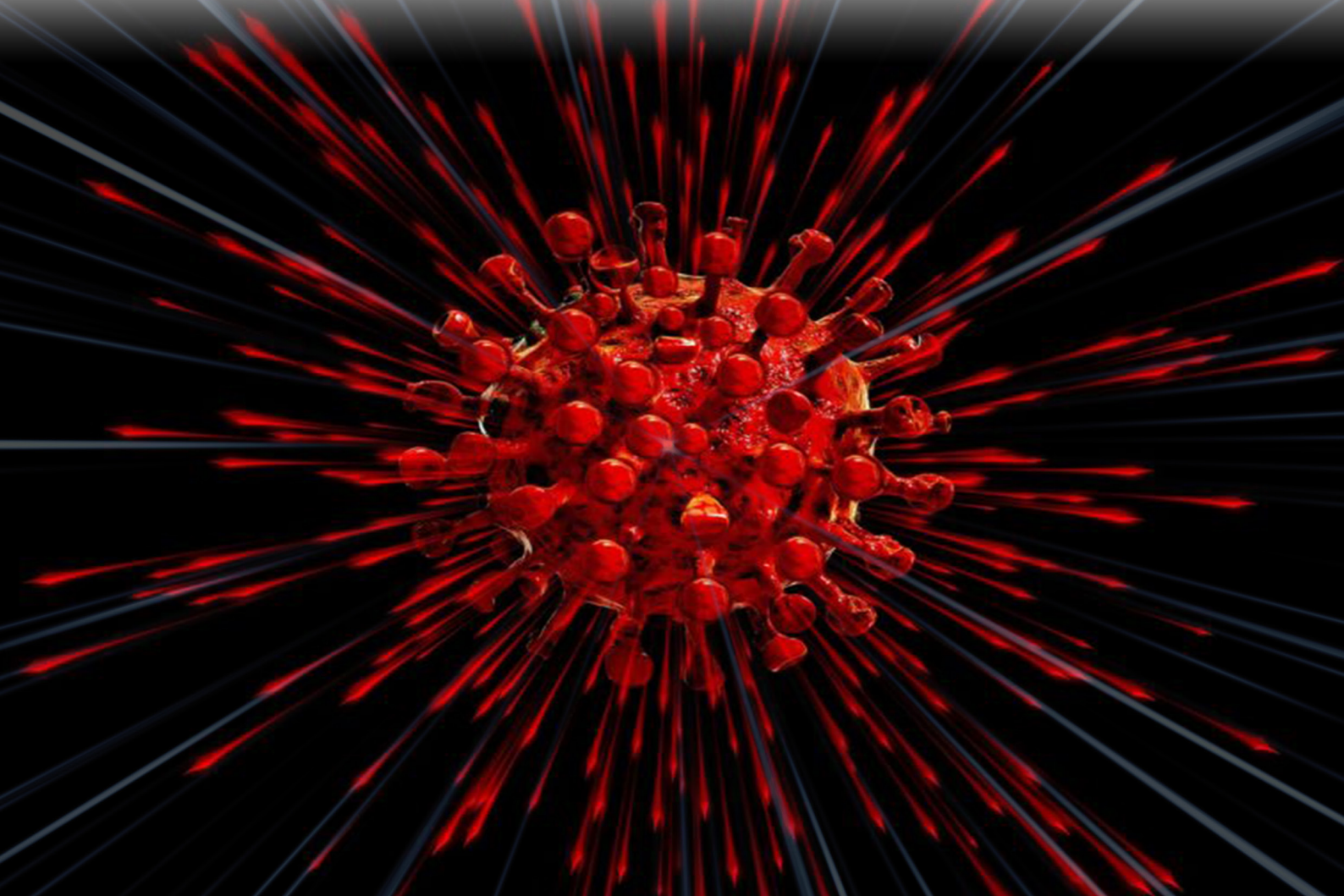


# ACMJ

**Anatolian Current Medical Journal**



VOLUME: 6

ISSUE: 1

YEAR: 2024

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## **EDITORIAL**

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We are excited to publish the first issue of the 6<sup>th</sup> year of our journal, Anatolian Current Medical Journal (ACMJ). In the new year, our Journal will be published as 6 issues per year. The quality of the articles in our journal, which is included in Ulakbim TR-index and many international indexes, is increasing day by day. We want to be included in stronger international indices in the near future. We want to raise the quality of the articles to a higher level and contribute to the academic literature on behalf of our country by entering valuable international indexes such as SCI-Expanded, Scopus, ESCI, Pubmed. We would like to thank the editors working in our journal, all the authors who sent their articles to our journal, and everyone who contributed to the publication, development and any stage of the journal.

Hoping that the new year brings health, happiness and peace to our country and all humanity...

**Prof. AYDIN IFCI**  
**Editor-in-Chief**

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# Duodenal IgE and mast cells changes in diabetes mellitus patients

©Ethem Ömeroğlu, ©Ayşe Nur Uğur Kılınç

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Cite this article as: Ömeroğlu E, Uğur Kılınç AN. Duodenal IgE and mast cells changes in diabetes mellitus patients *Anatolian Curr Med J.* 2024;6(1):1-5.

Received: 14.08.2023

Accepted: 10.11.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** To determine the differences in duodenal biopsies of diabetes mellitus (DM) patients and non-diabetic patients by investigating the numbers of immunoglobulin E (IgE) positive plasma cells, IgE positive mast cells, and eosinophils.

**Methods:** Patients diagnosed with chronic duodenitis and DM and those diagnosed only with chronic duodenitis within between 2010-2020 years were detected from the hospital information system. Paraffin blocks and hematoxylin-eosin-stained preparations of the patients' duodenal biopsies were obtained from the hospital's pathology archive. By performing IgE immunohistochemical staining for all blocks, the sections were evaluated through light microscopy.

