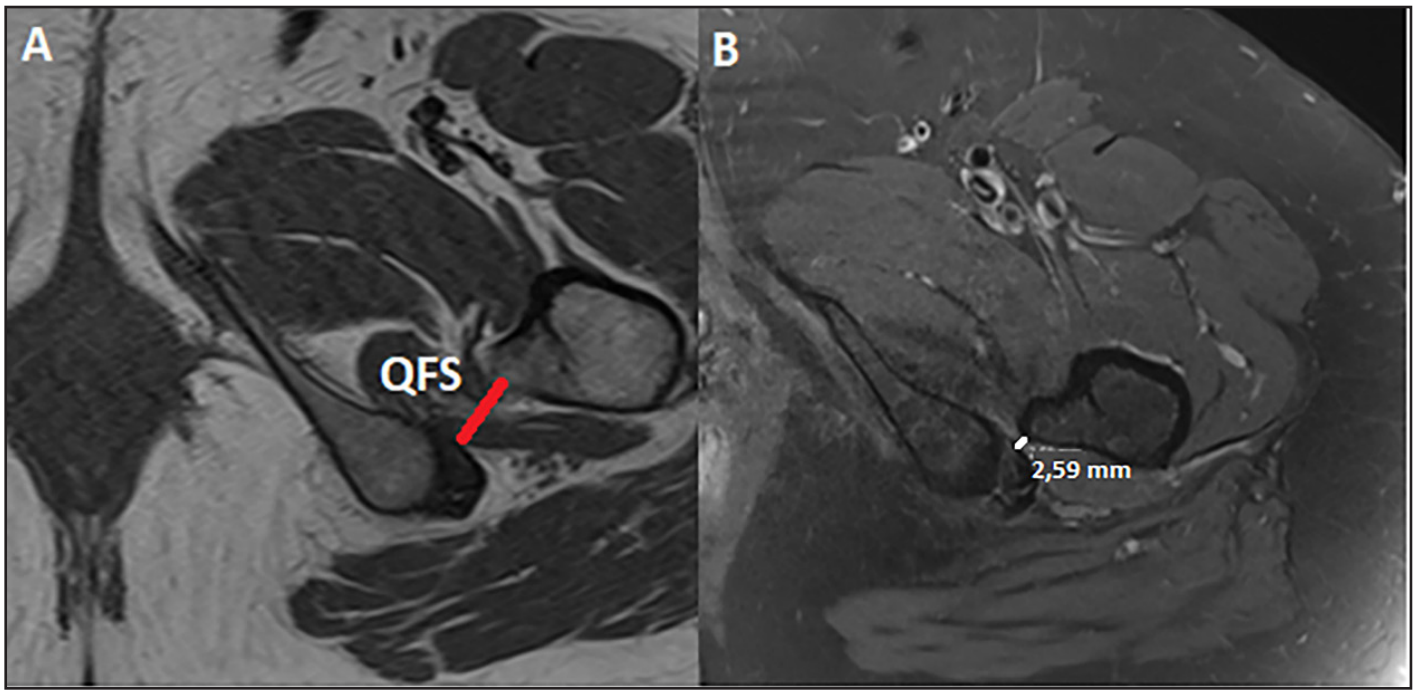

Figure 2. A Patient in the control group with a normal quadratus femoris space (QFS) in the axial plane as seen on the magnetic resonance imaging (MRI) (straight red line) and **B** The QFS measurement was acquired from the MRI of a female patient, aged 57, who reported left groin pain. The patient yielded a negative result in the ischiofemoral impingement (IFI) test and a positive result in the long-step walking (LSW) test

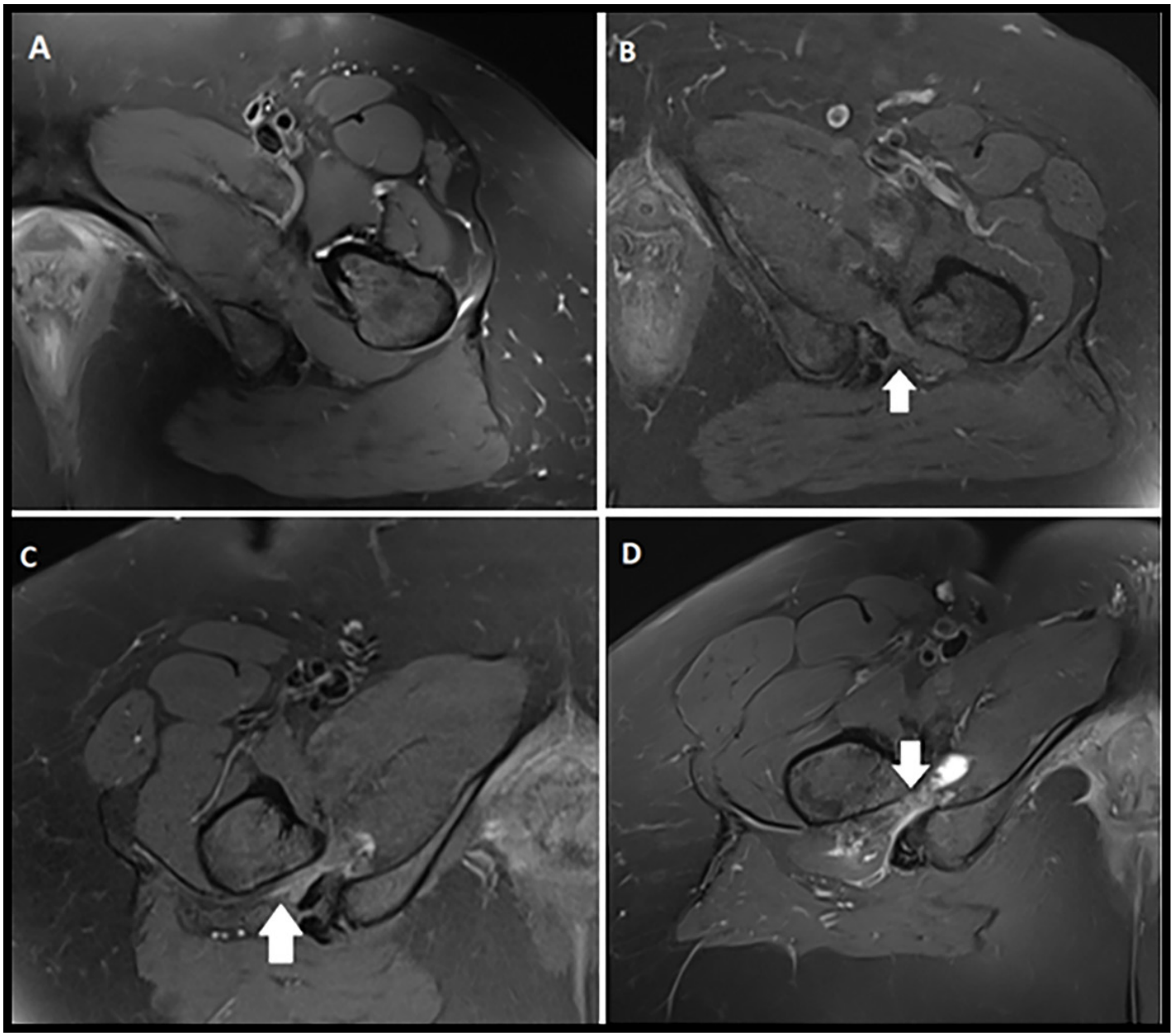

Figure 3. Grading of edema in the quadratus femoris muscle (QFM) on axial T2 MRI: **A** Grade 0 (no edema), **B** Grade 1 (mild edema), **C** Grade 2 (moderate edema), **D** Grade 3 (severe edema). White arrows indicate the location of the edema

According to this classification:
Grade 0 (none): Normal QFM density,
Grade 1 (mild): Presence of focal edema within the muscle,
Grade 2 (moderate): Presence of edema that spreads outside the area where IFS is measured but remains within the muscle,
Grade 3 (severe): Presence of edema that extends into the surrounding soft tissues.

The area where the tendons of the biceps femoris, semimembranosus, and semitendinosus muscles connect to the ischial tuberosity is referred to as the hamstring tendon area (HTA). The HTA was calculated on the axial plane of the MRI at the level where IFS and QFS were measured (Fig. 4).

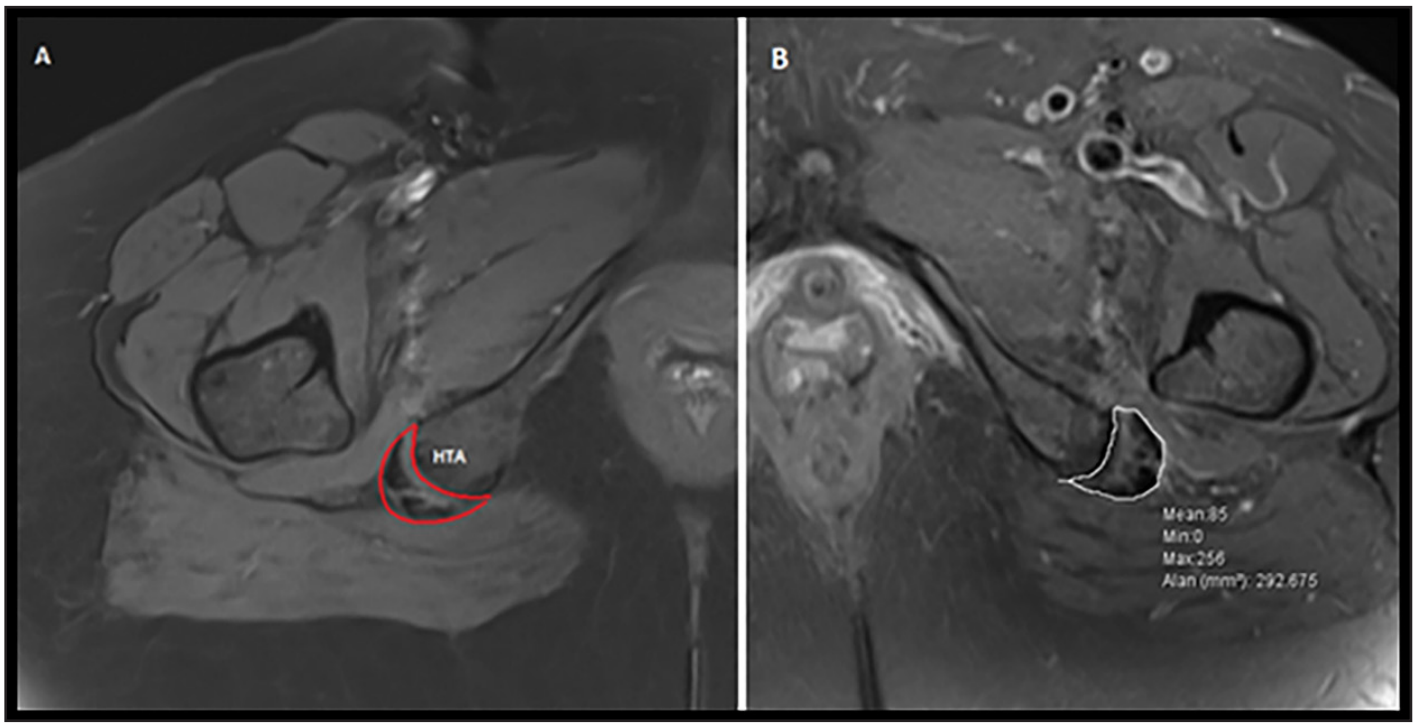

Figure 4. A Depiction of the hamstring tendon area (HTA) in the axial plane through magnetic resonance imaging (MRI), demarcated by red delineations and **B** Quantitative measurement of the HTA was derived from the MRI of a female patient, aged 59, who reported left groin pain. The patient demonstrated a negative result in the ischiofemoral impingement (IFI) test and a positive result in the long-step walking (LSW) test

In the LSW test, the anticipation is that the patient will experience hip pain when taking long strides, and a decrease in pain is expected when short strides are taken. In the IFI test, it is expected that the patient will experience pain when the affected hip is brought into adduction and extension while in positioned on healthy side, and a decrease in pain is anticipated during abduction.

An assessment was conducted by thoroughly examining the medical records of each patient to determine the positive and negative results of the LSW and IFI tests. Additionally, the study involved specifying the location and intensity of pain experienced by each patient, as well as determining the duration of the reported pain. To evaluate the frequency and intensity of pain during both movement and rest, the visual analog scale (VAS) was employed. Additionally, the severity of nocturnal pain was assessed as part of the evaluation process.

Statistical Analysis

The normality of the distribution of numerical variables was assessed using the Shapiro-Wilk test. When comparing normally distributed variables between two groups, the Student's t-test was utilized, while the Mann-Whitney U test was applied for non-normally distributed variables. The chi-square test was employed to examine the associations between categorical variables, whereas the Spearman rank correlation coefficient was used to determine the connections between numerical variables. The Intraclass correlation coefficient and Kappa test were employed to evaluate intra-observer agreement for numerical and categorical variables, respectively. ROC analysis was performed to establish the cutoff point for the IFS and QFS variables. The statistical analysis was conducted using SPSS 22.0 Windows version software. A p-value <0.05 was considered statistically significant.

RESULTS

In our study, a total of 67 hips from 40 individuals were evaluated, including 27 hips from 20 patients in the study group and 40 hips from 20 individuals in the control group. The ages of the patients in the study group ranged from 27 to 71 years (53.93±10.94), with 18 (90%) females and 2 (10%) males. The ages of the individuals in the control group ranged from 30 to 71 years (51.35±13.51), with 18 (90%) females and 2 (10%) males. No statistically significant differences were observed between

the study and control groups in terms of age, gender, and side (right-left) (p>0.05). Bilateral involvement was observed in 7 (35%) of the 20 patients in the study group.

Radiological measurements of IFS, QFS, and HTA were performed in the MRI examination of 27 hips in the study group and 40 hips in the control group. The IFS and QFS were significantly reduced in the study group compared to the control group (p<0.001). However, there was no significant difference between the study and control groups in terms of HTA (p>0.05) (Table 1).

The degree of edema in the QFM was graded in the study group. Among the cases, Grade 1 edema was observed in 13 cases (48.1%), Grade 2 edema in 12 cases (44.4%), and Grade 3 edema in 2 cases (7.4%).

The mean values of the parameters for the right and left sides in the study and control groups were calculated to determine the side-specific differences in the IFS, QFS, and HTA parameters. No statistically significant difference was found in these parameters according to the side (p>0.05).

To ensure the reliability and accuracy of the study, all measurements were conducted twice by the same researcher at specified time intervals. The mean value of the measurements was then utilized for statistical analysis. In order to evaluate the intra-observer agreement and assess the reliability of the radiological parameters, intraclass correlation coefficients (ICC) were calculated. The ICC was 0.974 for the IFS and 0.985 for the QFS. The ICC values indicate a high level of agreement and consistency in the measurements (Table 2).

Table 1. Mean, minimum and maximum values (mm, mm²) of IFS, QFS, and HTA in the study and control groups.

	Study Group n=27			Control Group n=40			
	Mean±SD	**Min.**	**Max.**	**Mean±SD**	**Min.**	**Max.**	**p**
IFS-1	12.34 ± 3.66	5.29	19.84	23.33 ± 4.64	15.00	35.27	0.001*†
IFS-2	12.55 ± 3.39	4.77	18.10	22.78 ± 4.53	14.30	35.60	0.001*†
IFS Mean	12.44 ± 3.49	5.03	18.58	23.06 ± 4.5	14.65	35.44	0.001*†
QFS	6.59 ± 2.16	2.96	10.27	15.46 ± 4.67	5.97	28.43	0.001*†
QFS-2	6.17 ± 2.09	2.59	10.27	15.26 ± 4.29	7.07	28.03	0.001*†
QFS Mean	6.38 ± 2.09	2.78	10.27	15.36 ± 4.45	7.21	28.23	0.001*†
HTA-1	253.53 ± 61.96	164.99	361.33	258.12± 56.95	125.27	373.54	0.557ǂǂ
HTA-2	259.95± 55.22	180.45	357.88	255 ± 60.94	145.72	376.28	0.636ǂǂ
HTA Mean	256.74± 57.67	177.00	359.60	256.56 ± 58.25	135.50	374.91	1.000ǂǂ

* Significant at the p<0.05 level. SD: Standard Deviation. †Student t test. ǂǂMann Whitney U test. IFS, QFS, HTA-1: Initial measurement of the observer. IFS, QFS, HTA-2: Second measurement of the observer. IFS, QFS, HTA-mean: Average of the first two values.

Table 2. Intraobserver reliabilities of IFS, QFS and HTA in the study and control groups

		IFS	QFS	HTA
Study Group	**ICC**	0.955	0.933	0.931
	95% CI	0.905-0.979	0.858-0.969	0.855-0.968
	p	<0.001	<0.001	<0.001
Control Group	**ICC**	0.928	0.969	0.951
	95% CI	0.827-0.961	0.941-0.983	0.910-0.974
	p	<0.001	<0.001	<0.001
Overall	**ICC**	0.974	0.985	0.940
	95% CI	0.957-0.984	0.976-0.991	0.904-0.963
	p	<0.001	<0.001	<0.001

ICC: Intraclass correlation coefficient, CI: Confidence interval

To diagnose IFI, the specificity, sensitivity, and predictive values of the radiological parameters were calculated (Fig. 5). Information was obtained about the clinical characteristics of the patients in the study group, including the presence and distribution of groin/hip pain, the duration of the pain (Fig. 6), and pain severity evaluated using the VAS (Table 3). In terms of pain duration, a majority of patients (51.9%) reported pain that lasted throughout the day. On the other hand, 37% of patients experienced pain episodes lasting less than half an hour, and 11% reported pain lasting an average of 1-2 hours.

Two physical examination tests (IFI; LSW) applied to the cases in the study group were evaluated. The IFI test and LSW test were positive in 12 cases (44.4%) and 16 cases (59.3%), respectively, with a higher positivity rate for the LSW test. IFS was significantly narrower in those who tested positive on the LSW test ($p<0.05$). There was no significant relationship between the LSW test and the radiological parameters QFS and HTA ($p>0.05$). The relationships between variables in the study and control groups were analyzed separately. In the study group, a moderate positive correlation was found between the severity of pain at rest, during activity and night pain intensity ($r=0.520$, $p=0.005$; $r=0.403$, $p=0.037$, respectively). Additionally, a moderate negative correlation was observed between edema and IFS in the study group ($r=-0.471$, $p=0.013$). In the control group, a significant positive correlation was found between IFS and QFS ($r=0.763$, $p=0.001$). Furthermore, a very strong positive correlation was observed between IFS and QFS in all cases of the study ($r=0.885$, $p=0.001$) (Fig. 7).

Table 3. The mean, minimum and maximum values of pain intensity according to VAS during activity, rest, and night in the study group.

	Mean±SD n=27	**Median (Min-Max) n=27**
The intensity of pain during activity	6.07 ± 2.18	6 (0 -10)
The intensity of pain during rest	3.78 ± 2.74	3 (0 -9)
The intensity of pain during the night	4.89 ± 2.56	5 (0 -10)

SD: Standard Deviation

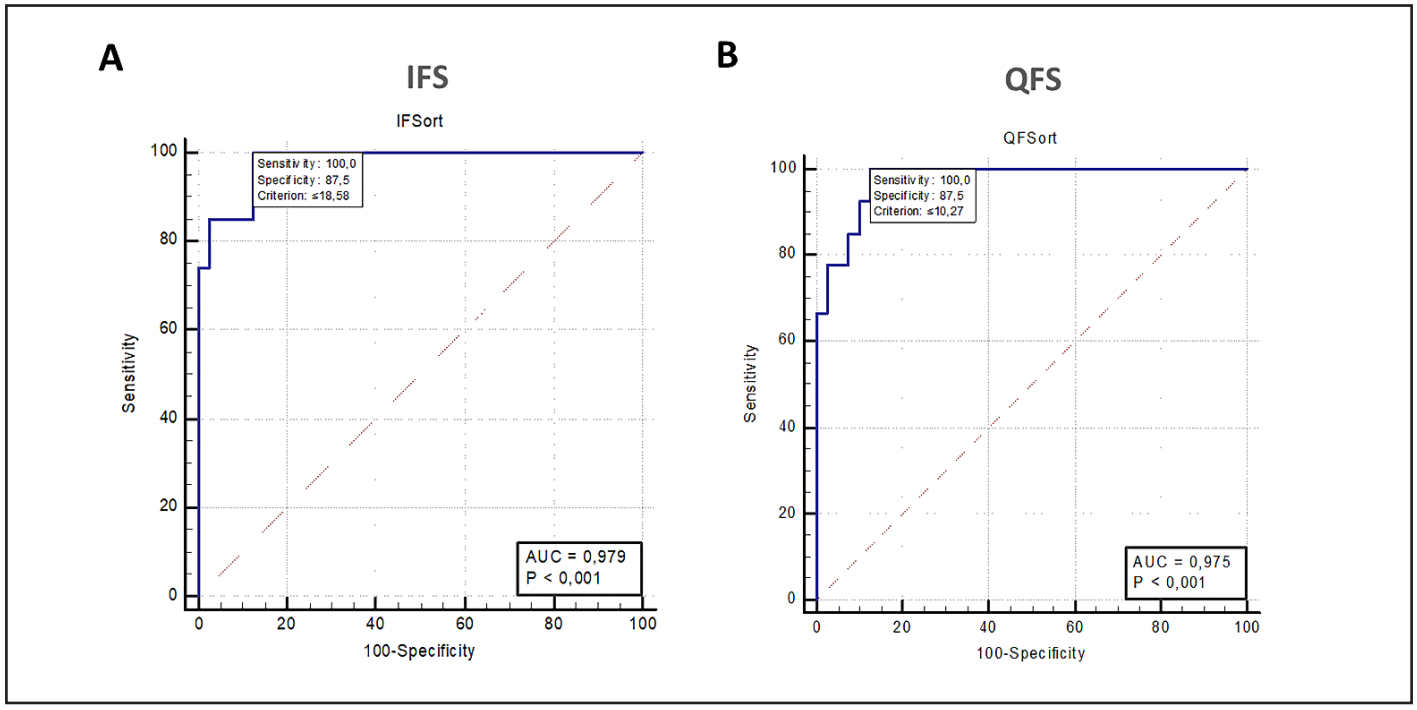

Figure 5. Specificity and sensitivity of **A** ischiofemoral space (IFS) and **B** quadratus femoris space (QFS) for ischiofemoral impingement syndrome (IFI)

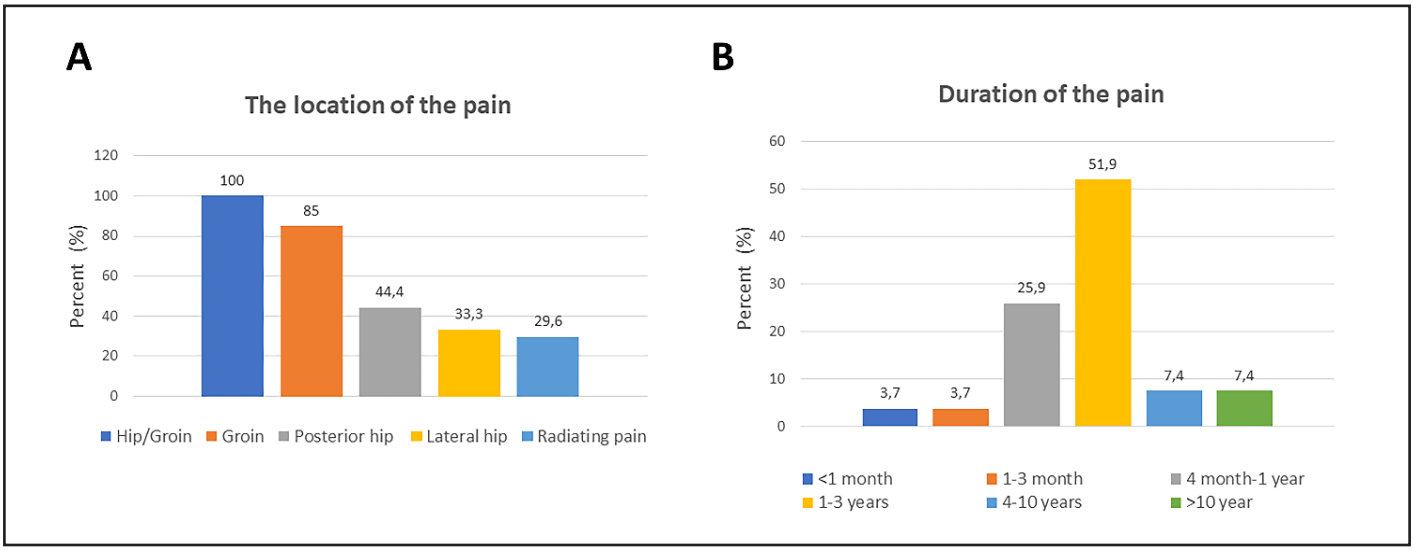

Figure 6. A Distribution and percentage of pain locations in cases, **B** Pain duration grouped by months and years