**Results:** A total of 75 patients, 45 with DM and 30 non-diabetic patients with chronic duodenitis were included in the study. While IgE accumulation was prominently detected in the plasma cells and mast cells of DM patients' duodenal tissue samples, no significant IgE accumulation was detected in the biopsies of non-diabetic patients with chronic duodenitis.

**Conclusion:** To date, the effectiveness of mast cells, IgE, and duodenal histological changes in DM have been proven, but our study is the first to detect the increase in mast cells and IgE in duodenal biopsies of DM patients. High IgE in the duodenum could support the relationship between DM and food allergy. We consider that higher IgE antibodies detected in diabetic patients' duodenums will reveal promising novel results in elucidating DM pathophysiology and regulating the treatment modalities, and will shed light on future studies.

**Keywords:** Diabetes mellitus, Ig E, mast cells

## INTRODUCTION

The small intestine is a major organ involved in the digestion of food and absorption of nutrients and minerals. The duodenum, which is the first part of the small intestine and connects to the stomach, is a primary site in the digestion and absorption of food.<sup>1</sup>

Diabetes mellitus (DM), a chronic metabolic disease with hyperglycemia, is associated with abnormalities in structures and functions in the gastrointestinal tract, especially the small intestine.<sup>2</sup>

In the literature, duodenal biopsies in DM cases, it was found to be associated with decreased diameter of blood vessels, reduced number of endothelial fenestrae, microvasculature, edema, and mucosal ulcers in various studies.<sup>3-5</sup>

Finally, comprehensive histomorphology and quantitative analysis results explain decreased goblet cells, increased number of paneth cells, thickened submucosal layer, and enhanced duodenal glands in the diabetes mellitus group.<sup>6</sup>

In addition to these histologic studies, a study on the duodenal microenvironment in DM; patients with hyperglycemia had a higher duodenal bacterial count, increased pathobionts, and reduction in flora compared to normoglycemic.<sup>7</sup>

Mast cells are capable of powerful inflammatory response programs triggered by surface IgE cross-linking or through pattern recognition receptors. Human studies point to pathogenetic or protective mast cell functions in patients with atopic conditions, autoimmune disorders, type 2 diabetes, chronic urticaria, mastocytosis, and cancer.<sup>8</sup>

The type I hypersensitivity responses of classic allergic reactions are mediated by allergen cross-linking of immunoglobulin E (IgE) bound to FcεRI receptors on the surface of tissue mast cells. GI tissues are an important reservoir for allergen-specific IgE-positive plasma cells in allergic participants and could contribute significantly to allergen-specific serum IgE in the tissues and perhaps systemically.<sup>9</sup>

Corresponding Author: Ayşe Nur Uğur Kılınç, aysenurugur@hotmail.com





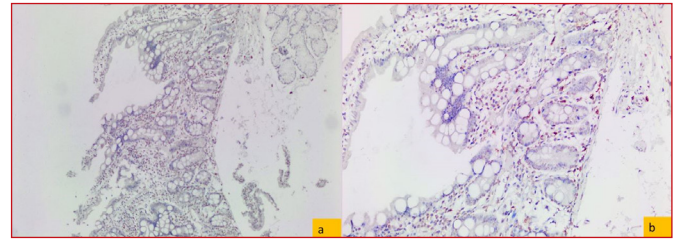
In line with studies reporting that duodenal histopathological examination and mast cells are important in DM patients, in the present study, we aimed to determine the differences in duodenal biopsies of DM patients and non-diabetic patients by investigating the numbers of immunoglobulin E (IgE) positive plasma cells, IgE positive mast cells, and eosinophils.

## METHODS

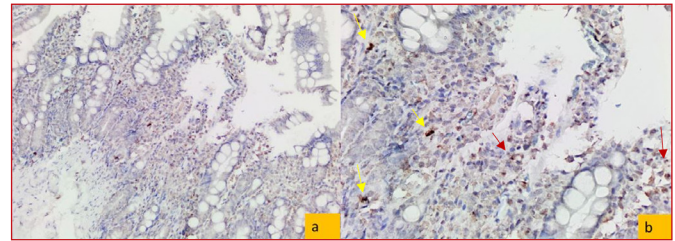
The study was carried out with the permission of the KTO Karatay University Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 25.12.2020, Decision No: 2021.006). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The duodenum biopsy materials obtained from 45 diabetic patients and 30 non-diabetic individuals diagnosed with non-specific chronic duodenitis in the pathology laboratory of our hospital between 2010 and 2020 years were included and investigated in the study. The patients diagnosed with chronic duodenitis and DM and non-diabetic individuals diagnosed only with non-specific chronic duodenitis were detected from the hospital information system. The patients with any malignancy or diagnosed with any known food allergy and autoimmune disease were not included in the study. The paraffin blocks of patients' duodenal biopsy samples and hematoxylin-eosin-stained preparations were obtained from the hospital's pathology archive. In preparing tissue sections, poly-L-lysine (PPL) was used to coat glass slides for IgE immunocytochemical staining. The primary antibody was anti-human IgE (rabbit, Abcam, polyclonal, prediluted, Ab75673).

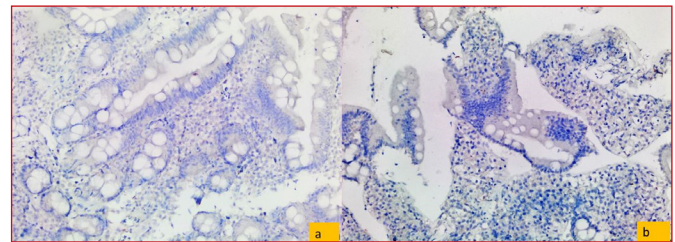
Therefore, immune-stained and hematoxylin-eosin-stained glasses were evaluated under a light microscope. With IgE staining, plasma cells with strong cytoplasmic staining were easily distinguishable from the mast cells with weaker membrane reactions. The numbers of Ig E-positive plasma cells and mast cells, eosinophils in the duodenal mucosa, and lamina propria were calculated by an ocular micrometer on a total area of mm<sup>2</sup> per sample. The IgE-containing mast cells were evaluated by counting cells in mm<sup>2</sup> in the areas where the cells were the most concentrated. However, the plasma cells containing IgE were graded as 1, 2, and 3 in light of their prevalence and density (Figure 1-4). The demographic data related to the patients' peripheral blood test results and ages were obtained from the hospital information system, and the data accessed were recorded.