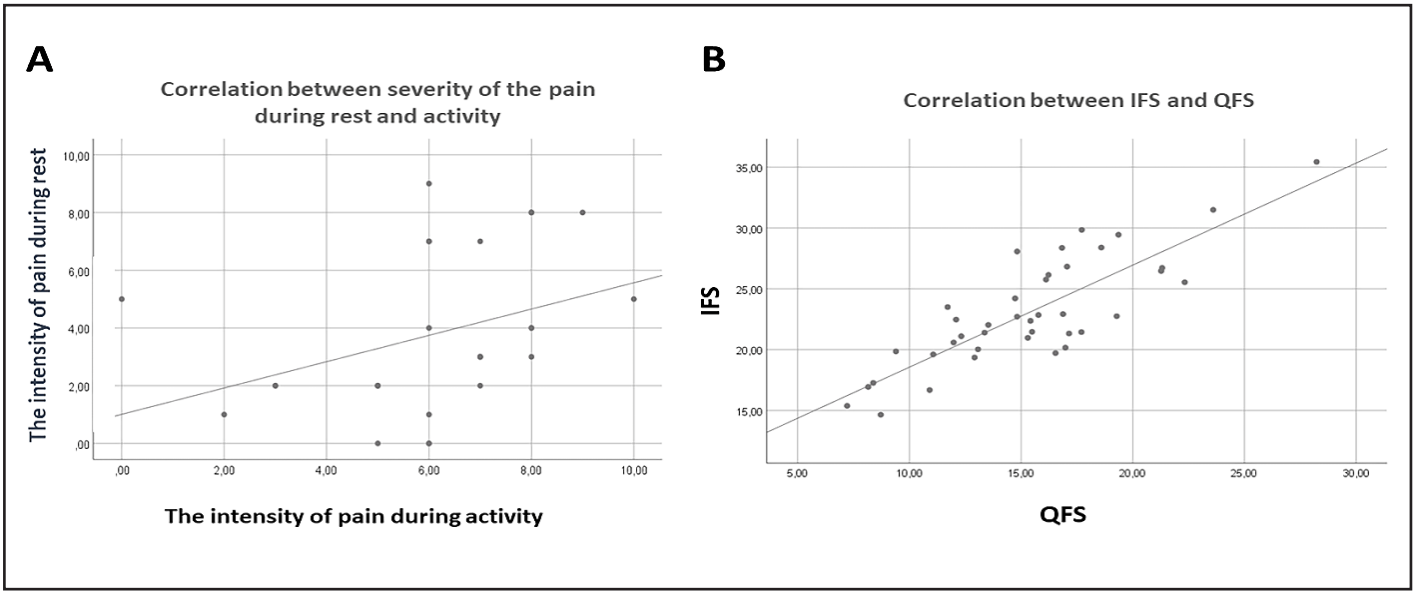

Figure 7. A Correlation between pain intensity during activity and rest, **B** Correlation between ischiofemoral space (IFS) and quadratus femoris space (QFS) in the control group

DISCUSSION

Hip/groin pain is a common symptom seen in many diseases, such as piriformis syndrome, hamstring tendinopathy, lumbar disc disease, spinal stenosis, and IFI [8]. Although IFI is less known, it is crucial for clinicians to be aware of it when diagnosing, as it can be confused with other illnesses. In our study, we aimed to explore the MRI findings in patients diagnosed with IFI, examine the relationship between physical examination tests and imaging methods, and identify the clinical characteristics associated with IFI.

Some studies have found that the occurrence of IFI is more common in women, while others have reported that the disease can also affect men [1, 2, 5, 9-11]. Similar to other studies in the literature, the number of women in our study has found to be higher. This gender difference is mainly attributed to the anatomical differences in the pelvis, such as a wider pelvic outlet and higher intertuberosity distance in women [12, 13]. Despite a limited understanding of the disease's etiology, it has been determined that certain causes are gender-neutral, independent

of female anatomy. Other factors, including prominent lesser trochanter, coxa valga, and abnormal femoral anteversion, may also contribute to the development of the disease [14, 15].

The phenomenon of bilateral occurrence of IFI has been reported in various studies, indicating the possibility of congenital causes [1, 10, 12]. In our study, 35% of the patients exhibited bilateral symptoms, which supports the idea that there may be congenital factors contributing to the development of IFI. In the literature, the IFS has been used as an indicator of the degree of impingement by measuring the narrowing of the area where the QFM is compressed. However, it should be noted that the reduction of the IFS may also lead to a decrease in the width of the QFS. Despite this, several anatomical variations in the IFS can cause QFS narrowing without a corresponding reduction in the IFS [1]. Therefore, both IFS and QFS have been examined in studies as important parameters (Table 4) [1, 5, 7, 9, 10-12, 16-19]. Our findings, consistent with the literature, showed that the affected group demonstrated significantly reduced IFS and QFS compared to the control group.

In his study, Johnson [2] reported that the space enabling femoral rotation without contacting the ischial tuberosity during adduction, external rotation, and extension of the hip joint is approximately 20 mm. This finding has been further investigated by various researchers, particularly in relation to the use of IFS and QFS for predicting IFI. Singer et al. [16] conducted a meta-analysis of 357 cases, in which they evaluated the predictive values of IFS and QFS for IFI. Consistent with previous literature, we demonstrated that the predictive values for IFS and QFS were ≤18.58 and ≤10.27, respectively, with high sensitivity and specificity, as summarized in Table 5 [1,5,11,16].

Table 4. Studies in the literature on IFI

Study	Method	Groups	n	Age	Gender	IFS	QFS
Torriani et al. (2009) [1]	MRI	Study group	12	53 (30–71)	9F	13 ± 5	7 ± 3
		Control group	11	67 (24–95)	10F	23 ± 8	12 ± 4
Tosun et al. (2012) [3]	MRI	Study group	70	51 (14–77)	42F/8M	13.05 ± 3.87	6.91 ± 2.63
		Control group	38	47 (18–66)	25F/5M	21.95 ± 5.91	13.42 ± 4.78
Bredella et al. (2014) [12]	MRI	Study group	97	53 (18–84)	73F/11	17.4 ± 5.5	12 ± 4.5
		Control group	71	52 (22–84)	33F/18M	30.6 ± 9.3	19.3 ± 7.1
Khodair et al. (2014) [11]	MRI	Study group	14	35.2 (24–49	12F/2M	15 ± 1.8	20.5 ± 1.3
		Control group	54	34 (24–48)	17F/3M	20.7 ± 1.4	15 ± 0.9
Singer et al. (2015) [16]	MRI	Study group	24	52.4 ± 2.28	18F/3M	12.91 ± 3.82	9.94 ± 3.39
		Control group	5			17.58 ± 3.28	12.86 ± 2.81
Gomez-Hoyos et al. (2016) [7]	MRI	Study group	17	46.7 ± 13.7	14F/3M	11.2 ± 3.7	6.4 ± 2.2
		Control group	13	53.7±11.2	7F/6M	25.3 ± 7.6	16.3 ± 6.6
Akça et al. (2016) [9]	MRI	Study group	30	49.5 ± 14.45	17F/3M	16.85 ± 4.9	7.05 ± 2.1
		Control group	25	43 ± 13.98	11F/6M	26.98 ± 7.9	16.32 ± 3.64
Stenhouse et al. (2016) [17]	MRI	Study group	12	10 (4–16)	7F/2M	11.5	7.2
		Control group	13	9.8 (3–16)	10F/3M	20.7	14.3
Kivlan et al. (2017) [19]	Cadaver	Dissection	25	46–91	7F/7M	28 ± 11	
Özdemir et al. (2021) [18]	MRI	Study group	24	56 ± 10.2	24F	11.1	6.3
		Control group	27	55.2 ± 11.1	27F	20.1	12
Xing et al. (2021) [10]	MRI	Study group	91	58.1 ± 10.9	43F/15M	15.2 ± 3.9	8.9 ± 2.4
		Control group	122	53.5 ± 13.2	44F/17M	24.2 ± 4.1	16.4 ± 4
The present study	MRI	Study group	27	53.93 ± 10.94	18F/2M	12.44 ± 3.49	6.38 ± 2.09
		Control group	40	51.35 ± 13.51	18F/2M	23.06 ± 4.5	15.36 ± 4.45

Table 5. Studies in the literature on the sensitivity and specificity of IFS and QFS used in IFI

Study Name		Cut-off value	Sensitivity (%)	Specificity (%)
Torriani et al. (2009) [1]	**IFS**	≤ 17	83	82
	QFS	≤ 8	83	82
Tosun et al. (2012) [3]	**IFS**	≤ 18.05	91.43	78.95
	QFS	≤10.3	91.43	78.95
Khodair et al. (2014) [11]	**IFS**	≤17	98.1	100
	QFS	≤13	96.2	100
Singer et al. (2015) [16]	**IFS**	≤15	76.9	81
	QFS	≤10	78.7	74.1
Present study	**IFS**	≤18.58	100	87.5
	QFS	≤10.27	100	87.5

In the study of Tosun et al. [5], HTA was found to be significantly higher in the study group, but the sensitivity and specificity of the test were found to be lower. In contrast, Stenhouse et al. [17] conducted a study on children and found no significant difference between the patient and control groups. Park et al. [20] reported similar findings in their study on adult patients. Likewise, we demonstrated no significant difference between the patient and control groups. The sensitivity and specificity of HTA were determined to be 37.04% and 47.5%, respectively. These findings suggest that there may not be a relationship between HTA and IFI. Due to the lack of significant relationships between the study and control groups in most studies in the literature, as well as differences between studies, we believe that HTA may not be a reliable parameter for diagnosing the disease.

The VAS to assess pain has been limited to a few studies available in the literature, and these studies have employed diverse parameters for evaluation [7, 18]. In our study, we took a different approach by utilizing the VAS to evaluate the presence and severity of pain in patients during rest and at night. Our findings indicate that the severity of pain was highest during movement and decreased during periods of rest and at night. These results align with the expected outcomes of physical examination tests, as movement can increase the likelihood of narrowing in the IFS, which in turn triggers pain. Furthermore, the persistence of movement can exacerbate the duration of pain experienced by the patient. Our findings highlight the dynamic nature of pain experienced by individuals with IFI, with movement playing a significant role in its intensity.

The lack of a definitive physical examination test for diagnosing IFI has led researchers to investigate various approaches. Johnson [2] and subsequently Hatem et al. [21] described localized pain in the hip and groin that increases with hip adduction, external rotation, and extension. Expanding on these studies, Gomez-Hoyos et al. [7] conducted a study on the specificity and sensitivity of two physical examination tests. Furthermore, IFS measurements have been taken at various angles and positions to confirm this condition [19, 22-23]. For instance, Kivlan et al. [19] measured IFS during external rotation, extension, flexion, internal rotation, adduction and abduction. Finoff et al. [23] found that IFS was lowest during hip external rotation, extension and adduction. Despite some inconsistencies with prior literature, we explored that the LSW test was more effective in the diagnosis of IFI. It is important to note that physical examination tests, while not guarantee diagnostic precision, can still serve as valuable tools in aiding the diagnosis process and providing guidance to clinicians.

Our findings revealed a moderate positive correlation between the severity of pain during movement and the severity of pain at rest in the study group. This indicates that there was a parallel increase in pain intensity in both scenarios. Furthermore, a moderate negative correlation was observed between the severity of QFM edema and the severity of pain during movement and at rest. These findings suggest that the presence of QFM edema may contribute to the severity of pain experienced by patients, both during movement and at rest.

Limitations

It should be noted that the retrospective design of our study limits its generalizability. Specifically, the exclusion of asymptomatic patients and the use of patients without hip pain as the control group may have introduced bias. Furthermore, the selection of

individuals without hip pain from the medical system as the control group instead of healthy individuals may limit the scope of our findings. Moreover, the absence of a control group for physical examination is another limitation. In routine clinical practice, patients without hip pain are typically not subjected to thorough physical examination, thus hindering the availability of a suitable control group for comparison.

CONCLUSIONS

In conclusion, pain is a significant symptom that has a considerable impact on the quality of life for patients, and identifying its underlying cause can be a challenging task for clinicians. IFI should be included in the list of potential differential diagnoses for individuals experiencing hip/groin pain. Our study makes a valuable contribution to the existing literature by conducting a thorough analysis of pain characteristics, evaluating the usefulness of physical examination tests, and investigating the relevance of radiological parameters in the diagnosis of IFI. We believe that the findings of our study provide valuable insights into different aspects of the disease, thereby enhancing the understanding and management of IFI.

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Conflict of interest: The authors declare that they have no conflict of interest.

Informed Consent: A formal informed consent procedure was waived due to the retrospective nature of this study.

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Ethical Approval: This study involving human participants was conducted in accordance with the ethical standards established by the institutional and national research committee, following the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval for the study was obtained from the Local Ethics Committee of the Selcuk University Faculty of Medicine, with the approval number 2022/115.

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Original Research

Correlating Cyberchondria and Health Anxiety: Demographic Insights from Stable Asthma Patients

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ABSTRACT

Objective: With the increasing ubiquity of internet, the phenomenon of cyberchondria is becoming progressively widespread in today's digital society. This study investigates the correlation between health anxiety and cyberchondria severity and evaluates the influence of demographic factors in stable asthma patients.

Methods: This cross-sectional study incorporated a sample of 51 patients with stable asthma. Sociodemographic data were systematically documented, and participants completed the Health Anxiety Inventory (HAI) and Cyberchondria Severity Scale-12 (CSS-12). Data analyses were performed using IBM SPSS Statistics v.22, Pearson and Spearman correlation analyses were employed to investigate relationships between variables, and multivariate linear regression was used to identify potential predictors of health anxiety.

Results: The sample primarily consisted of female (76.5%) and married (74.5%) individuals with a mean age of 41.47 years (SD:12.92). Smokers reported higher median scores in health anxiety compared to non-smokers, with a significant difference (p=0.023), while no significant difference in cyberchondria severity was seen across smoking statuses (p=0.380). A moderate positive correlation between health anxiety and cyberchondria severity scores was also identified (r=0.415, p=0.002). The regression analysis indicated that together, cyberchondria severity, smoking status, and education level accounted for a significant proportion of the variance in health anxiety scores (Adjusted R^2:0.374, p<0.001).

Conclusion: The study establishes a connection between health anxiety and cyberchondria severity in patients with stable asthma. The results suggest that health interventions targeting modifiable factors could be beneficial in reducing health anxiety within this patient group.

Keywords: Cyberchondria, Health Anxiety, Asthma, Cyberchondriac

INTRODUCTION

Asthma is a common respiratory disease, characterized by chronic airway inflammation and reversible airway obstruction, with coughing, sensation of chest tightness, and wheezing being the most frequently observed symptoms [1]. Along with environmental factors such as respiratory allergens, infections, and exposure to smoke, physical activities and psychological factors can also trigger asthma [2]. Additionally, psychological stress can affect our immune system, leading to an increase in airway inflammation [3]. Conditions such as depression and

anxiety are more prevalent in individuals with asthma compared to the general population and can disrupt asthma control and lead to exacerbations [4, 5].

The global spread of technological advancements and the increase in internet use are prompting individuals to seek more information about disease symptoms. Particularly with the widespread use of the internet and the ease of access to information, there is a notable surge in individuals' health information-seeking behavior. The ability to access information concerning disease symptoms enables people to become more conscious about their own health status and fosters a greater interest in health-related matters [6].

Cyberchondria was first described in 2001 in an article published by the British newspaper The Independent [7]. It is characterized by excessive or repeated online searches conducted by an individual to obtain information and reassurance about health and illness concerns [8]. Furthermore, this condition is also defined as the tendency of individuals to self-diagnose or self-treat by researching their perceived health problems on the internet [9]. Individuals referred to as cyberchondriacs experience distress and anxiety from researching symptoms that develop in their bodies on the internet, leading them to believe that they may have serious diseases that exhibit similar symptoms.

Health anxiety is a condition marked by an individual's persistent and excessive concern over their own health status. This anxiety often manifests as a fear of having, or the belief that one has, a serious illness, even when medical examinations suggest otherwise. These individuals may continuously scrutinize their bodily functions, misinterpret normal physical sensations as signs of illness, and seek constant reassurances through doctor's visits or health-related research, which can significantly impact their quality of life. Exaggerating normal physical signs and symptoms to the point where it affects their daily life, the concern that they may have a serious illness can lead to repeated hospital visits [10]. In a study conducted by Tanış et al., it was shown that individuals with high health anxiety were less satisfied with doctor examinations and tended to seek more information via the internet [11]. As a result, individuals with health anxiety may engage in more internet research, which can ultimately affect their daily functional levels, lead to a significant waste of time, and disrupt social interactions [12].

In recent years, rapid advancements in technology have led to an increase in research on cyberchondria. During the Covid-19 pandemic, it has been confirmed through the literature that individuals with high health anxiety are more prone to exhibit cyberchondriac behaviors [13].

Given that asthma can be triggered by stress and is often accompanied by anxiety disorders, it is hypothesized that individuals with asthma may exhibit different levels of health anxiety and cyberchondria compared to healthy individuals. A review of the literature has identified a lack of clinical research on this topic. This study aims to investigate the relationship between health anxiety and cyberchondria severity in individuals with asthma during stable periods, as well as the impact of sociodemographic factors on these variables.

Main Points:

- The study reveals high prevalence of smoking among medical students, particularly among males, indicating a gender disparity in smoking habits.
- Smoking correlate with lower cognitive flexibility levels in medical students.
- While no significant difference in dyspnea symptoms was observed between smokers and non-smokers in the short term, further research is needed to assess long-term respiratory effects.
- The findings highlight the urgent need for more effective interventions targeting smoking addiction among medical students and underscore the importance of multidisciplinary approaches in addressing this public health concern.

MATERIALS AND METHODS

This research is a cross-sectional clinical study conducted on asthma patients who are outpatient-followed at the chest diseases clinic, voluntarily willing to participate in the research, and who have completed the informed consent form. Inclusion criteria for the study include being between the ages of 18-65, being in the stable phase of asthma, and being literate. Exclusion criteria include being under 18 or over 65 years of age, having mental, neurological or any additional physical diseases apart from asthma, refusing to participate in the study, and being illiterate. Whether the patients were in the acute attack phase was evaluated by a chest diseases specialist through examination and application of the Asthma Control Test.

Ethical approval for the study was obtained from the Hitit University Clinical Research Ethics Committee with the decision dated 26/12/2023 and number 2023-165. This study complied with the research and publication ethics and was carried out in accordance with the Helsinki Declaration.

Patients who were voluntarily willing to participate and met the inclusion criteria were asked to fill out a sociodemographic data form inquiring about their gender, age, work status, educational level, smoking status, and marital status, in addition to the Health Anxiety Inventory (HAI) and Cyberchondria Severity Scale-12 (CSS-12). The obtained data were analyzed with appropriate statistical methods.

Health Anxiety Inventory (HAI)

This specific scale, tailor-made for the Turkish demographic through the efforts of Aydemir et al. in 2013 [14], was originally conceived by Salkovskis et al. back in 2002 [15]. The comprehensive scale features an array of 18 items, with a subset of 14 probing into the respondents' mental states and an additional four that explore their mental outlook under the hypothetical premise of enduring a severe illness. Responses throughout the scale are rated from 0 to 3, with a grading system as follows (for instance, "The fear of having a severe illness does not plague me generally; occasionally, I am apprehensive about having a severe illness; a significant illness concern is frequently on my mind; a continuous fear of severe illness prevails"). A ceiling score of 54 on the scale heightens the marker for acute health anxiety. The Cronbach's alpha reliability coefficient for gauging health anxiety in this study was found to be .89 [14].

Cyberchondria Severity Scale-12 (CSS-12)

The tool for measuring cyberchondria, recognized as heightened anxiety prompted by extensive online health inquiries, was crafted by McElroy and associates in 2019 [16]. The Turkish adaptation, alongside an assessment of its reliability and validity, was conducted by Söyler and colleagues [17]. This evaluation tool takes the form of a five-point Likert-type scale comprising 12 questions, with individual item scoring ranging from 1 to 5, where a higher tally indicates increased severity of cyberchondria. Scores on this scale can range from a low of 12 to a high of 60. The Cronbach's alpha correlation coefficient of the Turkish version was found to be 0.862 [17].

Statistical Analysis

The statistical analysis of the data was performed using the IBM Statistical Package for the Social Sciences (SPSS) software, Version 22, which was developed by IBM Corporation in Armonk, NY, USA. For each of the variables under consideration, we computed the means and standard deviations to summarize numerical data, while categorical data were presented through frequency distribution tables. We employed the Kolmogorov-Smirnov test to evaluate the normality of the distribution for the numerical dataset. To comparing numerical data between two distinct groups within the study, we utilized the non-parametric Mann-Whitney U test for datasets that did not follow a normal distribution. Conversely, for those datasets that were normally distributed, the parametric Student's t-test was the chosen method of analysis. To examine the relationships between different variables, we calculated Pearson or Spearman correlation coefficients, depending on whether the data were normally or non-normally distributed, respectively. In scenarios where there were three or more independent groups to compare, the Kruskal-Wallis test served as an efficient tool to assess the differences in medians. For the analysis of categorical data across different groups, the Chi-square test remained the standard approach. Throughout the analysis, a p-value of less than 0.05 was regarded as the threshold for statistical significance, beyond which the results were considered to hold true within a conventional confidence level.

RESULTS

A total of 51 stable asthma patients were included in our study, and the sociodemographic data of the patients are shown in Table 1.

The relationship between the smoking status of the patients included in the study and their health anxiety and cyberchondria severity scores is presented in Table-2.

The data pertaining to the correlation relationships between variables are summarized in Table 3.

No significant difference was detected between HAI (p:0.931) and CSS-12 (p:0.405) scores among patients grouped according to marital status (Mann-Whitney U test was applied.).

No significant difference was detected between HAI (p:0.228) and CSS-12 (p:0.962) scores between the groups according to

working status (Mann-Whitney U test was applied.).

No significant difference was detected between HAI (p:0.329) and CSS-12 (p:0.812) scores between the groups according to education level (Kruskal-Wallis test was applied.).

According to the multivariate linear regression analysis, which examined the effects of gender, age, marital status, employment status, educational status, smoking and CSS-12 score variables in predicting health anxiety, a significant regression model with a predictive power of 37.4% (Adjusted R2:0.374, p<0.001) has been detected. Regression analysis data is given in Table-4.