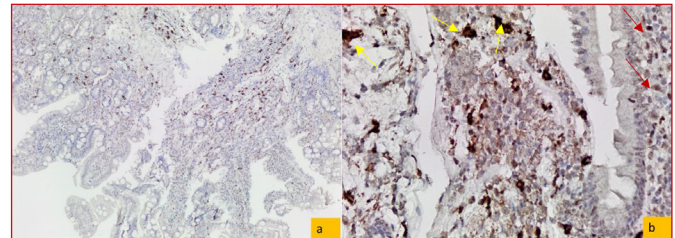
**Figure 1.** Diffuse and severe plasma cells containing IgE in the duodenum of the diabetic patient (IgE immunostaining image of 100X objective)(a), 200X objective(b)



**Figure 2.** Focal and moderate Ig E containing plasma cells in the duodenum of the diabetic patient (Ig E immunostaining image of 100X objective)(a), 200X objective(b) (yellow arrows show some of the mast cells and red arrows show some of the plasma cells with IgE accumulation)



**Figure 3.** No plasma and mast cells accumulating Ig E in control group patient's duodenum 200X objective (a-b)



**Figure 4.** Severe mast cells containing Ig E in the duodenum of the diabetic patient, low magnification-100X(a), high magnification-400X(b), and moderate Ig E-containing plasma cells (yellow arrows show some of the mast cells and red arrows show some of the plasma cells with IgE accumulation).

While the differences between both groups were determined by the Mann-Whitney U test for numerical variables, the chi-square test was used to investigate the categorical variables. A p-value of <0.01 was considered statistically significant.

## RESULTS

Our study included a total of 75 patients, 45 with DM diagnosis [27 with type-1 DM and 18 with type-2 non-insulin-dependent DM (NIDDM)] and 30 non-diabetic patients diagnosed with chronic duodenitis. The study participants were classified as the study group consisting of 45 DM patients and the control group composed of 30

non-diabetic patients diagnosed with chronic duodenitis. DM and non-DM patients consist of groups with similar age distributions

While Ig E accumulation was detected in the plasma cells in duodenal tissue samples of DM patients, no significant Ig E accumulation was observed in duodenal tissue of non-diabetic patients (**Table**) (**Figure 1-3**). In addition to that, while the mast cells were seen in varying numbers in 77% (35/45) of DM patients, the cells were present only in 20% (6/30) of the participants in the control group (**Figure 4**).

	Diabetes mellitus patients	The control group (non-diabetes mellitus) patients	p-value
Mean Age/y	40.8	38.1	p>0.05
The mean number of prevalence (diffusivity) of plasma cells containing IgE in duodenal biopsies	1.6	0.06	p<0.001
The mean number of intensity of plasma cells containing IgE in duodenal biopsies	1.9	0.06	p<0.001
Mast cells and plasma cells containing Ig E in duodenal biopsies/mm <sup>2</sup>	17.7	0.6	p<0.001

Based on our findings, both mast cells and IgE-containing plasma cells were found to be statistically significantly higher among DM patients, compared to those of the controls (p <0.01) (**Table**).

Given the number of peripheral blood and tissue eosinophils, no significant difference was found between the study and control groups (p >0.05). Considering the plasma cells in type-1 and type-2 DM patients, no difference was detected between the number of IgE and mast cells and the number of tissue eosinophils (p >0.05).