Table 1. Demographic Characteristics and Scale Scores of Participants

Sex	Female: 39 (%76.5) Male: 12 (%23.5)
Age	Mean: 41.47 (SD:12.92) Min: 18 Max:67
Illness Duration	Mean: 7.45 (SD:7.29) Min: 1 Max: 35
Marital status	Married: 38 (%74.5) Single: 13 (%25.5)
Smoking status	Yes: 6 (%11.8) No: 45 (%88.2)
Working status	Employed: 23 (%45.1) Unemployed: 28 (%53.9)
Education level	Primary education: 24 (%47.1) Secondary education: 10 (%19.6) Higher education: 17 (%33.3)
HAI score	Mean: 19.53 (SD: 7.63) Min:4 Max:45
CSS-12 score	Mean: 30.16 (SD: 9.01) Min:12 Max: 49

** For numerical variables, normal distribution was evaluated with the Kolmogorov-Smirnov test. Age, Health Anxiety Scale Score and Cyberchondria Scale Score data were normally distributed. Disease duration data were not normally distributed.*

Table 2. Relationship between smoking status with Health Anxiety and Cyberchondria severity scores

	Smoker (n:6)	**Non-Smoker (n:45)**
HAI score	Median:27.0 IQR:17.0	Median:19.0 IQR:9.5
CSS-12 score	Median:34.5 IQR:13.5	Median:31.0 IQR:12.5

** Mann-Whitney U test was used. p<0.05 was accepted as significant.*

Table 3. The correlations between numeric variables

	HAI score	**CSS-12 score**	**Age**	**Illness Duration**
HAI score	r:1.000 p:-	r:0.415* p:0.002	r:-0.021* p:0.886	r:-0.081** p:0.570
CSS-12 score	r:0.415* p:0.002	r:1.000 p:-	r:-0.119* p:0.406	r:0.070** p:0.623
Age	r:-0.021* p:0.886	r:-0.119* p:0.406	r:1.000 p:-	r:0.245** p:0.083
Illness Duration	r:-0.081** p:0.570	r:0.070** p:0.623	r:0.245** p:0.083	r:1.000 p:-

** Pearson Correlation Analysis was applied. **Spearman Correlation Analysis was applied. p<0.05 was accepted as significant.*

Table 4. Effects of variables in predicting HAI score

	β	Std.Error	Beta	t	p	%95 Confidence Interval	
						Lower	Upper
Constant	15,215	12,234		1,244	,220	-9,473	39,903
Sex	4,192	2,789	,235	1,503	,140	-1,435	9,820
Age	-,104	,090	-,175	-1,156	,254	-,284	,077
Marital status	-1,991	2,280	-,115	-,874	,387	-6,592	2,609
Working Status	-,587	2,397	-,039	-,245	,808	-5,425	4,251
Education Level	-4,927	1,584	-,578	-3,111	,003	-8,123	-1,731
Illness Duration	-,205	,131	-,196	-1,560	,126	-,470	,060
Smoking	7,816	2,771	,333	2,821	,007	2,224	13,408
CSS-12 score	,324	,104	,383	3,131	,003	,115	,534

** Multivariate Linear Regression Analysis was applied. HAI Score was determined as the Dependent Variable. The Enter method is preferred. $p<0.05$ was considered significant. (R2:0.474, Adjusted R2:0.374, $p<0.001$)*

DISCUSSION

This study evaluated the demographic factors related to health anxiety and cyberchondria severity and determined the correlation between these two constructs among asthma patients. Key findings indicated a demographic majority of female and married patients, with a mean age in the early forties. The mean duration of illness among these asthma patients suggests the presence of long-term medical conditions. Significantly, health anxiety levels were greater among smokers compared to non-smokers, although cyberchondria scores did not show a significant variance between both groups. A moderate positive correlation between health anxiety and cyberchondria severity was observed. Variations in marital status, working status, and education levels did not show significant impacts on the health anxiety or cyberchondria severity. Notably, cyberchondria severity, smoking status, and education level were major predictors of health anxiety in the asthma patient group.

This study has provided important insights into how specific demographic factors relate to health anxiety and cyberchondria severity among patients with asthma. The predominance of female and married individuals within the cohort, coupled with a fairly broad age range (mean age of 41.47), correlates with the demographic profile generally observed in asthma populations [18, 19]. However, it is worth considering how gender and marital status may contribute to or influence the coping strategies and support mechanisms available to patients, potentially affecting their health anxiety levels.

The illness duration, with its average of 7.45 years, indicates a patient group that is likely acquainted with the long-term management of their condition. Chronic illness is known to be a significant predictor of health anxiety, as patients need to navigate complex health information and make frequent health-related decisions [20]. These factors may contribute to a greater reliance on internet-based health resources, which can inform and also potentially amplify health-related concerns; this hypothesis is supported by our findings and relevant literature on the interplay between health anxiety and cyberchondria severity [20, 21].

The significant finding that smoking patients reported higher health Anxiety levels aligns with existing literature, which suggests that the perception of increased vulnerability to health complications can exacerbate anxiety in individuals with detrimental health habits like smoking [22-24]. Curiously, such a pattern was not repeated with cyberchondria severity. This lack of significant deviation may be indicative of the unique pathways through which health anxiety and cyberchondria develop and manifest; habits such as smoking might specifically trigger health anxiety due to the direct perceived risk they pose, whereas cyberchondria might be more closely aligned with information-seeking behavior and the resultant cognitive processes, regardless of smoking status.

The moderate positive correlation between health anxiety and cyberchondria severity ($r=0.415$, $p=0.002$) underscores a significant relationship worthy of further exploration. This link could be elucidated by the proposition that frequent online health information seeking, characteristic of cyberchondria, may not only reflect but also contribute to greater levels of health anxiety. Although the delineation of causality requires additional research, the correlation found in this study is in keeping with the

notion that seeking reassurance about health concerns online can lead to a cyclic pattern of anxiety. Positive correlations of varying degrees between these two variables have been identified in clinical studies conducted within different populations [12, 25]. Our research appears to be the first study specifically conducted among asthma patients.

Analyzing the patients' marital, working status, and education levels revealed no significant impact on health anxiety or cyberchondria severity. This could suggest a more complex interplay of individual psychological variables and the disease's characteristics, which overshadow the impact of these social and economic factors on the patients' psychological well-being [26]. Alternatively, this might reflect the homogeneity of the sample in terms of these variables, which could mask underlying trends.

In the regression analyses conducted, cyberchondria severity, smoking status, and education level were significant predictors of health anxiety levels, accounting for a considerable portion of the variance. The clear influence of education level emphasizes the importance of health literacy in managing health anxiety, aligning with previous research that has linked higher education levels with a better understanding and more effective management of chronic illness. The data compiled in Table -4 of the multivariate linear regression analysis further underscores the roles of these three major predictive factors, drawing attention to potential targets for intervention. There are numerous studies in the literature investigating the predictors of health anxiety, with results showing variability [27-29]. For instance, programs aimed at reducing smoking prevalence among asthma patients or educational initiatives designed to improve health literacy and promote critical evaluation of online health information could be beneficial in reducing health anxiety and mitigating the severity of cyberchondria.

In recent years, particularly due to the pandemic, disruptions in healthcare services have triggered cyberchondria and health anxiety, thereby accelerating academic research into these issues [13, 30, 31]. This study contributes to the growing body of literature on health anxiety and cyberchondria by highlighting specific predictors and correlates within a sample of asthma patients. It lays the groundwork for future research to develop more nuanced interventions tailored to the needs of this population, with an emphasis on modifiable lifestyle factors and the critical evaluation of health information in the digital age.

Limitations

The study on the relationship between health anxiety, cyberchondria severity, and demographic factors among asthma patients presents several limitations. The sample size is relatively small and demographically homogeneous, predominantly comprising women and married individuals, which may limit the generalizability of the findings to a broader population. The cross-sectional design prohibits the determination of causality and temporal relationships between the variables. The use of self-reported measures for health anxiety and cyberchondria severity could introduce response biases, and the lack of objective measures might affect the accuracy of the results. Additionally, the study does not account for other potentially influential unmeasured variables such as psychological traits, other comorbidities, and cultural factors that might impact health anxiety and cyberchondria. The influence of broader access to health information technology and the global digital divide also remain unexplored, presenting avenues for further research that should involve larger, more diverse samples and longitudinal study designs to validate and expand upon these findings.

CONCLUSION

In conclusion, this study enriches the existing literature by elucidating the intricate association between health anxiety and cyberchondria severity in asthma patients, while also factoring in demographic influences. Despite its limitations in size and scope, the research provides valuable insights into the predictive nature of cyberchondria severity, smoking status, and education level on health anxiety. These findings set the stage for future research to further explore these dynamics through larger, longitudinal studies that could offer more definitive information on causality and guide the development of targeted interventions. The study ultimately underscores the complex interplay between lifestyle factors, access to online health information, and the psychological well-being of individuals living with chronic health conditions.

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Ethical Approval: Ethical approval for the study was obtained from the Hitit University Clinical Research Ethics Committee with the decision dated 26/12/2023 and number 2023-165, in accordance with the Helsinki Declaration.

Author Contributions: Conception: D, B; EK, A, - Design: D, B; EK, A - Supervision: D, B; EK, A - Fundings: -Materials: D, B; EK, A - Data Collection and/or Processing: D, B; EK, A - Analysis and/or Interpretation: D, B; EK, A - Literature: D, B; EK, A - Review: D, B; EK, A - Writing: D, B; EK, A - Critical Review: D, B; EK, A.

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Original Research

Bibliometric Analysis of Publications on Stapedius Muscle

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ABSTRACT

Objective: The clinical importance of the stapedius muscle has been particularly emphasized in several publications. The purpose of this study is to bibliometrically analyze all publications on the stapedius muscle and to determine research trends related to this muscle.

Methods: The publications related to the stapedius muscle were identified by the Web of Science database. A total of 548 publications were discovered throughout the literature review. Bibliometric techniques were employed to analyze the identified publications (VOSviewer Version 1.6.13).

Results: The first studies were conducted in the 1980s. The highest number of publications related to the stapedius muscle was in 2020 (22 studies), while the lowest was in 1985 (2 studies). Most of the publications (90.11%) were written in English. The USA was the most prolific nation, with John J. Guinan having written the most articles on the stapedius muscle. Harvard University was also the most prolific institution.

Conclusion: The findings demonstrated the researchers' interest in the stapedius muscle and offered quantifiable information regarding the muscle's position within the scientific domain. Recent years have seen an increase in studies on this topic. To the best of our knowledge, it can be said that this study is the first bibliometric analysis on the stapedius muscle.

Keywords: Stapedius muscle, stapedius, bibliometric analysis, Vosviewer

INTRODUCTION

The stapedius muscle is known as the smallest skeletal muscle in the body and functions to modulate sound waves as an intratympanic muscle. The muscle is formed by fibers from the posterior belly of the digastric muscle, which pass through the stylomastoid foramen and extend to the neck of the stapes bone [1,2]. It contracts in reflex synchronization with the tensor tympani muscle. Its function is to prevent excessive movement of the stapes and reduce the amplitude of sound [3, 4]. The stapedius muscle is innervated by the facial nerve, and paralysis of the stapedius muscle may cause hyperacusis, a condition in which patients perceive normal sounds as abnormally loud [5, 6]. Regarding its relationship with the facial nerve, there are many studies on the imaging of the stapedius muscle and its relationship with the facial nerve [7]. It appears that auditory functions, auditory reflexes, hearing, and cochlear implants

are the main topics related to the muscle [8, 9]. The clinical importance of the muscle has been particularly emphasized in several publications in recent years.

A bibliometric viewpoint looks at publications through a quantitative lens, analyzing them with statistics. This analysis can be evaluative, such as citation analysis, to examine how much work has been done in a particular field, the types of these studies, and how these papers have influenced other research [10]. Bibliometric studies are able to detect worldwide research dynamics and trends in a scientific subject over time in this manner [11]. The authors of this study aimed to conduct a comprehensive and holistic bibliometric analysis of studies on the stapedius muscle and to emphasize the importance of the muscle in scientific research.

MATERIALS AND METHODS

Articles on the stapedius muscle were accessed through the Web of Science (WoS) database using the keywords "stapedius muscle" OR "stapedius," in all fields. The VOSviewer package program (Version 1.6.13, Leiden University: Centre for Science and Technology) was used to perform bibliometric analysis on all publications on the stapedius muscle in WoS that were downloaded using this search approach (access date: 20.11.2023) [12]. The searching strategy diagram can be appreciated in Fig. 1.

Data Analysis

The keywords "stapedius muscle" OR "stapedius" were found in the WoS database search by choosing "all fields." According to the years, 445 articles were examined from 47 different disciplines/fields, the oldest being 1980 and the newest being 2023. The data was analyzed by author-citation-journal-country-institution and keywords, then presented as frequency and percentage.

Main Points;

- Our study indicated an increasing trend in stapedius research since 2011.
- Our keyword analysis is advantageous to the research of hotspots in the field of stapedius muscle.
- Considering the clinical significance of the muscle, it is mainly emphasized in subjects such as hyperacusis, otitis media, birth defects, and cholesteatoma.

RESULTS

548 publications were found throughout the literature review. 445 of them were articles. Of these, 90.11% (401) were written in English. Others were written in German (6.9%), Spanish (1.3%), French (0.4%), Hungarian (0.2%), Polish (0.2%), Portuguese (0.2%), Serbian (0.2%), Turkish (0.2%). Other document types were shown on Fig.2.

The first studies on the stapedius muscle were in the 1980s. It was seen that the most publications related to muscle were in 2020 (22 studies) and the least publications were in 1985 (2 studies). There weren't many articles published between 1980 and 1991. When comparing the total number of articles published throughout all years, The quantity of publications published between 1980 and 1991 was discovered to be less than average (Mean±standard deviation: 10.11±4.39 articles). Since 2011, studies on this topic have exceeded the average number of articles. Fig. 2 shows the distribution of articles on stapedius muscle according to years.

Active Authors and Institutions

The author who wrote the most articles about the stapedius muscle was as follows; Guinan, John J. (11), Counter, S. Allen (11), Borg, E (8), Kawase, Tetsuaki (8), Volk, Gerd Fabian (7), Guntinas-Lichius, Orlando (7), Margolis, Robert H. (6), Feeney, M. Patrick (6), Keefe, Douglas H. (6), Laszig, Roland (5).

The highest ten institutions producing the most articles on the stapedius muscle were as follows; Harvard University (26), Karolinska Institutet (25), Harvard Medical School (16), Massachusetts Eye Ear Infirmary (14), Hannover Medical School (11), Karolinska University Hospital (11), Massachusetts Institute Of Technology Mit (9), Radboud University Nijmegen (8), Tohoku University (8), Friedrich Schiller University of Jena (7).

Popular WoS Categories and Active Research Areas

The highest number of articles were found in the field of otorhinolaryngology. The top ten research areas and numbers of studies related to stapedius muscle in WoS were found to be as follows: Otorhinolaryngology (288), Neurosciences Neurology (109), Audiology Speech Language Pathology (79), Anatomy Morphology (25), Surgery (22), Zoology (15), General Internal Medicine (13), Research Experimental Medicine (13), Pediatrics (11), Radiology Nuclear Medicine Medical Imaging (11).

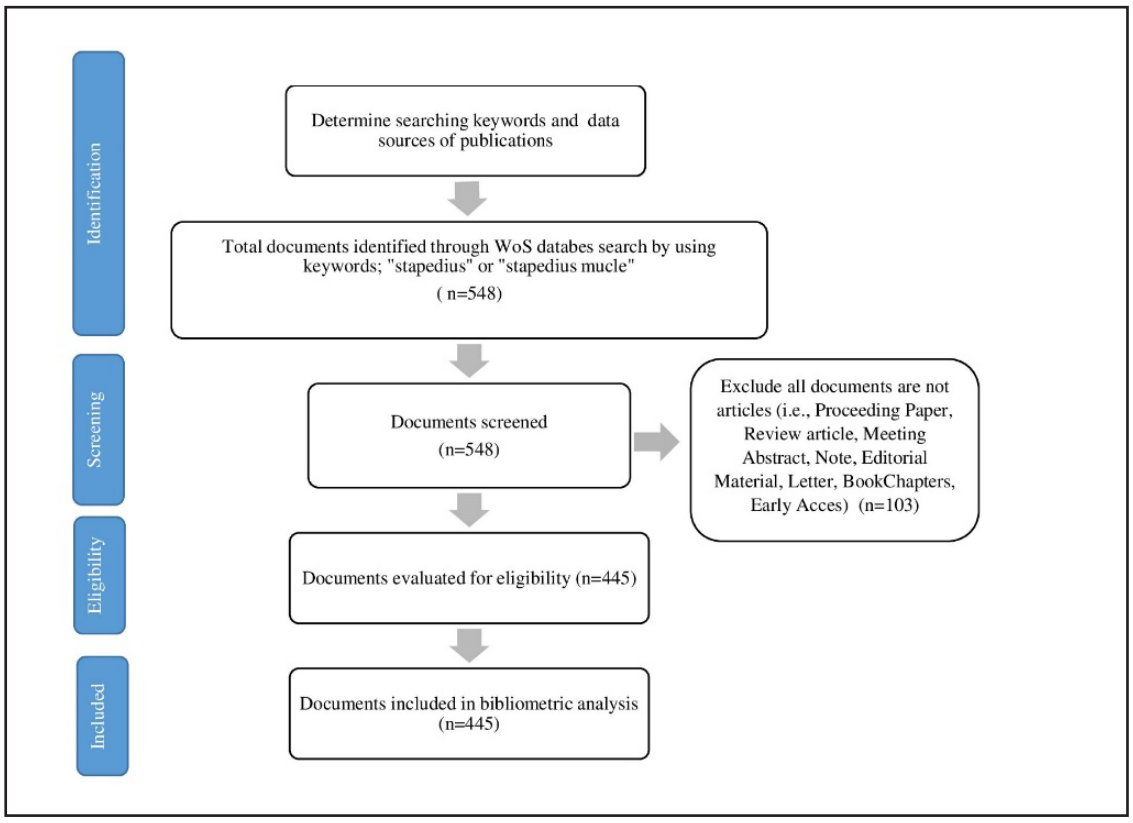

Figure 1. Flow chart diagram for the searching strategy

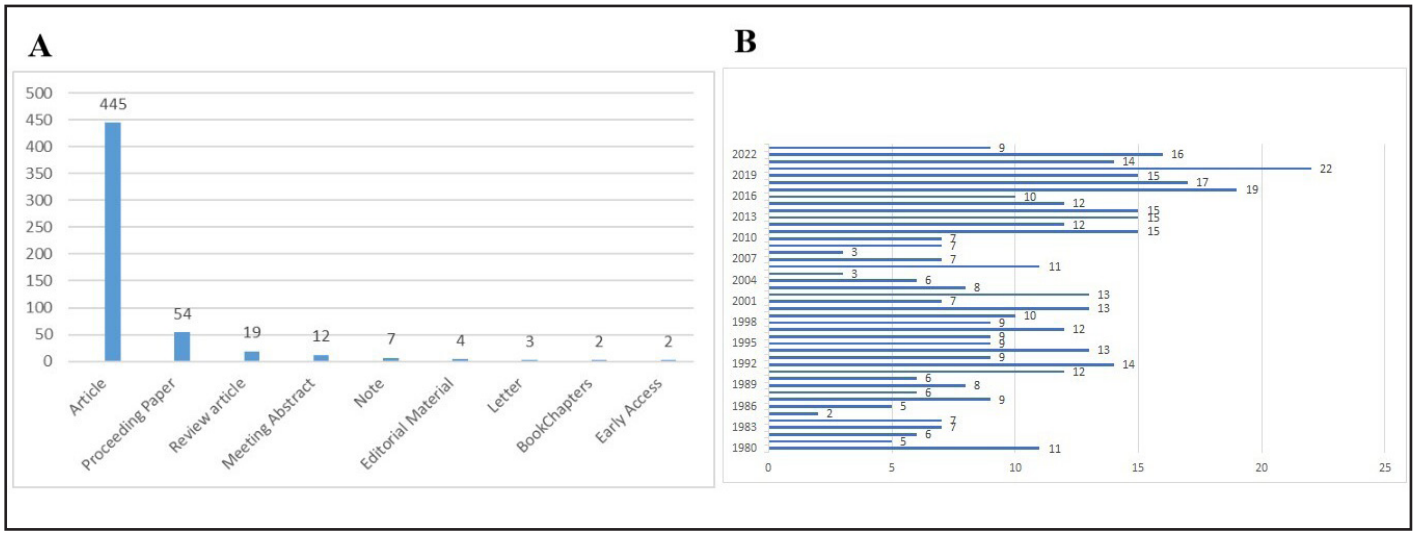

Figure 2. Overview of publications on stapedius muscle. **A:** Distribution according to the types of publications on stapedius muscle. **B:** Distribution of articles on stapedius muscle according to years.

Likewise, in the WoS category, it was seen that the first ranking studies were conducted in the otorhinolaryngology category. The top categories and numbers of stapedius studies in WoS were found to be as follows: Otorhinolaryngology (288), Audiology Speech Language Pathology (79), Neurosciences (68), Clinical Neurology (45), Anatomy Morphology (25), Surgery (22), Zoology (15), Medicine General Internal (13), Medicine Research Experimental (13), Pediatrics (11).

Active Countries

The ten nations with the highest number of producing the most articles about the stapedius were as follows : USA (118), Germany (59), Sweden (34), Austria (26), Japan (26), İtaly (23), Turkey (23), Canada (20), England (18), Netherlands (16). Fig. 3 shows the distribution of the all active countries on the publication of the muscle.

Countries of Co-Authorship Analysis

The network analysis of countries' co-authorship was used to analyze and present regional collaboration. Fig. 3 shows a network analysis of country co-authorship. The amount of documents in each country is represented by the size of the circle. The circle's size and the number of documents are parallel. As the number of documents increases, the circle's size increases. The thickness of the link represents collaboration between countries. The thicker the line, the greater the cooperation between the countries. The USA had the most articles and the first largest total link strength. The main partners of the USA were China, Ecuador, and Sweden. France also ranked second with the highest number of articles and strongest cooperation relations with major partners such as the USA, Canada, Austria, and England.

Active Journals

There were 151 journals that published articles about the stapedius muscle. Ten of these journals had more than ten articles each. As shown in Fig. 4, the majority of papers appeared in *"Acta Oto-laryngologica" (ISSN: 0001-6489*) which is an international journal for translational otolaryngology and head-and neck surgery. The journal presents cutting-edge papers on clinical practice, clinical research and basic sciences. Features of the journal include Inner and Middle Ear, Otoneurology, Audiology, Central Labyrinthine Pathways, Nose/Sinus, Mouth/ Pharynx, Larynx, Salivary Glands, Oncology.

Citation Analysis

A total of 4588 citations were made in the WoS database for studies on stapedius muscle between 1980 and 2023. The ten most cited studies and the number of citations are given below (Table 1) [13-22].

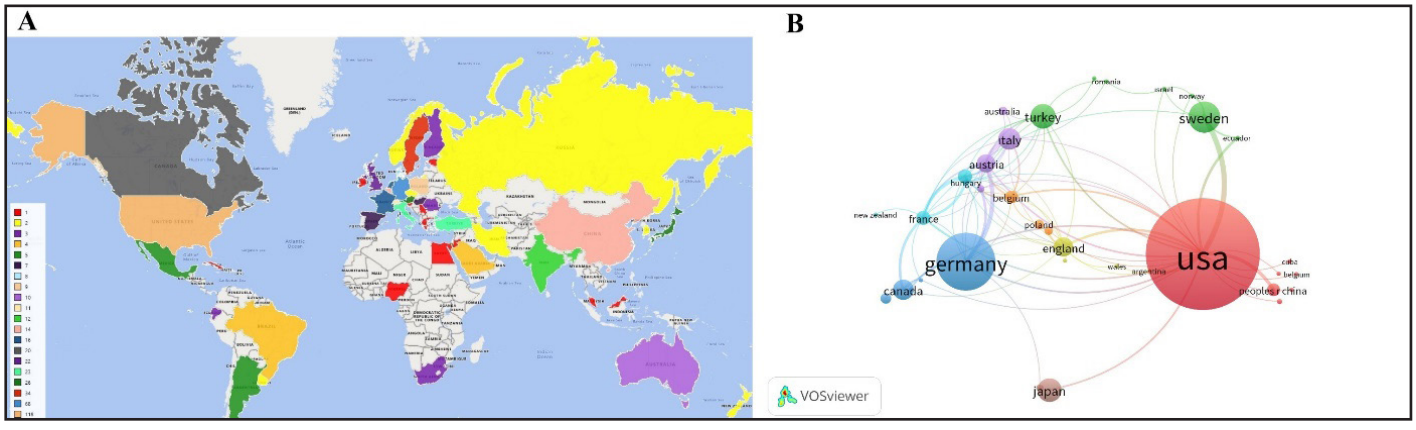

Figure 3. Analysis of publications and countries on stapedius muscle. **A:** The distribution of the active countries on the publications of stapedius muscle. **B:** Network analysis of co-authorship of countries.

Table 1. The ten most cited articles and the number of citations

Article	Citation number	Average citation per year
Peitersen [13]	630	28.64
McCue and Guinan [14]	247	8.23
Brantberg et al. [15]	158	6.87
Gordon et al. [16]	97	4.85
Thompson and Thompson [17]	91	2.76
Cafarelli Dees et al. [18]	75	3.95
Bergenius and Perols [19]	70	2.8
Mukerji et al. [20]	67	4.79
Feeney et al. [21]	61	8.71
Svensson et al. [22]	59	8.43

Keyword Analysis

The facial nerve, stapedius reflex, temporal bone, cochlear implant, and tensor tympani muscle were found to be the most frequently used terms in literature about the stapedius muscle. The rare topics related to the stapedius muscle were determined to be vocalization, stapedius muscle canal, speech discrimination, facial nerve palsy, and Bell's palsy. A prominent keywords map related to stapedius muscle research is displayed in Fig. 4.

DISCUSSION

Examining scientific studies with bibliometric approaches provides an understanding of the place of topics in the literature and offers insights into their popularity and future status [23]. The current study's findings, which examined research on the stapedius muscle worldwide, demonstrated the interest researchers have in the subject and provided quantitative information regarding the muscle's position within the scientific community.

Average number of publications per year, document types, article language, keywords related to this subject and citation analysis per publication were determined for all studies. Furthermore, the most cited works in the field among those covered by the data set were identified. The stapedius muscle has been the subject of 4588 citations in the WoS database; stapedius-related articles have been published in 151 journals, 47 domains, and 51 WoS categories. It is seen that several researches have been studied on the stapedius muscle in a variety of categories and fields.

In terms of the number of publications per year, it was discovered that more publications were made than average after 2011 and that academic interest in the subject area of stapedius muscle increased after 2011, and it was observed that 42.92% of the publications were formed by works published between 2011 and 2023. In terms of publication types, it was discovered that there are 9 different document types, with articles being the

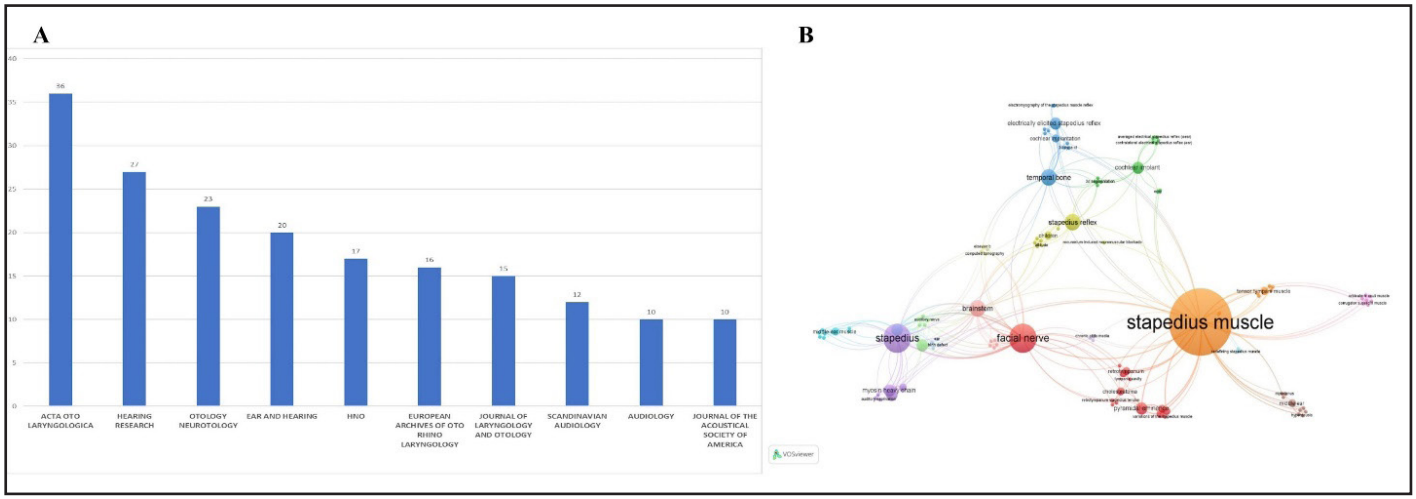

Figure 4. Analysis of journals and research hotspots on stapedius muscle. **A:** The top 10 most active journals that published articles on the stapedius. **B:** The network visualization map for cluster analysis based on keyword analysis on the stapedius

most common study type (81.2%). It was seen that almost all of the publication language of the works was English (90.11%), followed by German (6.9%).

Active country analysis identifies countries with a strong research platform in various disciplines. Cooperation between these countries strengthens the scientific network. It is necessary to increase research co-operation with influential countries and strengthen the network between countries [24]. This study revealed that USA, Germany, Australia, Sweden are the countries that have conducted the most studies on the stapedius muscle. Regarding country collaborations, the USA realized the highest number of cooperation with other countries. It could be said that France, Austria, and Germany guide the studies. It was also concluded that active countries are more effective in co-authorship. The economic size and opportunities of the aforementioned countries may have an impact on the productivity of publications [25]. When we evaluate the contribution of the institutes to stapedius muscle, we could say that the results are parallel to the prolific countries about the topic. The top active universities on this topic seem to be in the United States, Germany, and Sweden.

Keywords in academic studies are primarily used by indexing systems to identify the most relevant matches for a search query in search engines, scholarly databases, and library catalogs. Additionally, keywords are the predictors of the discoverability of academic articles and the keys to how articles are found [26]. We believe that using keyword analysis to study hotspots in the stapedius muscle field is advantageous. Regarding the keyword analysis, it is clear that tympanic cavity and temporal bone studies are closely related to the stapedius muscle. The noteworthy details are that there is a tendency to use computerized tomography and EMG in studies related to the muscle. Considering the clinical significance of the stapedius muscle, it was determined that the muscle is mainly emphasized in subjects such as hyperacusis, otitis media, birth defects, and cholesteatoma. It is seen that studies on the tensor tympani muscle also come to the forefront in the keywords map. In addition, the map analysis shows the stapedius muscle is important in the cochlear implant. In the literature, it was observed that the muscle's relationship with the auditory nerve and facial nerve was examined, it was the focus of studies on auditory functions and auditory reflexes, and it was studied in research conducted with children. Furthermore, analysis shows that the rare topics related to the stapedius muscle were determined to be vocalization, stapedius muscle canal, speech discrimination, facial nerve palsy, and Bell's palsy.

Citations are seen as a sign of scholarly achievement for authors and journals. Finding the articles that have been cited the most is crucial for obtaining high-quality papers about that topic [23]. The top 10 articles on stapedius muscle with the most citations provide valuable information to guide the researchers who want to write articles on this subject. According to a review of the journals where scholarly research on the stapedius muscle have been published, *"Acta Oto-laryngologica" (ISSN: 0001-6489*) had the most published works (n=36). Moreover, 3 articles, in the list of the 10 most cited articles, were found in this journal [13, 15, 19]. We think that the journal is an important source of publications that carry key importance in this field. It is seen that the 10 most cited articles are related to hearing and auditory function and emphasize the importance of the stapedius muscle in this field. In addition, the most cited articles are published in the journals that publish the most studies on this topic.

Regarding the citation analysis, the article written by Peitersen [13]. received the most citations and the most average citations per year. The most cited 10 articles and the number of citations table examined, the articles written by Feeney et al. [21], and Svensson et al. [22] were ranked 9th and 10th in the citation number, but these articles were found to be the second and third most cited articles according to the annual average number of citations.

Higher-quality outcomes, the acquisition of new skills, and interdisciplinary exchange of ideas are all made possible by collaborative research. Multidisciplinary research provides different approaches and perspectives on problems [27]. Since the mid-twentieth century, research has moved away from being done in a single discipline and toward collaboration. The reason for this trend is the result of both increased specialization and the growth of knowledge within the fields of academic inquiry. As a result, interest in collaborative research systems has increased [28]. Category analysis shows that Otorhinolaryngology, AudiologySpeech Language Pathology, Neurosciences, Anatomy Morphology, Surgery, Zoology and Paediatrics are the main categories for stapedius muscle in the WoS. The stapedius muscle was shown to be a part of numerous categories. This might arise from the fact that stapedius muscle is a topic of collaborative research.

Limitations

The current study has a few limitations. This study analyzed only published articles that were included in the WoS database. There was no use of databases like Scopus and PubMed. Journals from non-English speaking nations may therefore be underlooked. Furthermore, the analysis only included articles; other categories were left out. The lack of consideration for self-citations in the citation analysis could have led to a bias in the quantity of citations for certain nations, journals, and authors.

CONCLUSION

To the best of our knowledge, we could say that this study is the first bibliometric analysis on the stapedius muscle. A comprehensive summary of 445 articles on the stapedius muscle in WoS up to November 20, 2023 is presented in this study. In addition, the most interested and cited journals related to stapedius muscle were included. Trending topics and rare topics studied in conjunction with stapedius muscle were presented. Our study is a guideline for researchers who plan to study on the stapedius muscle.

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Original Research

Can Incidental Gallbladder Cancer Be Predicted Before Cholecystectomies?

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ABSTRACT

Objective: Gallbladder cancer is a rare disease with a high mortality rate. The gold standard of treatment is based on early diagnosis and eradication of the disease with effective surgery. Almost 70% of cases are detected incidentally in the final pathology report of routine cholecystectomies. Our study aims to predict incidental gallbladder cancer in patients scheduled for surgery for benign reasons.

Methods: Biological characteristics, medical history, family history of hepatobiliary disease, radiological imaging, and laboratory parameters were analyzed in 2852 patients operated on for benign reasons in the general surgery department over 63 months. Patients with incidental gallbladder cancer were compared with patients with cholecystitis. The effects of independent variables in predicting cancer between the two groups were analyzed.

Results: Of 2852 patients who underwent cholecystectomy, 13 (0.45%) had incidental gallbladder cancer. The cancer incidence rate was 0.28% (2/700) in men and 0.51% (11/2139) in women. This difference was not statistically significant (p: 0.34). Among the biological characteristics, history of acute cholecystitis (p: 0.001), and laboratory findings, neutrophil-to-lymphocyte ratio (NLR) (p: 0.001) were the most striking variables. When variables with proven statistical value were tested by logistic regression analysis, NLR (p: 0.001), biliary polyps (p: 0.001), and gallstones (p: 0.038) were ranked as the most valuable cancer predictors, respectively.

Conclusions: In older patients with a history of acute cholecystitis, especially if there are large stones, polyps, and wall thickening on imaging, the possibility of cancer should be considered considering the NLR value, and surgery should be performed under optimal conditions by informing the patient and relatives.

Keywords: Acute Cholecystitis, Cholecystectomy, Gallbladder Neoplasms, Gallstones, Polyps

INTRODUCTION

Gallbladder cancer is a very rare disease with devastating consequences. Early diagnosis is essential due to the failure of treatments other than surgery. It is known that the incidence rate in male patients, especially in Western societies, is less than 1 per 100,000 population, whereas it can be as high as 1.4 in women. In Eastern European communities, including our country, the incidence can be up to 5 times higher [1]. The

most important predisposing factors are gallstones (especially porcelain bladder), chronic cholecystitis, bile polyps, advanced age, female gender, and bile duct anomalies [2]. It is difficult to detect before it becomes symptomatic. Therefore, almost 70% of cases are detected incidentally after surgery [3]. It is known that incidental cancer is detected in 0.2-2.9% of cholecystectomies performed for benign gallbladder diseases [4]. When reviewing the final pathology report, this unpleasant surprise can leave inexperienced clinicians in a quandary. Simple cholecystectomy may be sufficient only for invasion of the gallbladder mucosa and lamina propria (T1a). In cancers invading the muscular layer (T1b and other T stages), management between surgery, systemic therapy, or palliative options is possible in better-equipped centers and with experienced clinicians [5]. Despite all these treatments, it is known that the 5-year survival rate of patients who cannot be detected at an early stage does not exceed 5% [6]. The gold standard in the surgical treatment of benign gallbladder diseases worldwide is laparoscopic cholecystectomy. Cholecystectomy operations constitute the majority of laparoscopic operations performed in the general surgery department. It is thought that predicting incidental cancer cases in the preoperative period may provide significant advantages in treatment management. The aim of this study is to contribute to the prediction of early-stage gallbladder cancers and improve treatment management.

MATERIALS AND METHODS

The study was conducted using the data of patients who underwent surgery for benign gallbladder diseases at Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital. Cholecystectomy operations performed in the 63 months between June 2018 and September 2023 were analyzed. Consent was obtained from patients to use medical records, and an official approval report for the study was prepared by the ethics committee within the hospital. Demographic information and detailed anamnesis were obtained by interviewing the patients or their companions. In addition to information about hepatobiliary pathologies, comorbidities, smoking, environmental exposure, and gallbladder pathologies of first-degree relatives were also questioned. Imaging findings, laboratory results, preoperative ASA scores (American Society of Anesthesiologists Classification), and operation reports were carefully analyzed using the hospital information management system. Patients operated on with a diagnosis of primary gallbladder tumor, cholecystectomies performed during surgical intervention for a different reason, patients who were currently being treated and actively followed up for malignancy, patients under 18 years of age, and pregnant women were excluded from the study.

Main Points

- Gallbladder cancer is a disease with a very high mortality rate when not detected early.
- It is known that the incidence of incidental gallbladder cancer can be as high as 1.4% in Western societies and even higher in Eastern societies.
- Prediction of incidental cancer requires additional preparations correlated with the extent of the surgical intervention.
- A history of cholecystitis, thickening of the gallbladder wall, large gallstones and polyps, and a high neutrophil-to-lymphocyte ratio in blood tests should warrant a careful approach to these patients.

Statistical Analysis

All analyses were performed using SPSS version 22 for Windows software. Numerical data were analyzed for normality using the Shapiro-Wilk test. Patients were divided into two groups: malignant pathology and normal cholecystitis. Pearson's chi-square test was used to analyze categorical variables, and Fisher's exact test was used in small groups. A comparison of numerical variables was performed using the Students T-test or Mann-Whitney U test. Logistic regression analysis was used to measure the predictive values of statistically significant variables. ROC (receiver operating characteristic curve) analysis was preferred for the cut-off value.

RESULTS

The mean age of the 2852 patients included in the study was 47 (18-87) years. The difference with the neoplasm group (mean 55) was statistically significant (p:0.02). 75.4% (2150) of the participants were women. Contrary to the literature, there was no difference in malignancy rates according to gender [7, 8]. The number of patients with life-threatening severe comorbidities was 364 (12.8%). Body mass index (BMI), comorbidities, and ASA scores increased with age (p:0.01). However, unlike age, the different distribution of these parameters between the two groups was not statistically significant. Patients with a history of hospitalization for at least one acute cholecystitis were almost 14%.

In contrast, those with a history of multiple episodes of cholecystitis were significantly higher in the neoplasm group (p:0.001). The cholecystectomy rate for benign gallbladder diseases in first-degree relatives was also higher in the neoplasm group (p:0.03). Demographic and biological data of the participants are summarized in Table 1.

When the participants' imaging, laboratory parameters, and operative findings were compared, it was found that the high neutrophil-to-lymphocyte ratio (NLR) was significantly characteristic of the neoplasm group (p:0.001). A cut-off value of 2.9 was also calculated for NLR (Figure 1). When the presence and size of polyps were evaluated categorically, it was the second most valuable parameter in terms of neoplasm (p:0.002). The other significant findings were gallstones and increased wall thickness (p:0.03, p:0.04, respectively). All these variables are summarized in Table 2.

When statistically significant variables were evaluated by logistic regression analysis, the presence of NLR and biliary polyp were the two most valuable predictive values (p:0.001), followed by the presence of large gallstones (especially porcelain gallbladder) (Table 3).

Table 1. Demographic and biological data of the participants

Variables	Neoplasm (n:13)	Cholecystitis (n:2839)	P value
Age (mean)	55 (39-67)	47 (18-86)	**0.02**
Sex(male/female)	2/11 (15.4% / 84.6%)	700/2139 (24.7% / 75.3%)	0.34
ASA Score (median)	2	2	0.93
Comorbidity	3 (23.1%)	361 (12.7%)	0.22
BMI (mean)	26.4 (22-31)	25.6 (18-42)	0.33
Smoking	5 (38.5%)	713 (25.1%)	0.21
HoC (1/1<)	1/2 (7.7% / 15.4%)	394/34 (13.9% / 1.2%)	**0.001**
HoF	2 (15.4%)	67 (2.4%)	**0.03**
DoS*	19.3 (2-60)	10.8 (1-60)	0.12

Chi-Square, Student's t-test, *Mann Whitney-U, ASA: American Society of Anesthesiologists; BMI: body mass index; HoC: history of acute cholecystitis; HoF: family history of cholecystectomy; Dos: duration of symptoms

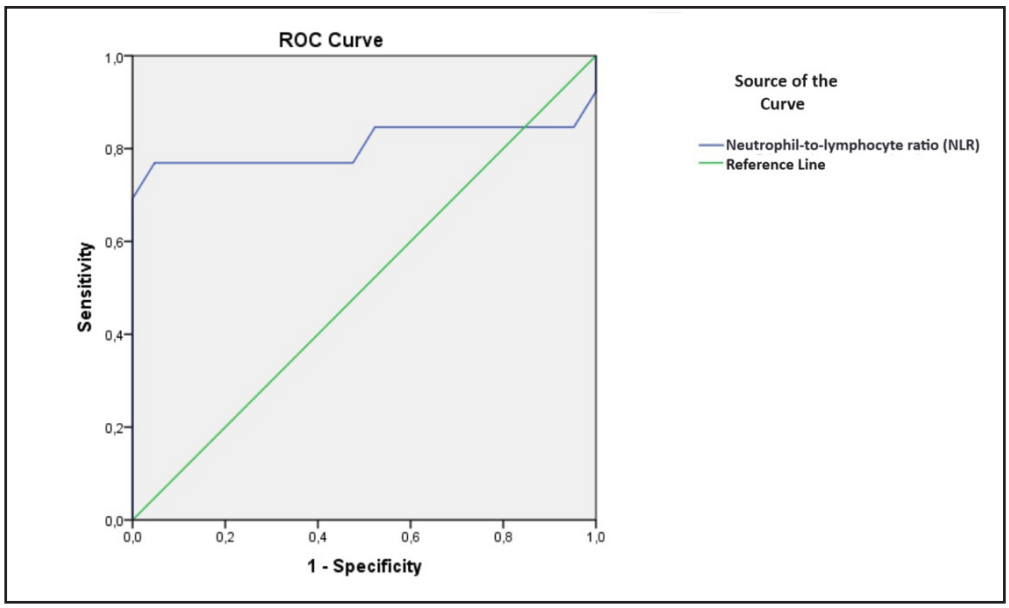

Figure 1. ROC analysis of neutrophil-to-lymphocyte ratio (NLR) in the prediction of gallbladder cancer.

Table 2. Clinical and laboratory differences between groups

Variables		Neoplasm (n:13)	Cholecystitis (n:2839)	P value
Wall thickening		5 (38,5%)	444(15,6%)	**0.04**
Gallstones	none	3	330	**0.03**
	<1cm	5	2182	
	1-2 cm	2	218	
	>2cm	2	81	
	porcelain	1	28	
Polyps	none	9	2575	**0.002**
	<5mm	1	215	
	5-10mm	1	43	
	>10mm	2	6	
HGB (g/dL)		13.24	13.89	0.14
WBC ($\times 10^9$/L)		9.16	8.75	0.55
Lymphocyte ($\times 10^9$/L)		2.02	2.09	0.71
Neutrophil ($\times 10^9$/L)		6.47	5.86	0.23
Platelet* ($\times 1000/\mu L$)		190	202	0.72
NLR*		3,2	2,8	**0.001**
PLR*		95.5	97	0.07
Operation type(laparoscopic)		12 (92.3%)	2643 (93.1%)	0.6
Difficult cholecystectomy		3 (23.1%)	120 (4.2%)	0.016

Chi-Square , Student's t-test, *Mann Whitney-U, HGB: hemoglobin; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Table 3. Predictive values of independent variables for incidental gallbladder neoplasm

Variables	Exp(B)	95% C.I. for Exp(B)		P value
		Lower	Upper	
Age	1.029	0.973	1.090	0.31
HoC	2.697	0.760	9.575	0.12
HoF	1.410	0.063	31.692	0.82
Wall thickening	3.232	0.735	14.210	0.12
Gallstones	2.086	1.041	4.179	**0.038**
Polyps	4.813	2.285	10.137	**0.001**
NLR	164593.042	617.362	43881640.26	**0.001**
Difficult cholecystectomy	4.097	0.573	29.290	0.16

Binary logistic regression-enter method (Nagelkerke R Square : 0,45)

HoC: history of acute cholecystitis; HoF: family history of cholecystectomy; NLR: neutrophil-to-lymphocyte ratio

DISCUSSION

Patients with a mass detected on imaging are generally in the locally advanced or metastatic stage, constituting approximately 30% of the cases. In the treatment of these patients, a multidisciplinary approach is needed in more advanced centers. According to the literature, survival between 3 and 22 months indicates failure of systemic treatment [9, 10]. All these data make early-stage surgery very important. This study aims to focus on cancers that may be detected incidentally in patients scheduled for cholecystectomy for benign reasons. Preoperative informed consent, preparation of the intensive care unit, reservation of the necessary blood products, and an experienced team are not always possible for routine cholecystectomies. In addition, frozen pathological examination may be required in cases where perioperative clues regarding cancer are insufficient, and an appropriate surgery time should be arranged during the day.

In stages more advanced than T1a, liver segment 4B and segment five resection and regional lymph node dissection must be added to cholecystectomy to save the patient from a second surgery. Extended hepatic resection and bile duct excision may sometimes be required to achieve negative surgical margins [5, 11]. Articles stating that residual disease is seen in up to 59% of cases where a second surgery is performed justify extensive resections [12].

Instead of providing this complex management, transferring the patient to an experienced hepatobiliary surgery center can solve many problems simultaneously. It has been observed that recent prediction models emphasize the importance of patient age along with female gender. It has also been stated that acute cholecystitis with jaundice and previous cholecystitis increase the risk [13]. Unlike other studies, Goussous et al. emphasized the importance of wall thickening seen on imaging without peri-cholecystic fluid [14]. Promising results have also been obtained from recent biomarker studies. In 2016, it was emphasized that circulating serum-free DNA levels were significantly higher in early-stage gallbladder tumors [15]. Kinugasa and his colleagues drew attention to circulating tumor DNA [16]. More prospective studies are needed for the reliability of this type of biomarkers, and there are concerns about accessibility and routine applicability. Although carbohydrate antigen CA 19-9, which is significant for other hepato-pancreaticobiliary cancers, is not significant for gallbladder cancer, there are articles claiming that both high specificity and a 100% positive predictive value are achieved thanks to its combination with CA 125 and CA 242 [17]. These markers, which can be measured in serum, may become even more critical in predictive ability when evaluated with other biological features. The correlation between high NLR levels and poor prognosis as stated in some articles, was found to be a predictor of incidental cancer in our study [18].

Limitations

Contrary to the literature, the lack of predictive value of the female gender may be related to the low number of malignant patients. Prospective studies by routinely measuring serum biomarkers in patients in the preoperative period may provide a more meaningful prediction model with existing data. When ultrasonography reports were examined, no case was found in which only wall thickness was noted without pericholecystic fluid. However, although increased wall thickness is an indicator of cholecystitis, it may be an indirect predictor of cancer. Although some ultrasonography reports could not distinguish between impacted bile sludge and polyp, these cases were accepted as bile polyps.

CONCLUSION

As a result, biomarkers can be studied in serum for patients with high NLR levels accompanying large gallstones or bile polyps. Genetic counseling may be considered for those with a family history of cancer. Depending on the situation, these patients' operations may be performed in the daytime by more experienced teams, or their transfer to more advanced centers may be considered.

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Review Article

Management of Ileosigmoid Knotting: A Literature Review

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ABSTRACT
Ileosigmoid knotting (ISK) is a rare double-segment intestinal obstruction form. Urgent surgery is the unique solution in the management of ISK. In surgical treatment, detorsion alone is generally used in patients with viable bowel, while cases with gangrenous bowel require resection. ISK recurrence is uncommon. However, due to the recurrence risk of sigmoid volvulus, the role of recurrence-reducing procedures is unclear. In this review, urgent treatment of ISK as well as the techniques and patient selection criteria of recurrence-reducing management are discussed.

Keywords: Ileum, sigmoid colon, ileosigmoid knotting, management ,follow up

INTRODUCTION

In ileosigmoid knotting (ISK), ileum or sigmoid colon twists around the other stricture (Figure 1.a) [1,2]. Abdominal pain, distention, and obstipation are the prominent clinical features of ISK [3,4]. Abdominal plain X-rays generally suspect intestinal obstruction or sigmoid volvulus (SV) by demonstrating multiple intestinal air-fluid levels in addition to 'coffee-bean sign' in sigmoid colon, while abdominal computerized tomography or magnetic resonance imaging are highly sensitive by revealing 'whirl sign' in both sigmoid colon and terminal ileum mesenteries in addition to X-ray findings [5]. Urgent surgery following resuscitation is essential in the treatment [6]. However, ISK has a relatively poor prognosis particularly in cases with bowel gangrene, perforation, or peritonitis [7,8].