## DISCUSSION

Increasing day by day and affecting individuals from all age segments across the world, DM is a chronic disease leading to fatal problems.<sup>10</sup> Numerous studies have been conducted to understand the pathophysiology of DM and are to be still performed.<sup>11,12</sup> In addition to these, medical science continues to create many medical and surgical novel treatment modalities to treat DM.<sup>13-15</sup>

There are many studies on the effectiveness of mast cells in DM patients.<sup>8,16-18</sup> Obesity is associated with adipose tissue inflammation and prominent M1 macrophage differentiation, as well as the dominance of type 1 cytokines, including TNF.<sup>16</sup> This spontaneous inflammatory response plays an important role in the

breakdown of adipose tissue glucose homeostasis and the development of type II DM.<sup>16</sup> The observation that mast cells accumulate in the inflamed adipose tissue and reports on beneficial effects of H1- blocking and mast cell-stabilizing drugs with potentially additional anti-inflammatory effects on obesity and type II diabetes.<sup>17,18</sup>

In our study, the fact that a difference was determined between the two groups by examining the number of IgE-positive plasma cells, and the number of IgE-positive mast cells in DM and non-diabetic patients' duodenum biopsies yielded remarkable results never studied before.

In recent years, various studies have been conducted to demonstrate the associations between chronic inflammation, autoimmune diseases, and mast cells.<sup>18,19</sup> Even so, in diabetic individuals, it has been found that the severity of DM in plasma and tissue cells is associated with the number of mast cells.<sup>19,20</sup> As consistent with the findings stated by those studies, our study revealed that the rate of IgE-containing mast cells was higher in diabetic patients, compared to the control group.

As well as the above-mentioned ones, there are also studies detecting IgE in the plasma concentration of patients with DM. While some of those studies found that IgE was within normal limits, others revealed that the plasma IgE concentration was increased with the severity of DM.<sup>19,21-24</sup> Based on the literature, however, there is no study investigating IgE antibodies in the plasma cells and mast cells of the duodenal tissue of diabetic populations. So, our study findings are the first to enlighten the issue in this respect.

Given the findings related to IgE antibodies in the tissues, there are studies in the literature evaluating only food allergies in the duodenum and Helicobacter pylori in the stomach.<sup>23-26</sup> As a result of such studies, the detection of IgE in the duodenum tissue was found to be highly predictive and sensitive in detecting food allergies.<sup>25</sup>

We know from the literature that one of the components of diabetic gastroenteropathy is bacterial overgrowth and that bacterial overgrowth is generally associated with food intolerance and food allergy.<sup>27,28</sup> The IgE increase we detected in the duodenum may be associated with food allergy, which will cause bacterial overgrowth in DM patients. More detailed studies are needed on this subject.

There are some new studies asserting the relationship between DM and food allergy. These studies support that food allergen elimination reduces DM.<sup>29,30</sup> Our study detected more IgE in the duodenum of DM patients than in the control group and supported the food allergen and DM relationship which could help to reduce or reverse the progress of DM by food allergen elimination.<sup>29,30</sup>

Although blood eosinophil levels were found to be lower in the patients with insulin resistance and DM, compared to the control group in a study including a large population.<sup>31</sup> Other studies related to tissue eosinophils reveal the opposite. However, in studies evaluating the lipomatous tissues of the patients with metabolic syndrome and the pancreatic tissues of DM patients, the number of eosinophils and eosinophilic chemotactic proteins were demonstrated to be higher among the patients than in the control group.<sup>31</sup> In our study, no difference was found between blood eosinophil levels and tissue eosinophils in DM patients and the controls.

## CONCLUSION

To date, the effectiveness of mast cells, IgE, and duodenal histological changes in DM have been proven, but our study is the first to detect the increase of IgE in mast cells and plasma cells in duodenal biopsies of DM patients. High IgE in the duodenum supports the relationship between DM and food allergy. We consider that higher IgE antibodies detected in diabetic patients' duodenums will reveal promising novel results in elucidating DM pathophysiology and regulating the treatment modalities, and will shed light on future studies.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the KTO Karatay University Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 25.12.2020, Decision No: 2021.006).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Information and approaches of emergency department physicians in the Cappadocia region regarding the preparation of forensic reports

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**Cite this article as:** Yakar Ş, Baykan N, İpekten F, Çakır YE. Information and approaches of emergency department physicians in the Cappadocia region regarding the preparation of forensic reports. *Anatolian Curr Med J.* 2024;6(1):6-10.