ISK is a very rare disease over the world with less than 1,000 cases reported to date [9,10]. However, it is relatively common in Turkey, particularly in Eastern Anatolia [11]. Our ISK experience of 58 years (from June 1966 to July 2024) and 81 cases constitutes one of the most comprehensive single-centre ISK series over the world [12]. In this review, we discuss the management and follow-up of ISK based on above-mentioned experience.

First-Line Management

Due to the fluid and electrolyte loss into the obstructive lumens and absorption of the toxic materials from the bowel surfaces, ISK rapidly causes hypovolemic and/or toxic shock [13,14]. In the management, an early and effective resuscitation is essential [15,16]. In the presence or suspicion of complicated colonic volvulus, without considering the bowel viability, urgent surgery is strongly recommended in all patients by actual guidelines [17,18]. Similarly, current reviews and articles support this idea [19,20]. Although endoscopic detorsion is effective in the

management of uncomplicated SV, the unravelling of the knot by endoscopy is very difficult or impossible in ISK, a complicated form of SV. Additionally, endoscopy doesn't demonstrate the viability of the ileum and endoscopy trying may cause missing the ileum gangrene resulting in toxic shock and related death [21,22]. For this reason, surgical treatment is the unique solution [2,12,23,24].

Management of Viable Bowel

If the bowels are viable, untying the knot may be enough in most cases. Detorsion alone has 1%-5% of mortality and 5%-15% of morbidity [2,6,10,12,14-16,23,24]. In such patients, ISK or SV recurrence is rare and one case has been reported in the actual literature for each [12,25,26]. For this reason, the therapeutic route and patient selection criteria are not clear [2,12,24]. In clinical practice, cecopexy (fixation of the anti-mesenteric edge of the cecum to the parietal peritoneum) (Figure 1.b) may be used in patients with mobile cecum, while no additional procedure including ileectomy (resection of the knotted ileum segment) (Figure 1.c) is necessary for viable ileum [2,11,12,22]. However, dolichosigmoid, an elongated and dilated sigmoid colon, is an anatomic indicator of recurrent SV [27,28]. For this reason, recurrence-reducing procedures such as sigmoidopexy (fixation of the anti-mesenteric edge of the sigmoid colon to the parietal peritoneum) (Figure 1.d), sigmoid mesopexy (fixation of the sigmoid mesentery to the parietal periton by using horseshoe-shaped sutures) (Figure 1.e), sigmoid mesoplasty (efformation of the sigmoid mesentery by cutting it longitudinally and suturing transversely) (Figure 1.f), or sigmoid extraperitonealization (fixation of the apex of the sigmoid colon to the extra-peritoneal area) (Figure 1.g) may be preferred in selected well-conditioned (American Society of Anesthesiologists – ASA score 1-3) and nonelderly (younger than 70-75 years old) cases with 1%-8% of mortality and 10%-20% of morbidity rates [2,12,24,29-31]. However, the role of percutaneous endoscopic sigmoidopexy (fixation of the apex of the sigmoid colon to the anterior abdominal wall by using stoma kits) (Figure 1.h) is unclear and it may be applied in bad-conditioned (ASA score 4) and elderly (older than 70-75 years old) patients [2,12,24,32,33]. On the other hand, sigmoidectomy (resection of the twisted sigmoid segment to prevent a recurrence) (Figure 1.i) is an alternative option with 1%-10% of mortality and 15%-25% of morbidity rates in above-mentioned ASA score 1-3 and nonelderly individuals [2,12,24,29-31].

Main Points:

- Ileosigmoid knotting is a rare double-segment intestinal obstruction form characterized with rapid progress and poor prognosis.
- In the treatment, early and effective resuscitation followed by urgent surgery is the unique option.
- In surgical treatment, detorsion alone may be used in patients with viable bowel, while cases with gangrenous bowel require primary anastomosis or stoma following resection.
- Recurrence of sigmoid volvulus is rare and the role of recurrence-reducing procedures are controversial.

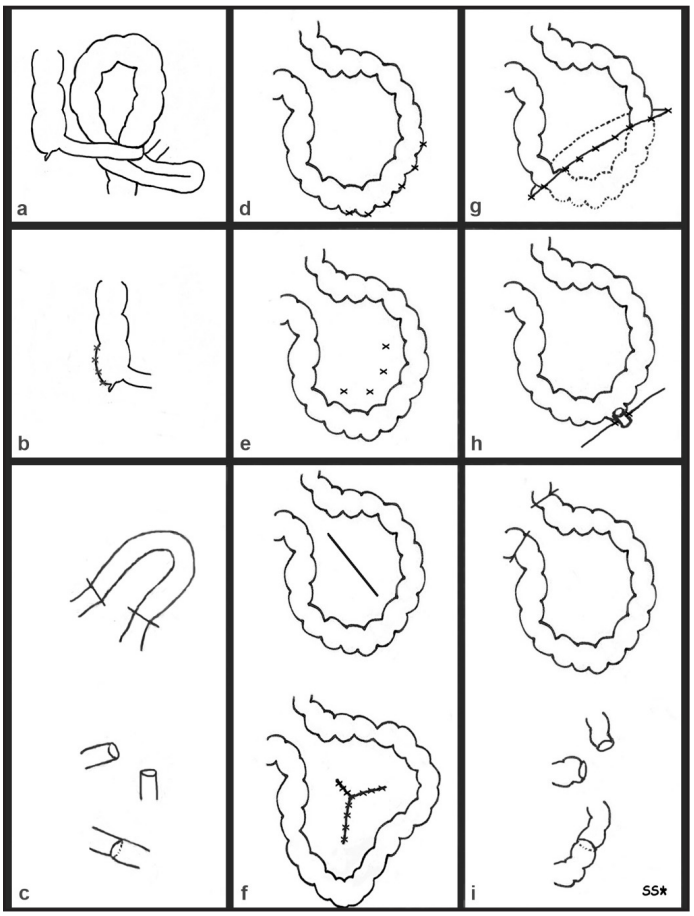

Figure 1. Schematic diagrams demonstrating ileosigmoid knotting and surgical procedures. **a.** Ileosigmoid knotting. **b.** Cecopexy. **c.** Ileectomy. **d.** Sigmoidopexy. **e.** Sigmoid mesopexy. **f.** Sigmoid mesoplasty. **g.** Sigmoid extraperitonealization. **h.** Tube sigmoidopexy. **i.** Sigmoidectomy.

Management of Single-Segment Gangrenous Bowel

In patients with ileum or sigmoid colon gangrene, following the resection, primary anastomosis is preferred in above-mentioned well-conditioned and nonelderly cases with 5%-20% of mortality and 10%-30% of morbidity rates, while stoma is life saver in most bad-conditioned and elderly patients with 20%-50% of mortality and 30%-60% of morbidity rates [2,12,24,32,33]. If the sigmoid colon is viable, one of the above-mentioned recurrence-reducing procedures may be added [2,12,24,29-33].

Management of Double-Segment Gangrenous Bowel

It is clear that both gangrenous segments require resection. Following this procedure, primary anastomosis is preferred in both segments in above-mentioned well-conditioned and nonelderly cases with 10%-30% of mortality and 20%-40% of morbidity rates. Bad-conditioned and elderly patients are treated with one anastomosis and one stoma (preferably ileum anastomosis and sigmoid colon stoma), the mortality and morbidity rates are 30%-60% and 40%-80%, respectively [2,12,24,29-33].

Ileosigmoid Knotting in Childhood

ISK in childhood is seldom with less than 30 cases reported in the literature [2,12,34,35]. Although the therapeutic principles are similar, if the bowels are viable, short-term procedures including detorsion alone may be preferred in most bad-conditioned children. However, the high recurrence rate in early-onset SV patients may necessitate a recurrence-reducing procedure in well-conditioned group [36]. The inability of a healthy medical anamnesis and clinical examination in addition to the complexity of the clinical features generally retard the diagnosis resulting in a relatively poor prognosis consisting of 15%-60% of mortality and 20%-60% of morbidity rates [2,24,34,35,37].

Ileosigmoid Knotting in Pregnancy

ISK is rare in pregnancy and puerperium with less than 20 cases reported to date [2,37-39]. The treatment requires a multidisciplinary approach. Surgical treatment principles are similar to that of non-pregnant individuals. Short-term surgery such as detorsion alone is the most preferred option in cases with viable bowel, while recurrence-reducing techniques are generally postponed post-delivery period. However, the prognosis is relatively poor with 15%-25% of maternal and 30%-50% of fetal mortality in addition to 40%-60% of morbidity rates [2,12,37-39].

Ileosigmoid Knotting in Elderliness

ISK generally affects middle-aged population and about one eight of the cases are over 80 years old [12,37,40]. Although the basic therapeutic principles are similar, due to the worse prognosis arising from high-rate comorbidities, short-term techniques including detorsion alone are generally preferred. The prognosis is relatively poor with 20%-80% of mortality and 30%-60% of morbidity rates [2,12,37,40].

Clinical Experience

ISK is relatively common in Eastern Anatolia. As a result, the experience of Ataturk University, which includes 81 patients treated over 58 years (from June 1966 to July 2024) constitutes the third large single-centre ISK series over the world [12]. In 20-case (24.7%) viable-bowel group, detorsion was applied in 15 patients, while additionally sigmoid mesopexy (two patients), sigmoidectomy with primary anastomosis (two cases), and sigmoidectomy with stoma (one patient) were other options with no mortality and 5.0% morbidity. In eight cases (9.9%) with ileum gangrene, the mortality and morbidity rates were similar, 12.5% for each. In this group, following ileectomy (in two patients, additionally right colon resection), primary anastomosis was preferred in seven cases, while one patient treated with stoma. Seven cases (8.6%) had sigmoid colon gangrene with 14,3% of mortality and morbidity rates for each. In this group, following sigmoidectomy, bowel continuity was obtained via stoma in six patients, while one case treated with primary anastomosis. Finally, in 46 patients (56.8%) with double-segment gangrene, both segment resection was followed by ileum primary anastomosis with sigmoid colon stoma in 38 cases (in 11 patients, additionally right colon resection), double-segment stoma in three, ileum stoma with sigmoid colon primary anastomosis in three. In the last group, one patient death during laparotomy, while mortality and morbidity rates were 28.3% for each.

Regarding the special considerations, seven cases were in childhood period. Detorsion alone was used in the management of one patient with viable bowel, while six cases with double-segment gangrene were treated with ileum primary anastomosis and sigmoid colon stoma following double-segment resection (in one patient, additionally partial jejunum resection) with 14.3% mortality and 42.9% morbidity rates. Three of 22 women (13.6%) were pregnant. Following the resections, two cases with double-segment gangrene were treated with ileum primary anastomosis and sigmoid colon stoma, while sigmoid primary anastomosis

was preferred in one patient with sigmoid colon gangrene alone. In this series, maternal and fetal mortality rates were 33.3% for each, while maternal morbidity rate was also 33.3%. Finally, 24 cases (29.6%) were over 60 years old, while the numbers of the patients older than 70, 80 and 90 years were 11, four and one, respectively. As expected, 11 (73.3%) of decedent cases were older than 60 years.

CONCLUSION

In ileosigmoid knotting (ISK), detorsion alone is generally used in patients with viable bowel, while cases with gangrenous ileum and/or sigmoid colon are treated with primary anastomosis or stoma following resection. In patients treated detorsion alone, ISK or sigmoid volvulus recurrence is rare. For this reason, the role of recurrence-reducing procedures is unclear. However, recurrence-reducing procedures such as sigmoidectomy, sigmoidopexy, sigmoid mesopexy, sigmoid mesoplasty, or extraperitonealization may be used in selected well-conditioned and nonelderly cases.

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Review Article

Use of Alloplastic Total Joint Replacement of the Temporomandibular Joint of Growing Patients: A Scoping Review

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ABSTRACT

Temporomandibular joint (TMJ) disorders pose unique challenges in pediatric patients undergoing craniofacial growth. Alloplastic total temporomandibular joint reconstruction (TMJR) techniques have emerged as promising solutions, offering immediate joint function and symptom relief. However, the efficacy and safety of TMJR in this population remain under scrutiny. This scoping review aims to comprehensively summarize the evolving literature on TMJR in growing patients with end-stage TMJ pathology. Our methodology adhered to PRISMA-ScR guidelines, identifying 9 relevant articles. The discussion emphasizes preoperative considerations, treatment selection criteria, and potential complications. While TMJR offers short-term benefits, concerns regarding long-term outcomes persist, necessitating further research. Collaboration among multidisciplinary teams is crucial for optimal patient care. Future research should focus on comparative efficacy and safety, refining treatment algorithms, and long-term follow-up to enhance outcomes and minimize complications in pediatric TMJ pathology.

Keywords: TMJ total joint replacement; TMJ surgery; TMJR; growing patient; skeletally imature

INTRODUCTION

Temporomandibular joint disorders (TMD) present unique challenges in pediatric patients, particularly those with ongoing craniofacial growth. Surgical management options for temporomandibular joint (TMJ) pathology in growing patients have evolved over the years, with a shift towards the utilization of

alloplastic total temporomandibular joint reconstruction (TMJR) techniques. Alloplastic materials offer the advantage of providing immediate joint function and alleviating symptoms associated with TMD. However, their efficacy and safety in the growing patient population remain topics of debate and investigation.

Several key studies have contributed to our understanding of TMJR in growing patients. Sinn *et al*. [1] conducted a preliminary investigation into the feasibility of TMJR in the growing patient population, shedding light on potential outcomes and considerations. Similarly, Hechler and Matthews [2] examined the role of alloplastic TMJ reconstruction specifically in patients with juvenile idiopathic arthritis, highlighting the unique challenges and benefits in this subset of patients.

Mercuri and Swift [3] provided valuable insights into the considerations for using alloplastic TMJ replacement in growing patients, addressing factors such as growth potential, adaptation, and long-term outcomes. Furthermore, Keyser *et al*. [4] conducted a pilot survey investigating the outcomes of TMJR in skeletally immature patients, contributing valuable data to the existing literature.

Case reports and small case series have also provided valuable insights into the clinical application of TMJR in growing patients.

Main Points:

- TMD poses a significant challenge in pediatric patients, specially ongoing craniofacial growth.
- Conditions such as JIA and ankylosis commonly affect the craniofacial imbalance and TMJR are considered a feasible choice for treatment.
- TMJR offer effective relief from chronic pain associated with end-stage TMJ pathology, thereby improving patient comfort and QoL. It also provides restoration of function to normal jaw function, facilitating chewing, speaking, and swallowing, thereby enhancing OOH and function.
- TMJR demonstrate long-term stability, but the need for revision surgery may arise in cases of implant failure, infection, or development of new TMJ pathology. Skeletally immature patients may require reoperation to accommodate ongoing craniofacial growth and development and address any skeletal discrepancies that arise over time.

Cascone *et al*. [5] reported on TMJ replacement utilizing patient-fitted devices in a child with re-ankylosis, demonstrating the feasibility and potential benefits of this approach. Similarly, Goker *et al*. [6] presented a case report on custom-made alloplastic TMJ replacement in an immature patient, highlighting individualized treatment options.

Resnick's article discusses the challenges and considerations associated with temporomandibular joint reconstruction in pediatric patients. It explores various surgical techniques and treatment modalities for managing TMJ pathology in growing children, emphasizing the importance of individualized treatment planning and careful consideration of growth factors. The article highlights the complexity of TMJR in pediatric patients due to ongoing craniofacial growth and development, emphasizing the need for long-term follow-up to assess treatment outcomes and monitor for potential growth disturbances [7].

Zimmerer *et al*. [8] explores the use of patient specific TMJR as an approach to treating congenital mandibular hypoplasia and complex craniofacial anomalies. Through a detailed analysis of patient cases, the study demonstrated the feasibility and effectiveness of this approach in restoring jaw function and improving facial aesthetics. In addition to clinical studies and case reports, systematic reviews have synthesized existing evidence on the use of TMJR in growing patients with end-stage TMJ pathology. Khattak *et al.* [9] conducted a systematic review to evaluate the success rates and outcomes of TMJR in this population.

Overall, the literature regarding TMJR in growing patients with TMJ pathology is evolving rapidly, with emerging evidence shaping clinical practice and decision-making. This scoping review aims to provide a comprehensive overview of the current literature regarding the use of TMJR in growing patients with end-stage TMJ pathology. By synthesizing evidence from recent studies and clinical reports, we seek to elucidate the role of TMJR in managing end-stage TMJ disorders in pediatric and adolescent populations.

MATERIALS AND METHODS

The data presented in this article was gathered by thoroughly examining existing literature, adhering to PRISMA-ScR guidelines. [10] A specific search strategy was implemented by two independent reviewers (BCL and RG), who searched online databases such as PubMed, Scopus, and Web of Science

(WoS). This strategy included keywords like “TMJ total joint replacement”; “TMJ surgery”; “TMJ reconstruction” and “growing patient”. All studies related to reconstructive surgery with TMJR in growing patients, except books, were considered. Additionally, a manual search of databases was conducted to identify potentially missed articles by reviewing the references of included articles. There were no language or publication year restrictions.

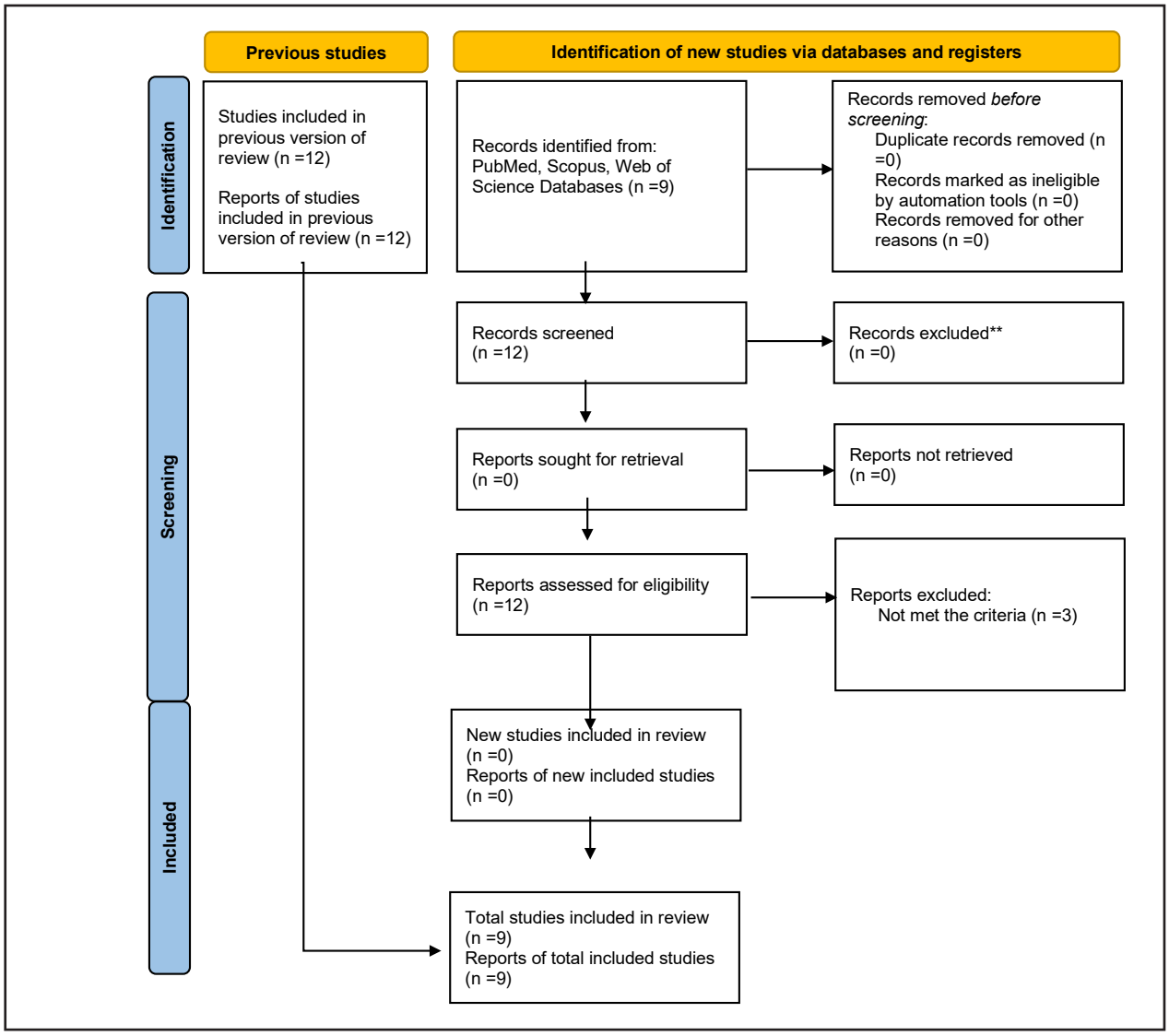
Titles and abstracts of search results were meticulously evaluated for relevance. Selected articles underwent full-text screening, during which authors thoroughly examined and extracted relevant data.

This study critically reviewed publicly available electronic sources and did not involve specific patient information, thus exempting it from institutional review board approval.

RESULTS

A total of 9 articles were identified that met the screening criteria. We accessed the use TMJR in reconstruction of growing patients and brought to discussion along with other renowned articles in the literature. The PRISMA flow of selection of articles was presented in Table 1.

Table 1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only



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DISCUSSION

Prior to undergoing TMJR, patients in the included studies were diagnosed with various TMJ pathologies, including degenerative joint disease, ankylosis, severe condylar resorption, and inflammatory arthritis. Preoperative diagnostic modalities often included clinical examination, imaging studies (e.g., MRI, CT), and functional assessments to evaluate TMJ function and severity of disease. The decision to select TMJR as the treatment modality for TMJ pathology in growing patients was influenced by several factors, including the severity of disease, patient age, growth potential, and treatment goals. In cases where conservative measures failed to provide symptomatic relief or preserve TMJ function, TMJR was considered as a viable option to restore joint function and alleviate pain. Additionally, in patients with congenital anomalies or developmental disorders affecting mandibular growth, TMJR offered a reconstructive solution to address functional deficits and optimize craniofacial development.

TMJ prostheses offer effective relief from chronic pain associated with end-stage TMJ pathology, thereby improving patient comfort and quality of life [3,11]. It also provides restoration of function to normal jaw function, facilitating chewing, speaking, and swallowing, thereby enhancing overall oral health and function [4,12,13].

By restoring normal joint anatomy and function, TMJ prostheses help prevent growth disturbances and asymmetries in skeletally immature patients [1]. The restoration of normal jaw function and facial symmetry enhances the aesthetic appearance of patients with TMJ pathology, boosting self-esteem and confidence [14]. Advances in technology allow for the customization of TMJ prostheses to match the patient's unique anatomical and physiological characteristics, optimizing surgical outcomes [6,15].

Also, patient-specific TMJ prostheses demonstrate long-term stability and durability, reducing the need for revision surgery, providing lasting relief from TMJ-related symptoms and functional limitations [5,12,13].

While some studies have focused on the efficacy of TMJR in pediatric patients with various TMJ pathologies, there remains a lack of consensus regarding its long-term outcomes and potential complications in this population. Limited long-term follow-up data exist to evaluate the durability and functional outcomes of TMJR in growing patients, raising concerns about the appropriateness of this treatment modality in this age group.

Due to its surgical complexity, TMJR surgery in growing patients is technically challenging and requires specialized training and expertise [3,15].

Also, implantation of TMJ prostheses may interfere with mandibular growth and development, leading to skeletal discrepancies [9,11,12]. Along with this, there are risks of complications such as infection, implant failure, and malocclusion may occur following TMJ replacement surgery, necessitating careful patient monitoring and management [4,15].

The major concern about TMJR in juveniles is the long-term success of the implantation. Long-term follow-up is one of the baselines in the realm of TMJR [12,13]. Data on the outcomes and complications of TMJ prostheses in growing patients are lacking, limiting the ability to predict their efficacy and safety over time [1]. The available literature on long-term outcomes of TMJR in pediatric and adolescent patients is limited and predominantly consists of case reports and small case series. Robust evidence regarding the longevity, adaptability, and patient satisfaction with TMJR in this population is lacking, necessitating further prospective studies with larger sample sizes and longer follow-up periods to elucidate the true efficacy and safety profile of this treatment modality.

The decision to undergo TMJR in pediatric patients should be weighed carefully against alternative treatment options, such as autogenous tissue grafting or conservative management strategies. While TMJR may offer advantages in terms of joint function restoration and pain relief, its utilization in growing patients carries inherent risks, including potential interference with mandibular growth and development, implant failure, and the need for revision surgery in the future [7].

The short-term outcomes of TMJ prostheses demonstrate favorable in terms of pain relief, restoration of function, and patient satisfaction [11,15]. The long-term predictability of TMJ prostheses in growing patients remains uncertain, highlighting the need for further research and long-term follow-up studies, [9] but certainly it has proved to have a long-term stability in skeletally mature subjects [12,13].

Autogenous tissue grafts, such as costochondral grafts, have shown potential for growth and adaptation, which is crucial

in pediatric patients. However, unpredictable growth patterns and overgrowth have been reported with costochondral grafts, posing challenges in achieving optimal functional and aesthetic outcomes [7].

Patients with end-stage TMJ pathology are the best candidates for TMJ replacement surgery, especially those with severe and refractory TMJ pathology that is unresponsive to conservative management [3,12,13]. Patients experiencing significant functional impairment, including limited mouth opening, malocclusion, and difficulty chewing, may benefit from TMJ prostheses [4,12,13]. TMJR offer significant improvements in pain relief, jaw function, and overall quality of life, allowing patients to resume normal activities and social interactions, [3,12,13] not mentioning that facial symmetry enhances the aesthetic appearance of patients with TMJ pathology, boosting self-esteem and confidence [6].

The timing of TMJ replacement surgery must be carefully considered to minimize the risk of growth disturbances and optimize long-term outcomes [3,7]. Besides that, the close collaboration between oral and maxillofacial surgeons, orthodontists, and pediatric specialists is essential to ensure comprehensive treatment planning and optimal patient care [4,16]. Treatment planning should be tailored to the patient's specific clinical presentation, etiology of TMJ pathology, and anatomical considerations [1,12,13].

Long-term follow-up studies have provided insights into the outcomes of different surgical techniques. Autogenous tissue grafts, despite their potential for growth, may present complications such as fracture or unpredictable growth, as evidenced by long-term studies [7]. For TMJR, this is not different. Close postoperative monitoring is necessary to assess the patient's progress, detect any complications early, and adjust the treatment plan as needed [3,11].

Patients and caregivers should receive comprehensive education regarding postoperative care, including dietary modifications, oral hygiene practices, and signs of potential complications [1,12,13]. Physical therapy and jaw exercises may be prescribed to promote optimal healing and functional outcomes following TMJ replacement surgery [4,16].

While TMJ prostheses demonstrate long-term stability, the need for revision surgery may arise in cases of implant failure, infection, or development of new TMJ pathology [5,12,13]. Skeletally immature patients may require reoperation to accommodate ongoing craniofacial growth and development and address any skeletal discrepancies that arise over time [1,3,7].

CONCLUSION

Future research should aim to elucidate the comparative efficacy, safety, and long-term outcomes of TMJR compared to other treatment modalities in pediatric patients with TMJ pathology. Collaboration between multidisciplinary teams comprising oral and maxillofacial surgeons, orthodontists, rheumatologists, and pediatric specialists is crucial to optimize treatment outcomes for this patient population.

The utilization of TMJR in growing patients with end-stage TMJ pathologies represents a valuable therapeutic option, offering the potential for significant improvements in pain relief, jaw function, and quality of life. However, careful patient selection, meticulous preoperative planning, and long-term follow-up are paramount to ensuring favorable outcomes and minimizing the risk of complications. Further research is warranted to elucidate the long-term efficacy and safety of TMJR in pediatric populations and to refine treatment algorithms to optimize patient care and surgical outcomes.

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Letter to Editor

Coexistence of Notalgia Paresthetica and Cervical Discopathy in a Young Girl

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Dear Editors,

The etiology of notalgia paresthetica (NP), which is generally accepted as a sensory neuropathy in which the posterior branches of T2-T6 spinal nerves are affected, causes itching and/or paresthesia symptoms limited to the scapular paravertebral region, and causes heterogeneous cutaneous pigmentation in the affected area, has not been fully determined. Many factors such as genetic predisposition, chemical neurotoxicity and spinal nerve damage due to chronic trauma, increased local skin innervation have been blamed in the etiology [1].

Although NP is reported to be a rare condition, it has been stated that it may not be rare in clinical practice due to diagnostic insufficiency [2]. In this context, the identification of NP cases will increase awareness. It will also enable clinicians to consider NP in diagnosis and differential diagnosis.

The aim of this paper is to discuss the coexistence between notalgia paresthetica and cervical discopathy in a young girl with a case report and to draw attention to the clinical importance of this rare condition in the young population.

Keywords: Notalgia Paresthetica, Cervical Radiculopathy, Chronic Pain

About Patient

A 21-year-old girl, who is a medical student at our university, applied with the complaint of pain radiating to the arm for 3-4 years in the neck and right upper-middle trapezius region. She stated that there was a local pruritic hyperpigmented lesion close to the midline in the upper part of the back on the right side, which is the dominant arm that started simultaneously with the pain. The case generally defined the severity of his complaints as approximately 7.5 out of 10 points according to the visual analog scale. Although the pain was not at a level to prevent activities of daily living, it increased with forward flexion of the neck and while studying [up to 9 severities]- it was relieved when taking a break.

She did not identify any factors, including trauma, for the etiology of NP or neck pain etiology in her medical history. The patient, who did not have a chronic disease, did not have a regular medication. There was no characteristic trait in her family history.

On physical examination, there were hyperpigmented lesion in the paraspinal region between the cervical 7-thoracic 4 vertebra levels on the right side and nail marks on the skin due to itching in the lesion area (Fig. 1). No limitation was detected in neck active/passive joint range of motion. Via palpation, spasm in the neck muscles and myofascial active trigger points were detected in the trapezius muscle, especially in the areas close to the lesion. During the Spurling test, she described sharp radicular pain radiating to the fingers along the right arm. The symptoms were relieved with the hyperabduction test. On neurological examination, muscle strength, deep tendon reflexes and superficial sensation were normal.

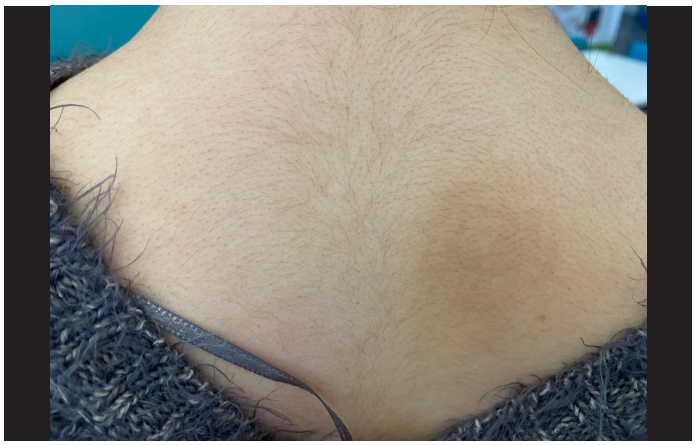

Figure 1. Hyperpigmented skin lesion in the paraspinal region between the cervical 7-thoracic 4 vertebra levels on the right side

Figure 2. Cervical MR imaging

Routine laboratory tests of the patient were within normal limits. No pathology was observed in the 2-way cervical radiography. Multiple central disc herniations were detected in MRI examination (Fig. 2).

The case was consulted to the dermatology clinic with a preliminary diagnosis of NP and the diagnosis was finalized. Burning-itching complaints of the patient who used topical capsaicin recommended by dermatology for 3 days increased, but pain complaints did not decrease. A physiotherapy program consisting of postural corrective exercises, stretching-strengthening exercises for cervical, scapular and pectoral muscles was initiated for the patient. A total of 15 sessions of conventional TENS treatment were applied to the neck and right arm [which will cover the entire complaint area] for 20 minutes, 5 days a week. At the end of the treatment, especially the complaint of pain regressed to a level of 3.5 according to the visual analog scale. Spurling test turned negative, myofascial trigger points partially resolved- relieved. There was no significant increase in complaints at the controls 1 month after the end of the treatment. Gabapentinoids and amitriptyline treatment were considered as secondary options. Since the patient was significantly relieved with TENS treatment, other treatments were not necessary. The patient was informed about the publication of case report and verbal consent was obtained.

DISCUSSION

The diagnosis of notalgia paresthetica is primarily made through a detailed medical history and physical examination. The clinical presentation of NP is often in the form of long-standing variable itching accompanied by a well-defined hyperpigmented macula located medial and lower 2/3rds of the scapula on the non-dominant hand side. In addition to itching, there may be complaints of pain, tingling, numbness. There is no primary cutaneous lesion in notalgia paresthetica. Secondary lesions such as hyperpigmentation and lichenification may be seen in patients with chronic pruritus. Deep excoriations are considered nearly pathognomonic for chronic pruritus of neuropathic origin [3, 4]. Our case had NP typical dermatological skin appearances. There are published a few case reports on the association of NP with cervical radiculopathy [3, 5]. Although the etiology has not been fully determined, have shown thoracic polyradiculopathy of the posterior branches of T2 to T6 as the primary cause. The most common causes of unilateral thoracic nerve compression are degenerative, osteoarthritic vertebral changes and herniated intravertebral discs [6]. Cervical radiculopathy accompanied

NP in our case. Clinical and radiological findings of cervical disc herniation were present. In addition, trigger points accompanying cervical disc hernias were detected in our case. Some studies have argued that muscle spasms cause symptoms and signs by compressing cutaneous and itch sensitive nerves [6].

Unlike NP that is typically observed in the elderly female population in the literature, our case was a 21-year-old young patient [6,7]. It is important to consider NP especially in cervical pain accompanied by radiculopathy in young patients. Inspection of the skin can confirm the presence of NP.

Regards,

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Letter to Editor

A Successful Intentional Replantation After Failed Regenerative Endodontics Caused by Foreign Body: 4-Year Follow-up

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Dear Editors,

Thin-root walls and divergent open apices of necrotic immature teeth are limiting factors in their endodontic treatment. The traditional treatment of these cases was long-term calcium hydroxide apexification or the placement of mineral trioxide aggregate (MTA). Although these techniques are successful, they cause root growth to stop and teeth become prone to root fractures because the dentin walls remain thin**.** Regenerative endodontic treatment (RET), in contrast to apexification and artificial apical barrier techniques in necrotic immature teeth, is a biological treatment based on revascularisation by bleeding in the canal and at the same time maintaining mineral deposition to strengthen dentin and grow roots**.** The outcomes of RET can be a high healing rate of 97% [1]**.** There are some important steps in RET technique. The root canal is disinfected with sodium hypochlorite (NaOCl) irrigation without mechanical instrumentation and the dried canal is filled with triple antibiotic paste (ciprofloxacin, metronidazole and minocycline). When the symptoms of infection have subsided, the antibiotic paste is removed and a blood clot is produced. Finally, the root canal entrance is sealed with MTA and the coronal restoration is permanently completed. When this technique is successful, root elongation, thickening of the root canal walls, apical closure and periradicular healing can be seen [1].

Intentional replantation (IR) is a treatment approach that consists of planned extraction of a tooth followed by evaluation and endodontic repair of the root surfaces, root resection, and retrograde hermetic sealing with a biocompatible root-end filling material and placement of the tooth back into its original socket [2]. IR is indicated in the following situations: crown-root fractures, external root resorption/perforations, failed non-surgical root canal treatment [3], periodontally compromised teeth, and when the patient refuses more expensive treatments. The contraindications to IR include periodontal involvement with excessive mobility of the tooth, septal bone loss in the labial or buccal region or at the bifurcation [2].

The most important advantage is that it allows direct visualisation of inaccessible areas of the tooth surface. In addition, ankylosis, external root resorption and enlargement of apical

radiolucency are expected complications [4]. IR maximizes the healing potential when performed with the correct indication and by current information and apical microsurgery. In addition, preoperative and intraoperative factors can significantly influence the prognosis [5]. The IR technique has been modified over time; today, atraumatic tooth extractions, root resection, and preparation are performed with piezoelectric systems. In addition, root-end filling is applied with current biomaterials [5].

In a meta-analyzed systematic review, the survival rate of intentionally replanted teeth was reported to be approximately 90% [6]. This case report describes the 4-year follow-up of IR treatment and devital whitening after the failed regeneration of a maxillary central incisor due to a foreign body.

Patient Information

A 10-year-old male patient was applied to our clinic with the complaint of severe pain in the anterior maxillary region. The patient had no systemic disease. The dental history revealed trauma on the right upper maxillary tooth #11 two years before, which resulted, according to his mother's statement in a crown fracture, but they didn't have treatment because there was no pain. Clinical examination revealed an uncomplicated crown fracture of tooth #11 and a black-grey-colored zone in the middle of the fracture line. Periapical radiography showed (Fig 1a.) that the tooth apex was open, a large periradicular lesion. It was decided to perform RET for tooth #11 and informed consent was obtained. A root canal access cavity was opened wide enough to see all the walls after local anesthesia (LA-Maxicaine 4%, VEM Medicine, Ankara, Türkiye). Working length was determined radiographically.

The root canal was gently irrigated with 20 ml of sterile saline and 20 ml of 2.5% NaOCl, provided that it was 1 mm shorter than the canal length, without any instrumentation. After checking the dryness of the canal with paper points, the triple antibiotic paste was placed into the canal with a lentulo spiral. The access cavity was filled with glass ionomer cement on a moist cotton pellet (Kavitan Plus Kerr, USA).

At second appointment 3 weeks later, there was no palpation or percussion pain and intraoral swelling on clinical examination. To apply Platelet-rich fibrin (PRF) for root canal revascularisation; the patient's blood was collected from a vein in the arm, and centrifuged using a PRF kit (Fig 1b). After LA with 3% mepivacaine, the temporary filling was removed. The antibiotic paste was removed with irrigation with 20 ml of sterile saline and then 20 ml of 17% EDTA solution gently. Then, dried with sterile paper points. After checking that the root canal was dry and clean, a sterile 25 K-File (Dentsply Maillefer, Ballaigues, Switzerland) was passed 3 mm out of the apex and gently irritated the periapical tissues to induce bleeding [1]. While waiting for the blood to fill the root canal, PRF was sent into the canal. Then, a 3 mm thick layer of MTA was then placed in contact with the scaffold to seal the root canal orifice. The tooth access was temporarily sealed with a moist cotton pellet and glass ionomer cement on MTA. Two days later, the tooth was permanently restored with composite resin after the MTA set was confirmed (Fig 1c).

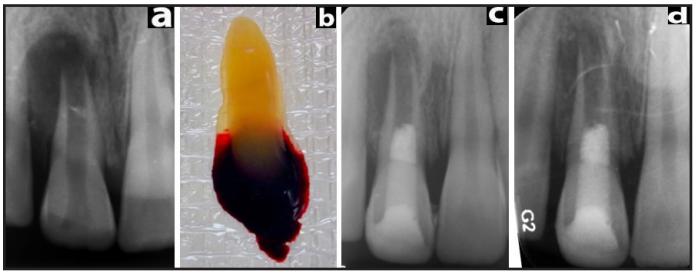

Figure 1.(a) Preoperative radiograph **(b)** PRF **(c)** Post-operative radiograph **(d)** Radiograph taken at 1-year of follow-up showing lesion

One year later, the patient came recall appointment (Fig 1d). The radiograph showed that the periapical lesion was still unhealed. The tooth was asymptomatic but there was discoloration in the crown. Devital bleaching treatment using sodium perborate bleaching agent was performed for 2 weeks. After 15 months treatment, the patient applied to the clinic with sinus tract and pus drainage at tooth #11. Amoxicillin, analgesics, and 0.12% chlorhexidine mouthwash were prescribed for 1 week. At the follow-up visit, the drainage was stopped, and the gingiva had healed. The patient didn't want Cone-beam computed tomography (CBCT) for economic reasons and periapical radiographs were taken. After discussing treatment options (apexification, regenerative endodontic retreatment, IR, removable appliance after extraction), a decision arose to perform an IR of tooth #11, and informed consent was obtained for the treatment plan from the patient's parents.

Two operators worked simultaneously to reduce the extraoral time of the tooth. The tooth #11 was gently extracted with dental forceps without root contact, without the use of a dental elevator after LA.

After tooth extraction (Fig 2a), a mass of granulation tissue and a foreign body were observed in the socket (Fig 2b). When asked, the patient reported that before the treatments he couldn't bear the severe pain and that he had stuck a pencil in his gums for relief and the pencil broke. While one operator prepared the tooth, the other operator prepared the socket for IR. The socket was curreted to clean only the apical lesion site and the whole was gently irrigated with sterile saline (Fig 2c).

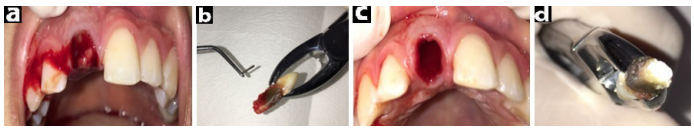

Figure 2.(a) Intraoral image immediately after extraction **(b)** Pencil tip coming out of the socket **(c)** Cleaned socket **(d)** After retrograde filling

When performing extraoral procedures, sterile gauze was bitten to prevent contamination of the blood-filled socket [4]. On the other hand, while the tooth was held in forceps from the crown, 2 mm root tip resection was performed using a diamond bur, retrograde preparation and irrigation were performed. The root surface was moistened with sterile saline to prevent drying. After drying, the prepared retrograde cavity was filled with injectable MTA (BIOfactor MTA, Konya, Türkiye) (Fig 2d). The tooth was reinserted into the socket with finger pressure and occlusion was carefully checked [5] (Fig 3a). The extra-oral processing time was 8 minutes. The tooth was semirigid splinted for 4 weeks. When the patient came recall appointment after 1 week, there was no symptom and the gingiva was healthy.

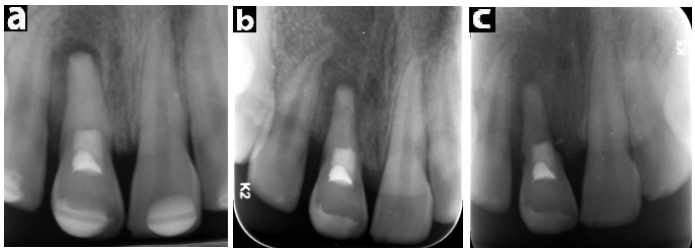

Figure 3.(a) After IR radiograph**; (b)** Post-operative 6 months periapical radiograph; **(c)** Post-operative 4 years radiograph

Six months later, at follow-up appointment, there were no symptoms. Radiographic examination showed that the lesion had reduced in size and bone trabeculation had formed (Fig 3b). The patient attended the follow-up appointment every year. At the 4th year follow-up appointment, the periapical radiograph showed external resorption of the root surface (Fig 3c). However, there were no symptoms. Since the patient stated that he wanted to use his tooth until the indication for extraction, the tooth was kept under follow-up.

Discussion and Conclusion

In this case report, the successful result of IR treatment applied after the RET technique, which failed due to the presence of a foreign body at the root tip of the tooth, although its success rate was high, is presented. Unlike apexification and artificial apical barrier techniques in the treatment of necrotic immature teeth, RET is a biologically based approach that revascularises the canal by causing bleeding in the canal and also continues mineral deposition to strengthen dentin and grow the roots of immature teeth [1]. In addition, in the ways described below, a scaffold or biological procedure is applied to stimulate the formation of vital tissue within the root canal: 1. blood clot revascularization (BCR), 2. platelet-rich plasma (PRP) 3. platelet-rich fibrin (PRF). In a study, stem cell scaffolds were compared and PRP and PRF were found to be more successful than BCR in terms of root apex closure, periapical healing response and root elongation [1]**.** In our case report, in addition to BCR formation with a K-file passed through the root apex, it was aimed to provide a scaffold by placing PRF. As a chemical irrigant, 2.5% NaOCl and sterile saline were used in the first appointment, and sterile saline and 17% EDTA were used in the second appointment as recommended in the literature. At the 2nd appointment of the RET, only irrigation with EDTA was recommended because EDTA supports the survival of stem cells of the apical papilla (SCAP). [7]. We irrigated the clean canal cavity with EDTA after removing the triple antibiotic paste using sterile saline at the 2nd appointment. SCAP are defined as mesenchymal stem cell populations located in the apical papilla around the root apices of immature permanent teeth and are known as the main cell source. In addition to dental pulp stem cells; periodontal ligament stem cells and bone marrow mesenchymal stem cells may also participate in pulp regeneration. All these cells need to be stimulated to migrate into the root canal space. It is thought that by removing the file from the apex during treatment, BCR is created and stem cells are stimulated for migration [7].

The outcomes of RET show a high survival and cure rate of 97%[1]. All treatment steps were performed following the literature and as recommended in the guideline. The patient's oral hygiene was at an acceptable level. However, RET failed

as the tooth presented with sinus tract and pus drainage at 15 months of follow-up. Unfortunately, the failure, in this case, can be explained by a foreign body reaction due to the broken pencil tip in the affected tooth area and inhibition of biological healing, as was later realized.

The treatment options for failing regenerative endodontic procedures, include apexification, regenerative endodontic retreatment, or IR [1,3]. In tooth #11, apexification or orthograde retreatment was not preferred due to the presence of a persistent periapical lesion involving the apical region and thin-short root walls. In addition, compared to alternative techniques, IR promotes healing by preserving the natural tooth and bone tissue and offers a conservative, cost-effective last resort option compared to tooth extraction and prosthetic rehabilitation.

IR is a procedure by intentionally extracting a tooth atraumatically and replanting it into original socket after the root-end resection is performed extra-orally [2]. According to previous studies, the shorter the extra-oral time and the more atraumatic the extraction, the higher the success rate [8]. Although some studies report that a single operator is more advantageous in that a single operator masters all aspects of the treatment and extraoral times are similar to those using 2 operators, many authors, such as Grossman [2], have recommended 2 operators during intentional replantation: one for tooth extraction and one for endodontic surgical manipulation. In this case report, two operators worked simultaneously to shorten the extraoral time and completed the procedure in 9 minutes.

In the literature, there is a consensus on atraumatic extraction without the use of dental elevators to minimize trauma to periodontal ligament (PDL) cells [5]. In this case report, the authors performed atraumatic extraction without the use of an elevator and with forceps grasping only the crown of the tooth; at the same time, the roots were continuously flushed with saline to prevent drying of the roots. Some studies have reported that curettage of the socket will damage the PDL cells. Therefore, they recommended removing the blood clot and irrigation with saline [4]. However, in this case, since there was a persistent periapical lesion, only the lesioned area of the socket was curetted and then irrigated with saline. To prevent ankylosis, a short-term splint that allows physiological tooth movement should be applied [8]. In this case report, the tooth was placed in the socket with finger pressure, a semirigide splint was applied for 4 weeks. After 4 years of follow-up, the replanted tooth had healed the periapical lesion, with no percussion/palpation pain. Also, the tooth was aesthetic and functional. External root resorption, which was an expected complication as a result of IR, was present but there was no clinical mobility. Therefore, it can be considered an acceptable success after IR treatment.

Intentional replantation in correctly selected cases, such as in the presence of failed non-surgical root canal treatment, perforations, external root resorption and crown-root fractures, is a unique procedure that provides direct vision to the lesion site and has the potential to promote tooth preservation.

Sincerely yours,

Keywords: Dental Infection Control, Foreign-Body Reaction, Intentional Replantation, Pediatric Dentistry, Regenerative Endodontic Treatment , Tooth Bleaching

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Letter to Editor

A Rare Cause of Unilateral Breast Mass: Burkitt Lymphoma

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Dear Editor,

A 45-year-old patient with no known medical history presented with swelling in the left breast that started 1 month ago. On physical examination, global volume increase, redness and edema were observed in the left breast. The patient's blood tests were normal. Breast ultrasonography showed signs of increased echogenicity and edema with unclear borders without forming a mass in the left breast. Subsequently, contrast-enhanced breast magnetic resonance imaging (MRI) was performed. During the breast MRI scan, a large lesion was discovered in the left breast. In T2 sequences, the mass lesion most completely filled the outside half of the breast and had same intensity as the breast parenchyma. It showed a heterogeneous contrast enhancement pattern with some centrally placed non-enhancing areas and demonstrated severe diffusion restriction in diffusion-weighted imaging (Fig. 1).

Tru-cut biopsy was performed under ultrasonography guidance. In the tru-cut biopsy material, medium-sized tumor cells with narrow cytoplasm that eliminated the normal breast parenchyma in most areas and formed diffuse infiltration were observed. In immunohistochemical examination, CD20 was diffusely positive, CD10 positive, c-myc positive, bcl-6 focal positive, MUM-1 focal positive, and Ki-67 proliferation index was determined as 100%. In the light of morphological and immunohistochemical data, a diagnosis of Burkitt lymphoma was made (Fig. 2).