Received: 03.10.2023

Accepted: 19.11.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** Forensic reports; these are physician's opinion and opinion reports, which are mostly prepared by emergency room physicians regarding the medical conditions of people and reported to the judicial authorities. In this study; it was aimed to examine the attitudes and behaviors of emergency physicians working in the Cappadocia region regarding the preparation of forensic reports.

**Methods:** This cross-sectional study; it was conducted with a survey applied to 73 emergency physicians working in Nevşehir city center and districts. The data was created based on the answers given to this survey form.

**Results:** The majority of physicians participating in the study are general practitioners (87.7%). The average length of service of the participants is 2.3 1.1 years. Most physicians reported that the forensic medicine training they received was insufficient (75.3%). Survey answers of the participants; They were compared in terms of their titles, length of service and forensic medicine training.

**Conclusion:** Regular in-service training should be provided at intervals so that more appropriate forensic reports can be kept and physicians can have more information about the legal part of forensic reports.

**Keywords:** Forensic medicine, forensic report, emergency service

## INTRODUCTION

Forensic medicine; It can be defined as a branch of science that deals with the application of medical science to the law and justice system and legal situations in the healthcare system.<sup>1</sup> As a result of the person's will, unwillingness or negligence; A person who is actively or passively affected by a situation that can be called a physical or mental illness is considered a judicial case.<sup>2</sup> Traffic accidents, falls, assault cases, work accidents, poisonings, burns, electric and lightning strikes, all kinds of asphyxia cases, stabbing & cutting tool injuries, gunshot wounds, abuse cases or suspected abuse and suicide attempts are considered as legal cases.<sup>2,3</sup> Forensic reports are; It is defined as reports prepared by physicians regarding the medical conditions of forensic cases and requested by judicial authorities.<sup>4</sup>

Since forensic cases are most frequently seen in emergency departments; Emergency room physicians encounter these cases more frequently and prepare more forensic reports.<sup>5</sup> Physicians are responsible for examining forensic cases in detail, recording the examination findings completely and keeping a forensic report.<sup>3</sup>

In this study, emergency room physicians working in the Cappadocia region; A survey was conducted to measure their knowledge and approaches to preparing forensic reports. Factors such as title, length of service and forensic medicine training; It is aimed to prepare forensic reports and examine their impact on the approach to forensic cases.

## METHODS

Our study is cross-sectional and was conducted between 01.01.2022 and 30.06.2022 in the city center and districts of Nevşehir, called the Cappadocia region. Approval for our study was received from Nevşehir Hacı Bektaş Veli University Ethics Committee (Date: 25.10.2021, Decision No: 2021.09.318). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Physicians working in emergency departments in this region and volunteering to participate in the study were included in the study. A 20-question survey form prepared by an emergency

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medicine specialist and a forensic medicine specialist was applied to the physicians participating in the study. Survey forms were delivered to participants by phone and e-mail, and their identity information was not collected. Survey form; It includes questions about the participants' sociodemographic information (gender, title, length of service, etc.), and their attitudes and behaviors regarding forensic medicine and forensic report preparation.

### Statistical Analysis

The data were analyzed in the SPSS 22.0 for Windows package program. Pearson  $\chi^2$  analysis and Fisher exact  $\chi^2$  test were used for comparisons of categorical data. Analysis of the data was performed in R 4.0.3 ( www.r-project.org ). The significance level was accepted as  $p < 0.05$ .

## RESULTS

73 physicians working in emergency departments in the city center and district hospitals participated in the study. 9 (12.3%) of the physicians are emergency medicine specialists and 64 (87.7%) are general practitioners. 30 (41.1%) of the participants were women and 43 (58.9%) were men. The average service period of the participants  $\pm$  was calculated as 2.3 1.1 years. Only 18 (24.7%) of the physicians reported that they received adequate forensic medicine training. The type of forensic report that the physicians participating in the study usually prepared was questioned; It was determined that 26 (35.6%) of them prepared mostly temporary reports and 47 (64.4%) of them prepared final reports. The sociodemographic characteristics of the participants, their participation in the examination of the dead and the internal body examination are summarized in **Table 1**.