Primary breast lymphoma accounts for 0.5% of all breast malignant neoplasms. The majority of breast lymphomas are of the non-Hodgkin's B-cell type, with the most common subtype being diffuse large B-cell lymphoma [1]. Roughly 1% to 5% of all non-Hodgkin lymphomas are Burkitt lymphomas [2]. BL is divided into three clinical groups by the World Health Organization (WHO): endemic, sporadic, and immunodeficiency-related. Their morphology and immunological phenotypic features are similar, despite differences in their clinical presentation and geographic distribution. They are all associated with c-Myc gene translocation and deregulation, which most commonly results from t (8;14), though variant translocations like t (8;22) and t (2;8) have been reported [3]. Although the head and neck can also be impacted, the abdomen is usually the main location of sporadic BL [4]. Primary breast lymphoma Burkitt

type is extremely rare. Of the very rare primary breast Burkitt lymphomas reported in the literature, more than half are bilateral and associated to pregnancy and lactation [5].

Even it is rare it should be remembered that unilateral global rapid breast enlargement with large dimensions, marked diffusion restriction and intense contrast enhancement on breast MRI, as in the case we present, may be caused by lymphoma, especially Burkitt lymphoma.

Yours sincerely.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: No funding was received for this study.

Informed Consent: Informed consent was obtained from the subject described in this report .

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ornational research committee and with the 1964 Helsinki declaration and its lateramendments or comparable ethical standards.

Author Contributions: Conception: O,C- Design: O,C - Supervision: K,S -Materials: O,C; G,HE; K,S - Data Collection and/or Processing O,C; G,HE; K,S - Analysis and/or Interpretation: O,C; G,HE- Literature: O,C - Review: G,HE - Writing: O,C - Critical Review: G,HE; K,S

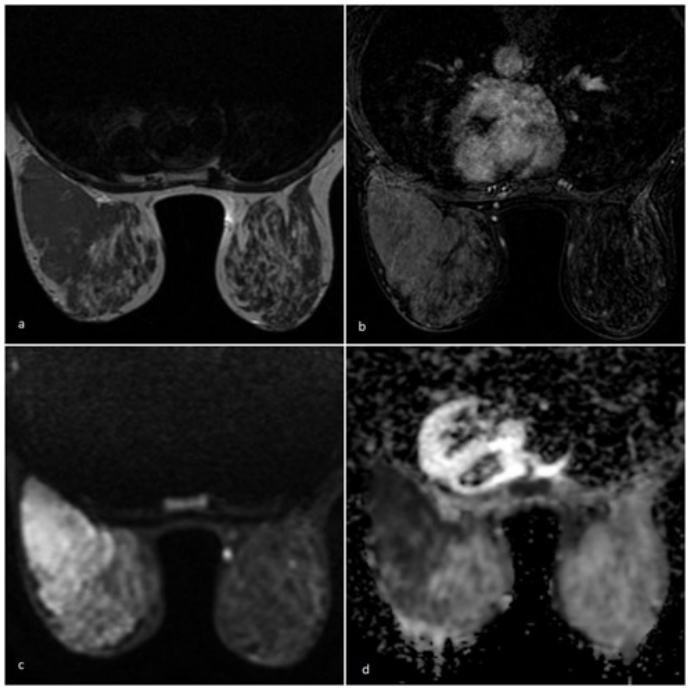

Figure 1 a. Hypointense lesion on T2 images, **b.** Enhanced lesion on postcontrast subtracted images, **c and d.** Diffusion-restricting lesion that is hyperintense on diffusion-weighted images and hypointense on ADC mapping

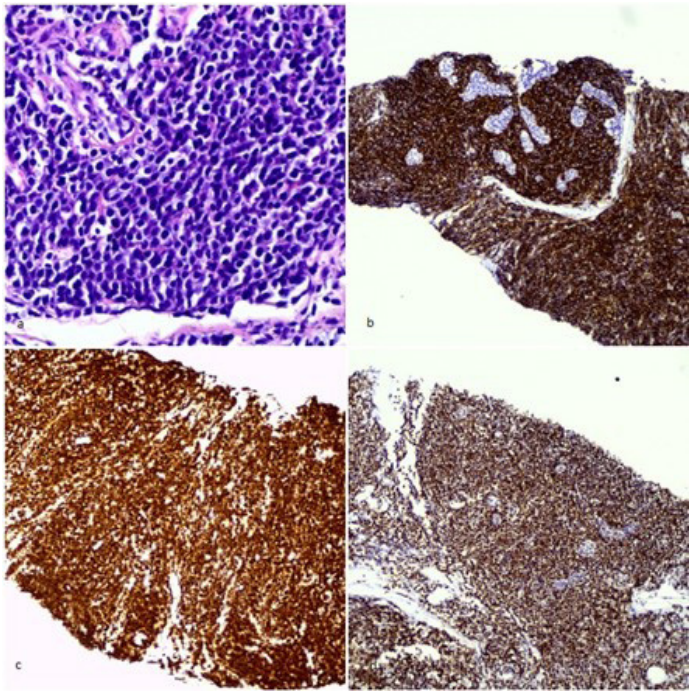

Figure 2 a. Diffuse invasion of tumor cells that leave a few normal mammary gland components intact, **b.** CD20 positive tumor cells, **c.** The Ki-67 proliferation index is nearly 100% in tumor cells, **d.** C-myc positivity in tumor cells

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Letter to Editor

Artificial Intelligence in Periodontology: Advantages and Challenges

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Dear Editor,

I am writing this letter to evaluate the position of artificial intelligence (AI) in Periodontology, which has become very popular in the diagnosis and management of periodontal diseases recently, and to comment on the advantages and challenges of using AI.

AI is a term for specially designed computer systems that mimic human intelligence and behavior [1]. Nowadays, subcategories of AI such as machine learning, deep learning, robotics, cognitive computing, and neural networks are used [2]. Some of them are used in the diagnosis of periodontal disease.

Periodontitis is a chronic inflammatory disease that progresses with damage to the periodontal attachment apparatus of the tooth and loss of alveolar bone [3]. If it is not treated, it can lead to tooth loss. Early diagnosis of periodontitis is extremely important. This point is very serious for the design an appropriate and detailed treatment plan and the positive progress of the disease prognosis. Clinical parameters (probing pocket deep, bleeding of probing and clinical attachment level) and radiological methods are used in the diagnosis of periodontitis [4]. Especially in the new classification, radiographic evidence of bone loss has an important role in determining the severity of periodontitis [3]. In this regard, studies using AI in the radiographic diagnosis of periodontitis have reported that AI gives promising results in periodontal diagnosis and is a valuable auxiliary diagnostic tool [5–7]. Additionally, AI has been shown to provide very helpful results in the assessment of periodontal bone loss [8]. Therefore, AI has a wide range of uses in diagnosis and disease classification, treatment planning, disease prognosis and risk assessment in Periodontology [9]. It can be useful in increasing the efficiency of data management and reducing the time spent on patient care. Maybe, in the near future, AI will be able to be used to create an individualized treatment plan for each patient suffering from periodontal disease, and in parallel, it will be able to reduce human-caused medical errors. Although AI applications in Periodontology have not yet shown their peak potential [10] they hold great promise for data collection, evaluation, treatment planning and management towards providing personalized treatment.

However, the challenges that AI should not be ignored. The most important of these difficulties is the need to verify the reliability of these innovative prediction techniques with further studies. Additionally, protocols, ethical concerns regarding patient trust, and potential technical issues such as the update needs for software have been reported among other challenges [11]. Another important issue is the possibility of security breaches in AI algorithms and data [12]. Additionally, for widespread use of AI, its integration into healthcare systems, training for clinicians, and the need to provide adequate funding may be other challenges to overcome [9].

Considering all these points, it can be said that AI cannot completely replace periodontists. The importance of clinical findings, especially in the diagnosis of disease in the periodontal area, reinforces this situation. However, it would be beneficial to integrate AI into regular training programs to increase both the development and motivation of periodontists [13]. The reported lack of awareness of AI in dentistry may confirm this need [14]. As a result, AI applications may serve as an auxiliary tool for maximizing the clinician's abilities and the 'clinical decision support systems' [15] in the future. It can be said that AI has a bright and revolutionary potential in healthcare for the future.

Yours Sincerely,

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Letter to Editor

Iatrogenic Median and Ulnar Nerve Damage Accompanying Acute Spinal Cord Ischemia

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Abstract

Peripheral arterial catheterization can be performed for hemodynamic monitoring during major cardiovascular operations. Different neurologic and cardiovascular complications may develop depending on the site of intervention. Peripheral nerve injuries are a rare complication of these catheterizations. Herein, we report median and ulnar nerve injury due to axillary catheterization in a patient with paraplegia due to spinal cord ischemia and rehabilitation results.

Keywords: Acute spinal cord ischemia, Axillary catheterization, Peripheral nerve injury

Dear Editor,

Acute spinal cord ischemia is a rare but highly significant clinical outcome, and aortic dissection (AD) is one of the causes of spinal cord ischemia [1-3].

Peripheral arterial catheterization can be performed for hemodynamic monitoring during major cardiovascular operations. Radial, brachial, and axillary arteries in the upper extremity can be used for this purpose and different neurologic and cardiovascular complications may develop depending on all these intervention sites [4]. Although peripheral nerve injuries due to these catheterizations are rare, they should be kept in mind due to the functional limitations they cause.

In order to emphasize these rare cases, we aimed to present a patient who underwent surgery for AD and was followed up for rehabilitation due to paraplegia and in whom we found median and ulnar nerve neuropathy in the right upper extremity due to axillary cannulation.

A 47-year-old woman presented to our clinic with complaints of weakness in the right upper and bilateral lower extremities. Her medical history was unremarkable. From her medical history and records, it was learned that she was admitted to the emergency department 1.5 months ago with complaints of sudden onset of

back and chest pain, nausea and vomiting and was operated under emergency conditions for Type 1 AD. During the operation, cardiopulmonary bypass was performed by cannulation from the right axillary artery due to pericardial tamponade and dissection repair was performed (Fig. 1). The patient was admitted to the intensive care unit in the postoperative period and cardiac arrest occurred. Cardiopulmonary resuscitation was performed and spontaneous circulation was established. Thoracic computed tomography showed pericardial fluid and extravasation of the ascending aortic graft was suspected. The patient was re-operated on the 10th postoperative day. After the operation, when the patient's hemodynamics stabilized and she regained consciousness, weakness in the right upper and both lower extremities was noticed.

Figure 2. Inability to make the round 'O' sign due to weakness in flexion of the thumb interphalangeal joint and distal interphalangeal joint of the 2nd finger (O Sign)

Figure 1. Right axillary artery cannulation site

The patient could not walk and had no sitting balance. She had weakness in flexion of the right thumb interphalangeal joint and distal interphalangeal joint of the 2nd finger. The patient was unable to make a round 'O' sign between these two fingers (Fig. 2) and had difficulty flexing the first 3 fingers of his right hand (Hand of Benediction) (Fig. 3). Finger abductors and wrist flexors of the right hand were 3/5 muscle strength.

Figure 3. Difficulty in flexing the first 3 fingers (Hand of Benediction Sign)

Muscle strength in the lower extremities was evaluated as hip flexion 2/5 bilaterally, knee extension 2/5 on the right and 4/5 on the left, 1st toe dorsiflexion 1/5 bilaterally, ankle dorsiflexion and plantar flexion 5/5 bilaterally. The patient with deep anal sensation, pressure and voluntary anal contraction was evaluated as ASIA D and neurologic level T1 according to the

American Spinal Injury Association (ASIA) Impairment Scale. Wound care was performed, indwelling catheter was withdrawn and clean intermittent catheterization was started in the patient with stage 2 compression of the sacrum. The functional independence measurement score was 44, including 24 motor assessment scores.

Electroneuromyography (ENMG) was performed, and reported as "The electrophysiological findings obtained are consistent with moderate partial axonal degeneration in the median and ulnar nerves, in the proximal forearm.". The cause of these nerve injuries was thought to be intraoperative axillary catheterization. The patient underwent three weeks of rehabilitation including electrical stimulation of the upper and lower extremity muscles and right median and ulnar nerves, respiratory, range of motion, strengthening exercises, balance and ambulation training and occupational therapy. The patient showed significant improvement in both upper and lower extremity muscle strength and regression of hand symptoms due to the nerve injuries. The patient started to ambulate alone with supervision. The functional independence scale score was calculated as 116 at discharge, 81 of which were motor assessment scores.

Although the vessels supplying the spinal cord have unique anatomical connections, some regions are more susceptible to ischemia. AD, which has a reported mortality of 80%, may cause malperfusion or occlusion of segmental arteries supplying the spinal cord and paraplegia may develop in 2-8% of patients [5,6].

It is known that the prognosis of acute spinal cord ischemia is generally not very good. In one study, 115 spinal cord ischemia patients were followed up for three years and it was observed that approximately 23% of the patients died, 42% of the survivors were wheelchair dependent, 26% could mobilize with support and only 32% could walk without support [7]. Our case achieved independent ambulatory status after 3 weeks of rehabilitation.

Although peripheral nerve injuries related to angiography and endovascular interventions are rare, they may cause significant functional impairment. Most of the arteries used for these procedures are very close to a nerve, and this nerve may be injured by direct injury, hematoma, pseudo-aneurysm or compression [8].

In the literature, nerve injuries secondary to axillary and brachial artery procedures have been reported most frequently. From the axilla to just above the elbow, the medial brachial fascial compartment consists of a thick brachial fascia covering a thin axillary sheath containing the axillary and brachial vessels as well as the median and ulnar nerves. These anatomical factors make homoeostasis difficult and facilitate nerve injury [8]. In our case, axillary catheterization was performed during emergency surgery for AD, which caused partial axonal damage to the median and ulnar nerves.

In conclusion, it should be kept in mind that detailed neurological evaluation of each patient after major surgery is important for early diagnosis and treatment of possible lesions. It should also be kept in mind that nerve lesions that may develop after cardiac operations may be due to cannulation attempts.

Kind Regards

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Letter to Editor

Hypo-Hyperdontia Associated with Mandibular Mesiodens and Double Mandibular Mesiodens: Two Rare Cases

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Dear Editor,

I am writing this article with two cases to provide information about a rare dental anomaly. Hyperdontia refers to the presence of additional teeth in the mandible or maxilla. Hyperdontia can be found in deciduous or permanent dentition and may be unilateral or bilateral. In a recent study conducted in the Turkish population, the prevalence of hyperdontia was 7.8% [1] . Although the etiology of hyperdontia is not clear, increased dental lamina activity is thought to cause this condition [1]. Hyperdontia is twice as common in males as in females [2].

In terms of morphology, supernumerary teeth may be conical, tuberculate, or molar shaped. Supernumerary teeth are named according to the region where they are located, with those found between the central teeth called mesiodens and those found in the wisdom tooth region called paramolars or distomolars [3]. The most common tooth types in hyperdontia are mesiodens, maxillary lateral incisors, maxillary distomolars or paramolars, and supplemental premolars in the mandibular premolar region [4]. In approximately 90–98% of cases, hyperdontia affects the maxilla, mostly in the anterior region [5]. In the anterior region of the mandible, the incidence of supernumerary teeth is just 0.01% [6]. In addition to causing crowding in the dental arch [6], hyperdontia can interfere with tooth eruption and cause malpositions [7].

Hypodontia, also known as selective tooth agenesis or congenital tooth absence, is the developmental absence of at least one permanent tooth and is a common dental anomaly in man [8].

Concomitant hypo-hyperdontia (CHH) refers to hyperdontia and hypodontia [9]. The reported incidence of CHH in orthodontic patients is 0.7% [10].

Figure 1. Intraoral photos of case 1

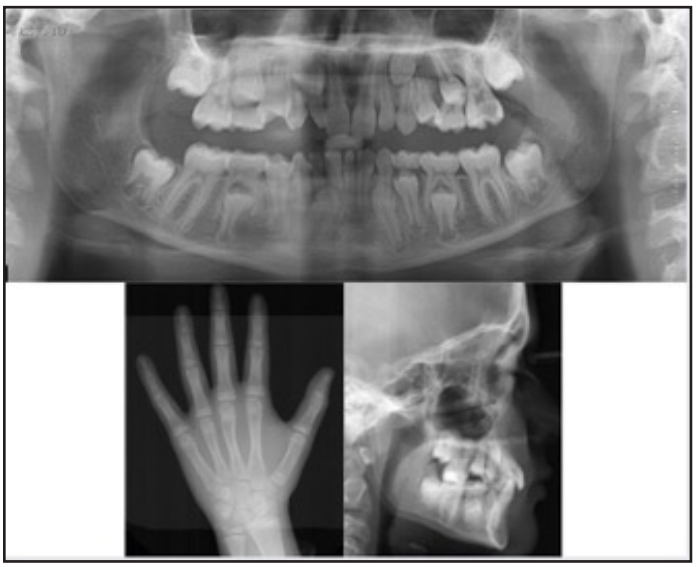

Figure 2. Panoramic radiograph , cephalometric radiograph and hand-wrist radiograph of case 1

Patient 1

A male patient presented to our clinic with orthodontic problems. The chronological age of the patient was 12 years and 3 months, and the patient's bone age was 13 years and 6 months. Routine extraoral and intraoral examinations were performed, in addition to radiological examinations. Extraorally, the patient was observed to have a flat profile. The intraoral examination of the patient, who was in the late opposition period, revealed an overjet of 3 mm, an overbite of 5 mm, and a crossbite of tooth number 12. Tooth 26 had deep dentin caries with large loss of material and a conical-shaped tooth between the mandibular permanent central teeth compatible with mesiodens, which is very rare in the mandible (Figure 1). The radiological examinations revealed that tooth numbers 25 and 43 were ectopically positioned, the tooth between the mandibular central teeth was a mesiodens with complete root development, and the mandibular lateral teeth were congenitally missing. Cephalometric radiography analysis revealed a skeletal class III (SNA: 73°, SNB: 74°, ANB: -1°) malocclusion (Figure 2).

Congenitally deficience of mandibular lateral teeth and an additional tooth in the mandibular central tooth area is a very rare presentation. Our patient provides an example of both a very rare case of mandibular mesiodens and a case of hypo-hyperdontia (Figure 2). A follow-up visit to the orthodontic clinic 3 months later was scheduled to evaluate the direction of eruption of the ectopic teeth and the crossbite of tooth number 12 with mesiodens and bilateral tooth deficiency.

Patient 2

An 18-year-old female patient who presented to our clinic with severe toothache in her mandible was examined extraorally, intraorally, and radiologically. The extraoral examination revealed a convex profile. The intraoral examination revealed deep dentin caries in the region of tooth number 37, which caused excessive loss of material on the occlusal surface. This tooth was the source of the patient's severe pain. Overjet was -1 mm, and overbite was -1 mm. Tooth numbers 46 and 36 were missing, and there were two extra teeth in the mandibular anterior region, one of which was more conical in shape than the other (Figure 3). The radiological examination revealed that tooth number 46 had been recently extracted and that tooth number 36 had been extracted a long time ago (Figure 4). The two extra teeth in the mandibular anterior region were double mesiodens that had completed their development. Mandibular mesiodens are very rare, and double mandibular mesiodens are even rarer. Cephalometric radiography analysis revealed a skeletal class I (SNA: 83°, SNB 82°, ANB: 1°) malocclusion (Figure 4). The patient was referred to an orthodontic clinic because of a bite problem due to the excess teeth in the anterior region.

Additional informed consent was obtained from all patients for which identifying information is included in this article. Considering the etiology of tooth number and size anomalies, it has been suggested that developmental dental anomalies such as hypodontia result from a complex set of interactions involving genetic, epigenetic and environmental factors [11] A family

study on hypodontia in Sayada, Tunisia showed that congenitally deficient teeth are probably inherited as an autosomal dominant trait [12]. In the first case, the patient's mother was also found to have a similar deficience of teeth.

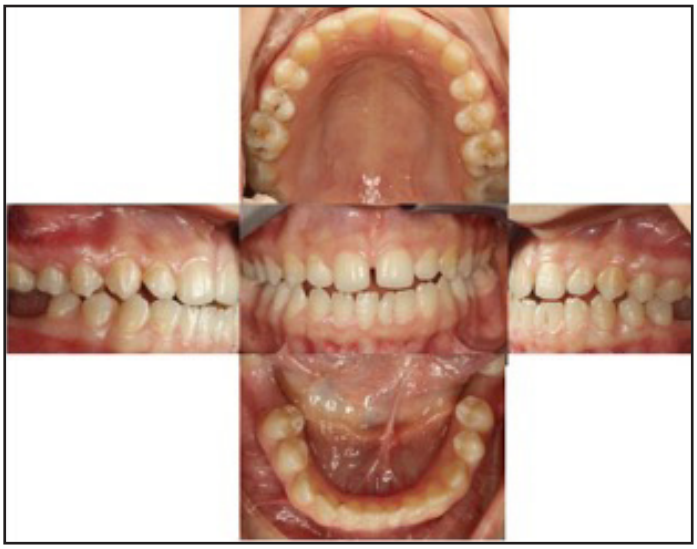

Figure 3. Intraoral photos of case 2

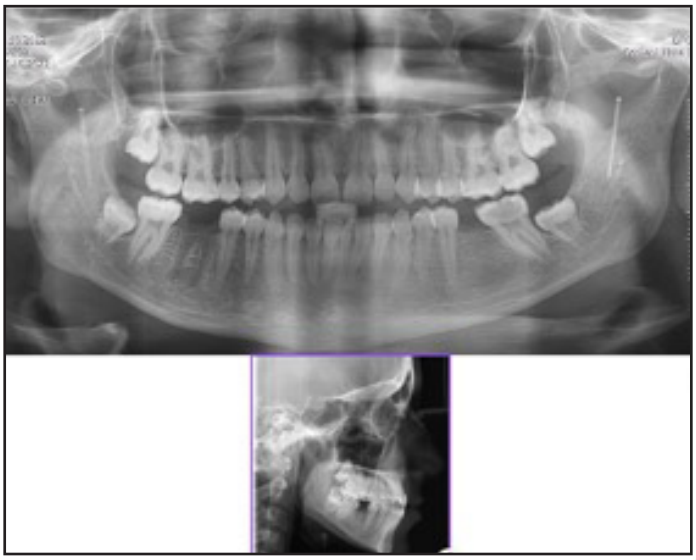

Figure 4. Panoramic radiograph and cephalometric radiograph of case 2

Previous research reported that the incidence of supernumerary teeth during permanent dentition is twice as high in males as in females. These permanent teeth are mostly mesiodens in the maxillary region [2]. In the literature, reports of mesiodens in the anterior region of the mandible are rare. There are cases of hypo-hyperdontia with mandibular mesiodens associated with the absence of permanent mandibular central teeth [13]. The finding of hypo-hyperdontia with congenitally missing mandibular lateral teeth and mandibular mesiodens in the present case report (Patient 1) is similar to that reported in the literature [13]. In accordance with the literature [13], the patient in our case was male. Tooth number anomalies, such as hyperdontia-hypodontia, not only affect the aesthetic appearance but also cause problems in arch length and occlusion in the jaw [14].

Tanaka et al. described the case of a female patient with erupted double mandibular mesiodens similar to that seen in our patient (Patient 2) [15]. In other cases of mandibular mesiodens, fusion of some teeth with the surrounding teeth has been found [16]. Fusion was not encountered in either of our cases. Mesiodens can cause displacement of adjacent permanent teeth [17].

Panoramic radiographs are very useful in the radiological diagnosis of the eruptive teeth such as mesiodens, but in some cases the superposition of the cervical vertebrae in the anterior region does not allow a clear evaluation of this region. In these cases, periapical radiographs will be very effective in making the diagnosis [18]. It should not be forgotten that there may be similar rare conditions in tooth deficiencies. In addition, diagnosed individuals should be consulted between disciplines for preventive or therapeutic treatments.