Again, the physicians who participated in the study were asked, 'How do you find the approach of judicial law enforcement officers to forensic cases?' The question was posed. 37 (50.7%) of the physicians answered that it was sufficient and 36 (49.3%) answered that it was inadequate.

Participants were asked 11 questions to measure their approach to forensic cases and their level of knowledge on legal issues and forensic cases. Two of these questions aimed to evaluate an exemplary forensic case. Physicians' answers to the questions; They were compared in terms of their titles, length of service and forensic medicine training (**Table 2**). Participants; They were divided into two groups according to their titles: general practitioner and specialist physician, according to their length of service, those who worked for 5 years or less and those who worked for more than 5 years, and whether they received forensic medicine training or not. Physicians' answers to the questions; They were compared in terms of their titles, length of service and forensic medicine

training (**Table 2**). Participants were asked: 'Do you know which cases are considered judicial cases?' When the question was compared in terms of service period, a statistically significant difference was found ( $p=0.036$ ). Again, 'Do you know the legal responsibility of forensic reports?' When the question was compared according to titles, a statistically significant difference was found ( $p=0.003$ ). In the survey; 'In a case injured with a cutting tool, if it is thought that the tool entered the abdomen but there was no major vascular or organ injury, the forensic report to be given; Is there a life-threatening situation?' The sample forensic case question asked was compared for all groups, but no statistically significant difference was found ( $p>0.05$ ). Again, 'Do you use the lists and tables prepared by the Forensic Medicine Institute and the association of forensic medicine experts in your reporting?' Only 21 (28.8%) of the participants answered yes to the question.

In the survey; 'How would you evaluate simple medical intervention (STM) in a forensic case admitted due to head trauma, with normal physical examination findings and no injuries to the head or face?' The sample forensic case question was compared for all groups; A statistically significant difference was found only in the comparison made according to titles ( $p<0.001$ ). Details of the comparison of the survey questions asked to the participants according to groups are summarized in **Table 2**.

**Table 1.** Distribution of sociodemographic characteristics of participants

Sociodemographic characteristics	n	%
Gender		
Woman	30	41.1
Male	43	58.9
Organisation		
Nevşehir state hospital	33	45.2
District state hospitals	35	48
Private sector	5	6.8
Title		
Specialist Physician	9	12.3
General practitioner	64	87.7
Service time		
≤ 5 years	46	63.1
>5 years	27	36.9
Have you received adequate forensic medicine training?		
No	55	75.3
Yes	18	24.7
Type of forensic report prepared		
Temporary	26	35.6
Thick	47	64.4
Forensic death examination procedures		
I agree	35	47.9
I do not agree	38	52.1
Internal body examination		
I do	12	16.4
I don't	61	83.6

**Table 2.** Comparison of the survey conducted to measure the level of awareness of forensic cases according to the participants' titles, length of service and forensic medicine education