Yours sincerely,

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Letter to Editor

Risks of Oral and Maxillofacial Surgery in Patients with Thyroid Dysfunction: Proper Management Strategies

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Abstract

Oral and maxillofacial surgery encompasses procedures for correcting mouth, jaw, and facial issues, posing challenges in patients with thyroid dysfunction due to its impact on the coagulation system. Many authors noted a rise in thyroid disease among younger adults, affecting surgeries traditionally performed in this demographic. Thyroid dysfunction alters hemostasis, with hyperthyroidism increasing thromboembolic risks and hypothyroidism impairing wound healing and causing bleeding tendencies. In OMF surgery, hyperthyroid patients face thromboembolic risks, requiring preoperative assessment, thyroid normalization, and anticoagulant prophylaxis. Hypothyroid patients need optimized hormone therapy, careful hemostasis, and postoperative monitoring. Multidisciplinary collaboration among endocrinologists, surgeons, and hematologists is crucial for tailored management strategies. In conclusion, understanding thyroid dysfunction's hemostatic impact is vital for safe OMF surgery, necessitating personalized perioperative care strategies.

Keywords: Oral and maxillofacial surgery; thyroid dysfunction; hyperthyroidism; hypothyroidism; coagulation system

Dear Editor,

Oral and maxillofacial surgery encompasses a range of procedures aimed at correcting structural abnormalities, injuries, or aesthetic concerns in the mouth, jaw, and face. While these surgeries are generally safe, patients with thyroid dysfunction, including hyperthyroidism and hypothyroidism, present unique challenges due to the intricate interplay between thyroid hormones and the coagulation system.

Zhang *et al.* [1] provides insight into the prevalence and trends of thyroid disease among adults from 1999 to 2018. Over this period, there has been a notable shift in demographic characteristics, with an observed increase in the incidence of thyroid disease among younger adults. This shift is particularly significant as thyroid disorders were traditionally more prevalent in older age groups. Factors such as changes in lifestyle, environmental exposures, and diagnostic practices may contribute to this trend. Traditionally, procedures such as orthognathic surgery, third molar surgery and aesthetic surgery are performed in young adults, raising a "red flag" for OMF surgeons [2].

The information presented in this article was compiled through a comprehensive examination of existing literature. A specific search strategy was employed by two independent reviewers (BL and RG), who conducted searches in online databases, including PubMed, Scopus, and Web of Science (WoS). This search strategy incorporated the use of keywords such as "Oral and maxillofacial surgery"; "thyroid dysfunction"; "hyperthyroidism"; "hypothyroidism"; "coagulation system".

The titles and abstracts of the search results were carefully assessed to determine their relevance to the study. Subsequently, selected articles underwent a full-text screening, during which the authors thoroughly examined and extracted pertinent data.

This study involved a critical review of publicly available electronic sources and did not entail the use of specific patient information. Consequently, it was granted exemption from institutional review board approval.

Thyroid Dysfunction and Hemostasis

Thyroid dysfunction has long been recognized for its impact on hemostasis. Studies such as those by Franchini *et al.* [3] and Elbers *et al.* [4] have highlighted the complex relationship between thyroid function and the coagulation system. Hyperthyroidism is associated with a prothrombotic state, characterized by increased levels of coagulation factors and platelet activation, predisposing patients to thromboembolic events. Conversely, hypothyroidism can lead to impaired platelet function and decreased levels of coagulation factors, resulting in a bleeding diathesis.

Specific Considerations in Oral and maxillofacial Surgery

Reconstructive surgery and orthognathic surgery are a few examples of surgical procedures with great potential for bleeding, since the usage of osteotomies may cause rupture of vessels, that in a compromised thyroid imbalance, would cause trouble for both patient and surgeon.

In the context of oral and maxillofacial surgery, these alterations in hemostasis pose significant challenges. Patients with hyperthyroidism undergoing surgical procedures are at an increased risk of thromboembolic complications such as deep vein thrombosis and pulmonary embolism. Therefore, meticulous preoperative assessment and prophylactic measures, including the use of anticoagulants, may be warranted to mitigate these risks.

On the other hand, patients with hypothyroidism may present with impaired wound healing and an increased tendency for postoperative bleeding. Hoffmann *et al.* [5] demonstrated that hypothyroid metabolic status could lead to the acquired von Willebrand syndrome, further complicating hemostasis in these individuals. Thus, careful intraoperative hemostasis and postoperative monitoring are essential to prevent excessive bleeding and facilitate optimal wound healing.

Management Strategies

Proper management of patients with thyroid dysfunction undergoing OMF surgery requires a multidisciplinary approach involving endocrinologists, surgeons, and hematologists. Preoperative evaluation should include a thorough assessment of thyroid function, coagulation profile, and bleeding risk. Close collaboration between healthcare providers is essential to tailor perioperative management strategies to individual patient needs [4].

In hyperthyroid patients, normalization of thyroid function through pharmacological or radioiodine therapy should be considered prior to elective surgery whenever feasible. Additionally, perioperative prophylaxis with anticoagulants such as low-molecular-weight heparin may be indicated to reduce the risk of thromboembolic events [4].

For patients with hypothyroidism, optimization of thyroid hormone replacement therapy is crucial to ensure adequate hemostasis and wound healing. Intraoperative hemostatic agents and meticulous surgical technique should be employed to minimize bleeding complications. Postoperatively, close monitoring for signs of bleeding or hematoma formation is imperative, with prompt intervention as needed [4].

Normal hormonal levels and therapeutics for each thyroid disfunction are displayed in Table 1.

Table 1. Hormonal normal range, correct supplementation and substance used for each of the thyroid disfunction. TSH - thyroid stimulating hormone; T3- triiodothyronine; T4 – thyroxine

Hormone	Normal Range	Correct Supplementation
TSH	0.4 - 4.0 mIU/L	- Hyperthyroidism: < 0.1 mIU/L
		- Hypothyroidism: > 4.0 mIU/L
T3	80 - 200 ng/dL	- Hyperthyroidism: Normal or elevated
		- Hypothyroidism: Low
T4	5.0 - 12.0 µg/dL	- Hyperthyroidism: Normal or elevated
		- Hypothyroidism: Low
Levothyroxine	-	- Hypothyroidism: T4 replacement, adjusted according to TSH and free T4 levels.
Methimazole	-	- Hyperthyroidism: Inhibitor of thyroid hormone synthesis. Dosage adjusted according to T3 and T4 levels.

Thyroid dysfunction exerts profound effects on hemostasis, posing unique challenges in the context of OMF surgery. While hyperthyroidism predisposes patients to thromboembolic complications, hypothyroidism is associated with impaired wound healing and increased bleeding risk. Proper management of these patients requires a comprehensive understanding of the underlying pathophysiology and a tailored approach to perioperative care.

Yours Sincerely,

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Letter to Editor

Adalimumab Treatment in a Case of Treatment-Resistant Acne Conglobata

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This study was presented as an oral presentation at the 31. National Dermatology congress held in Antalya on 18-22 october 2023.

Dear Editors,

Acne conglobata is a chronic inflammatory disease that significantly impacts the quality of life due to the formation of numerous cystic nodules, sinus tracts and severe atrophic scars. Conventional treatments for acne conglobata include oral and topical antibiotics, systemic isotretinoin, and dapsone. Our patient had previously used all these agents, benefiting initially but later experiencing ineffectiveness or reduced efficacy. Anti-TNF agents used in the treatment of inflammatory diseases such as hidradenitis suppurativa have been demonstrated to be effective in acne conglobata through literature case presentations. In our case, we administered adalimumab with an 80 mg subcutaneous loading dose, followed by a weekly 40 mg subcutaneous maintenance dose. At the second week, nodular acne lesions decreased, and after nine months, there were no new acne eruptions, and existing nodules and cysts had completely regressed. Adalimumab may be a promising agent in cases of acne conglobata that are unresponsive to known guideline agents.

Acne conglobata is a rare chronic inflammatory disease that significantly impacts the quality of life due to the formation of numerous cystic nodules, abscesses, sinus tracts, and severe atrophic scars [1]. The pathogenesis of acne involves abnormal follicular keratinization, excessive sebum production, Propionibacterium acnes colonization, and inflammation [2]. P. acnes stimulates the release of IL-1B and TNF-alpha from keratinocytes, leading to an abnormal immune response and inflammation [3]. Therefore, anti-TNF therapy is considered to play a central role in suppressing inflammation in the pathogenesis. Here, we present a case of acne conglobata that was unresponsive to various treatments but showed successful results with adalimumab therapy.

A 34-year-old male patient with a 20-year history of widespread acne on the face and body presented to our clinic. Dermatological examination revealed draining nodules and atrophic scars on the face and body. The patient had previously undergone five courses of systemic isotretinoin at appropriate doses. Treatment with dapsone 3*50 mg initiated by our team resulted in a two-year remission with intermittent flare-ups. During flare-ups, systemic and topical antibiotic therapies such as oral tetracycline, cephalosporin, and azithromycin were

administered. No growth was observed in the cultures obtained from the lesions for gram-negative folliculitis. Endocrinological and immunological examinations were normal, with no history of inflammatory bowel disease. Laser epilation for hair was performed, but no expected benefit was observed. Due to the exacerbation of acne lesions and non-response to dapsone treatment, informed consent was obtained, and adalimumab treatment was initiated.

The patient received adalimumab at a subcutaneous loading dose of 80 mg, followed by a maintenance dose of 40 mg subcutaneously once a week, based on literature-derived case presentations. At the nineth month of treatment, the examination revealed regression of acne lesions with no new acne eruptions, and no adverse effects related to the medication were observed (Figs. 1 and 2).

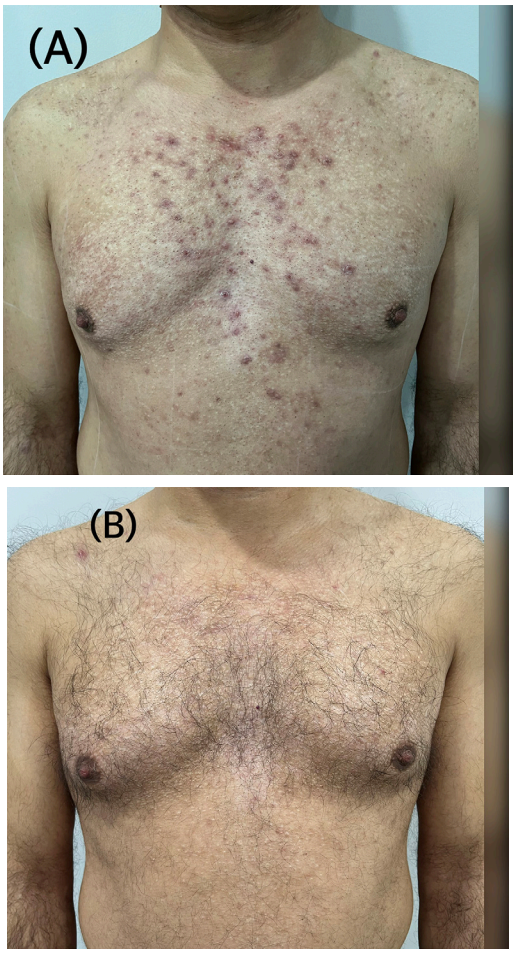

Figure 1. A: Inflammatory nodulocystic acne lesions on the patient's chest before treatment with adalimumab and **B:** 36 weeks after treatment with adalimumab.

Figure 2: Inflammatory nodulocystic acne lesions on the patient's face before and 36 weeks after treatment with adalimumab

Acne conglobata is typically seen in adult males, affecting the body and upper extremities more than the face [4]. It is part of the follicular occlusion tetrad along with dissecting cellulitis, hidradenitis suppurativa, and pilonidal sinus. Additionally, it may accompany syndromes such as SAPHO, PAPA, and PASH. Our case was a middle-aged male with acne conglobata for many years, showing no syndromic conditions or alignment with the follicular occlusion tetrad. Conventional treatments for acne conglobata include oral and topical antibiotics, systemic isotretinoin, and dapsone [5]. However, patients often show resistance and experience relapses. Our patient had previously used all these agents, benefiting initially but later experiencing ineffectiveness or reduced efficacy. Anti-TNF agents used in the treatment of inflammatory diseases such as hidradenitis suppurativa have been demonstrated to be effective in acne conglobata through literature case presentations. In a study by Sand et al. [6] an 18-year-old male with adalimumab treatment showed a decrease in nodular lesion size at the fourth week and complete regression at the twelfth week. Similarly, Yiu et al. [1] reported successful adalimumab treatment in a 26-year-old male with acne conglobata, with inflammatory nodules decreasing at the fourth week and disappearing entirely at the twelfth week. In our case, we administered adalimumab with an 80 mg subcutaneous loading dose, followed by a weekly

40 mg subcutaneous maintenance dose. At the second week, nodular acne lesions decreased, and after nine months, there were no new acne eruptions, and existing nodules and cysts had completely regressed.

In conclusion, adalimumab may be a promising agent in cases of acne conglobata that are unresponsive to known guideline agents. However, further studies are needed to validate its effectiveness in this context.

Regards,

Keywords: Acne, Adalimumab, TNF alfa

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Letter to Editor

Cavitating Mesenteric Lymph Node Syndrome in a Patient with Celiac Disease: Differential Diagnosis Based on Radiological Findings

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Abstract
Mesenteric lymph node syndrome is a rare condition characterized by cystic or cavitating changes in mesenteric lymph nodes. It is commonly associated with celiac disease. We present a case of a 59-year-old woman with known celiac disease who presented with abdominal pain, abdominal swelling, and weight loss, ultimately diagnosed with mesenteric lymph node syndrome. This case highlights the importance of radiological findings when considering rare complications of celiac disease in the differential diagnosis.

Keywords: mesenteric lymph node syndrome, celiac disease, cavitating lymph node

Dear Editor,

Cavitating mesenteric lymph node syndrome (CMLNS) is an uncommon but poor-prognosed complication of celiac disease, characterized by the development of cystic or cavitating lesions within the mesenteric lymph nodes [1]. In advanced cases, fat-fluid levels may be observed in the lymph nodes. The precise connection between CMLNS and celiac disease remains a subject of ongoing research. However, some reports suggest that due to mucosal damage in the small intestines, mesenteric lymph nodes undergo cystic or cavitary changes as a result of increased exposure to antigens [2].

The pathogenesis of CMLNS is not clearly understood. Patients often present with symptoms such as weight loss, diarrhea, fatigue, and abdominal pain [3]. It may be accompanied by splenic atrophy [4]. The diagnosis of CMLNS is based on clinical and radiological findings including computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI) [2]. Tuberculosis, lymphoma, necrotic metastases, Whipple disease, and germ cell tumors should be considered in the differential diagnosis of hypodense mesenteric lymph nodes [5]. In the literature, studies related to CMLNS typically exist in the form of case presentations or case series. Despite the previously described radiological findings of the disease, with this case, we aimed to illustrate the defining features of advanced disease in more detail.

Patient's history

A 59-year-old female patient presented to our hospital with an abdominal pain, marked weight loss, gastrointestinal complaints, abdominal distention, weakness, and cough. Notably, she

was diagnosed with celiac disease approximately two years prior, following a period of persistent diarrhea, occurring up to 6-7 times a day. The definitive diagnosis of celiac disease was established through endoscopic biopsy, which revealed characteristic mucosal changes in the small intestine.

Although the initial diagnosis, the patient struggled to adhere to a strict gluten-free diet. For the past year, she experienced a precipitous decline in her health, with an astonishing weight loss of 35 kilograms, bringing her current body weight to a mere 35-40 kilograms. This dramatic weight loss led to a state of cachexia and weakness. The patient's presentation, with abdominal pain, uncontrolled celiac disease, and a history of severe weight loss raises concerns about potential complications.

Examination and investigation

Laboratory investigations indicated elevated inflammatory markers, leukocytosis, hyponatremia, and hypochloremia. The other complete blood count and biochemistry parameters were within normal range.

In the thorax CT taken for respiratory symptoms, cystic and cylindrical bronchiectasis areas, peribronchial consolidations, and occasional mucus plugs were observed in both lungs. After the detection of mass-like heterogeneous lesions on abdominal US, contrast-enhanced abdominal CT was recommended to the patient. In abdominal CT, predominantly filling the left upper quadrant, extending to the right of the midline, conglomerate masses with the largest measuring 130x90mm were observed. These lesions show dense content and exhibit fluid-fat levels. The jejunal segments have been compressed towards the periphery (Fig. 1). There was free fluid present in the Douglas pouch at a depth of 3cm. Additionally, there was an appearance compatible with an atrophic spleen in the splenic chamber, approximately 30x12 mm in size. In the abdominal CT image taken at another hospital eight months ago, low-density (5-10 Hounsfield units) conglomerate lymph nodes with the largest measuring 25x20mm were observed in the left upper quadrant at the mesenteric root (Fig. 2).

Treatment

The diagnosis was confirmed based on the patient's history and characteristic imaging findings. The patient, who was hospitalized and placed under intensive care for monitoring, was planned to receive antibiotic therapy and supportive treatment for electrolyte imbalances. The patient received clarithromycin for nine days and piperacillin/tazobactam for eleven days. Following a consultation with a dietitian, it was determined that the daily calorie requirement was 1200 kcal, and a plan was made for the patient to receive 1500 kcal daily for weight gain. Total parenteral nutrition therapy was initiated for the patient. Electrolyte values were closely monitored through daily observations.

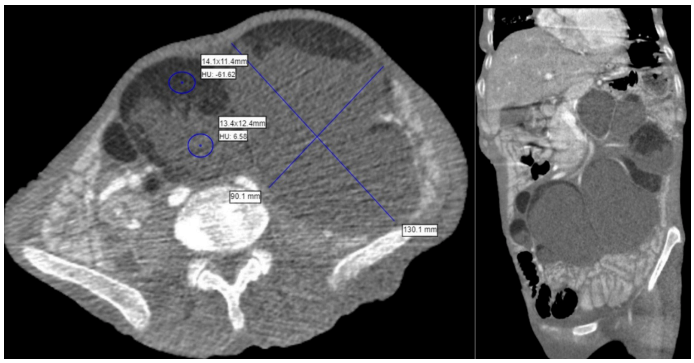

Figure 1. Axial and coronal contrast-enhanced abdominal CT images on September 2023 show conglomerate cavitating lymph nodes containing fat-fluid levels (avg HU:-61.62 and 6.58) and reaching large sizes (130x90mm). The intestinal segments appear to be pushed peripherally.

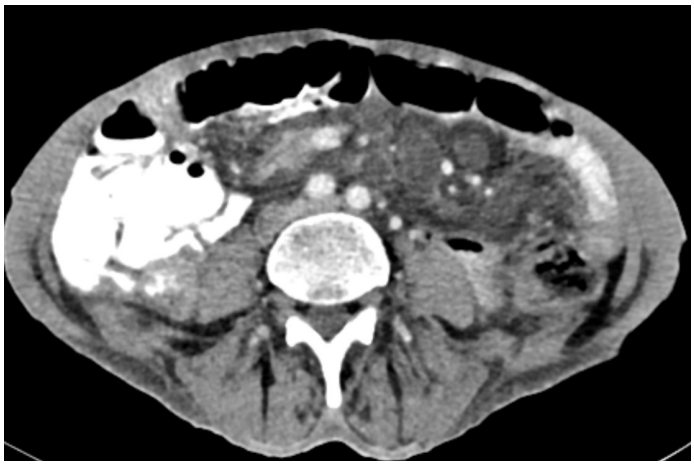

Figure 2. The abdominal CT performed on 15 January 2023 showed that the lymph nodes in the mesenteric root were smaller. In the patient who did not comply with the diet, it was observed that the lymph node size increased 5 times within 8 months.

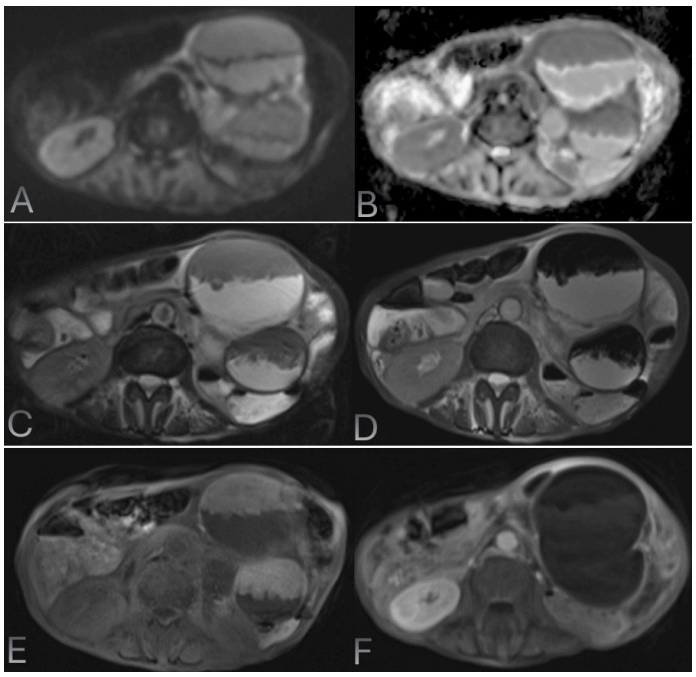

Figure 3. MRI performed six weeks after treatment showed mild regression of the cavitating mesenteric lymph nodes. The axial sequences are as follows: A) DWI, B) ADC C) T2W-fat saturated, D) T2W-TRUFI, E) T1W, F) T1W-fat saturated+contrast enhanced.

Follow-up

The patient, whose condition stabilized, was advised on a gluten-free diet during discharge. When the patient came for a follow-up visit six weeks later, since the patient described pain in the right upper quadrant, an abdominal MRI were performed. The MRI images showed cavitary mesenteric lymph nodes, with the largest measuring 100x90mm and containing fluid-fat levels (Fig 3). The findings were interpreted in favor of minimal regression in the patient who adhered to the diet.

DISCUSSION

This case report presents the advanced disease of CMLNS in detail. There is limited literature information on this rare condition. This report stands out because it contains the most revealing radiological findings, thus facilitating differential diagnosis.

In a previous study by Keer et al, a multicyclic complex lesion with the largest measuring 43x37 mm in the anterior region and reaching a total size of 116x69mm was reported [3]. In our patient, the largest singular mesenteric lymph node size detected on abdominal CT was 130x90 mm. The development of CMLNS in patients with celiac disease is considered to be associated with a poor prognosis [6]. In our patient, abdominal CT taken 8 months ago showed mesenteric lymph nodes much smaller, with a maximum size of 25x20 mm. However, in the patient who did not adhere to a gluten-free diet, there was rapid progression, reaching a huge size.

The pathogenesis of CMLNS, which was first described by Hemet et al. in 1969, is not clearly understood [7]. Patients often present with symptoms such as weight loss, diarrhea, fatigue, and abdominal pain [3]. Our patient was complicated by bronchiectasis and pneumonia, along with these similar symptoms. The cachexia caused by this disease is expected to trigger recurrent infections and increase complications. As mentioned in the literature, splenic atrophy may also accompany this disease, and in our patient, the spleen size measured 30x12 mm.

Although mesenteric lymph nodes with fat-fluid levels are typically seen in CMLNS, which is a complication of celiac disease, differential diagnosis of similar-looking lymph nodes should be made. In lymphadenopathy associated with tuberculosis, central caseation-related hypodensity and calcification are frequently observed in lymph nodes. In the early stages, the affected lymph nodes often have a regional location near the cecum. In cases of abdominal involvement by tuberculosis, most patients show thickening of the intestinal wall and the presence of ascites [8]. Tubercolous lymph nodes generally shows peripherally enhancement [9].

In lymphoma-related abdominal lymph node involvement, the involvement is often characterized by regionally located, multiple, well-defined lymph nodes that occasionally coalesce to form a mass-like appearance, showing mild homogeneous contrast enhancement. In some cases, rim enhancement may also be present. The majority of these patients have extranodal abdominal disease, with involvement in the gastrointestinal system in more than half of the cases [10].

Lymph nodes containing fatty density can also be observed in Whipple's disease. Whipple's disease, also known as intestinal lipodystrophy, is a rare infectious disorder that primarily affects the small intestine. Adenopathies can occur not only in the mesenteric region but also in the cervical, retrocrural, and retroperitoneal regions [11].

Germ cell tumors are a type of neoplasm that can occur in various parts of the body, most often in the gonads. Teratomas in this group typically present a heterogeneous appearance with features such as fat, calcifications, and soft tissue density [12].

CONCLUSION

It is important to be aware of the radiological features of CMLNS, a rare complication of celiac disease, for an accurate diagnosis. Using radiological imaging methods to monitor the development of this condition and determine treatment strategies can play a critical role in the management of patients.

Regards

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During the preparation of this work the authors used ChatGPT to translate parts of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author Contributions

SO was involved in writing and study design. HK was involved in data collection and literature review. MH provided editing and review of the manuscript.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

No data available.

Informed Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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