Survey questions	Title		P	Service time		P	Forensic medicine education		P
	Practitioner n=64 (%)	Expert n=9 (%)		≤ 5 years n=46 (%)	>5 years n=27 (%)		Sufficient n=18 (%)	Insufficient n=55 (%)	
Do you get nervous when a forensic case comes?									
No	9 (14.1)	4 (44.4)	0.062	5 (10.9)	8 (29.6)	0.116	5 (27.8)	8 (14.5)	0.444
Partially	30 (46.9)	2 (22.2)		21 (45.6)	11 (40.8)		7 (38.9)	25 (45.5)	
Yes	25 (39)	3 (33.4)		20 (43.5)	8 (29.6)		6 (33.3)	22 (40.0)	
Do you know which cases are considered criminal cases?									
Partially	30(65.2)	2 (22.2)	0.069	38 (59.4)	10 (37.0)	0.036	6 (33.3)	34 (61.8)	0.067
Yes	16(34.8)	7 (77.8)		26 (40.6)	17 (63.0)		12 (66.7)	21 (38.2)	
Do you remove people's clothes during forensic examination?									
Partially	49 (76.6)	7 (77.8)	0.999	37 (80.4)	19 (70.4)	0.487	14 (77.8)	42 (76.4)	0.999
Yes	15 (23.4)	2 (22.2)		9 (19.6)	8 (29.6)		4 (22.2)	13 (23.6)	
Can emergency physicians give a definitive report?									
I don't know	5 (7.8)	0	0.619	2 (4.3)	3 (11.1)	0.352	2 (11.1)	3 (5.5)	0.591
Yes	59 (92.2)	9 (100)		44 (95.7)	24 (88.9)		16 (88.9)	52 (94.5)	
Do you know the legal responsibility of forensic reports?									
No	4 (8.7)	1 (11.1)	0.003	5 (7.8)	2 (7.4)	0.104	1 (5.6)	5 (9.1)	0.169
Partially	35 (76.1)	2 (22.2)		48 (75)	15 (55.6)		10 (55.6)	40 (72.7)	
Yes	7 (15.2)	6 (66.7)		11 (17.2)	10 (37.0)		7 (38.8)	10 (18.2)	
Do you know the effects of forensic reports on prosecution?									
No	6 (9.4)	1 (11.1)	0.186	5 (10.9)	2 (7.4)	0.520	1 (5.6)	6 (10.9)	0.140
Partially	46 (71.9)	4 (44.4)		33 (71.7)	17 (63.0)		10 (55.6)	40 (72.7)	
Yes	12 (18.8)	4 (44.4)		8 (17.4)	8 (29.6)		7 (38.8)	9 (16.4)	
Do you know the impact on the trial process of whether the injury can or cannot be treated with simple medical intervention?									
No	23 (35.9)	3 (33.3)	0.691	18 (39.1)	8 (29.6)	0.710	10 (55.6)	16 (29.1)	0.113
Partially	35 (54.7)	6 (66.7)		24 (52.2)	17 (63.0)		7 (38.9)	34 (61.8)	
Yes	6 (9.4)	0		4 (8.7)	2 (7.4)		1 (5.6)	5 (9.1)	
Do you use the lists and tables prepared by the Forensic Medicine Institute and the association of forensic medicine experts in your reporting?									
No	26 (40.6)	6 (66.7)	0.169	17 (37.0)	15 (55.6)	0.301	7 (38.9)	25 (45.5)	0.440
I don't know	20 (31.3)	0		14 (30.4)	6 (22.2)		7 (38.9)	13 (23.6)	
Yes	18 (28.1)	3 (33.3)		15 (32.6)	6 (22.2)		4 (22.2)	17 (30.9)	
In a case injured with a sharp object, if it is thought that the tool entered the abdomen but there was no major vascular or organ injury, the forensic report to be given; Danger to life									
There is no	15 (23.4)	2 (22.2)	0.89	11 (23.9)	6 (22.2)	0.114	3 (16.7)	14 (25.5)	0.344
I don't know	13 (20.3)	1 (11.1)		12 (26.1)	2 (7.4)		2 (11.1)	12 (21.8)	
Has	36 (56.3)	6 (66.7)		23 (50.0)	19 (70.4)		13 (72.2)	29 (52.7)	
Have you prepared a percent fixed trace report?									
No	54 (84.4)	8 (88.9)	0.999	41 (89.1)	21 (77.8)	0.309	16 (88.9)	46 (83.6)	0.721
Yes	10 (15.6)	1 (11.1)		5 (10.9)	6 (22.2)		2 (11.1)	9 (16.4)	
Do you use the No BTM SMI required pattern?									
Yes	50 (78.1)	5 (55.6)	0.424	33 (71.7)	22 (81.5)	0.696	13 (72.2)	42 (76.4)	0.798
No	10 (15.6)	3 (33.3)		9 (19.6)	4 (14.8)		3 (16.7)	10 (18.2)	
I don't know	4 (6.3)	1 (11.1)		4 (8.7)	1 (3.7)		2 (11.1)	3 (5.5)	
How would you evaluate BTM SMI in a forensic case with normal physical examination findings and no head or facial injuries?									
Remediable	18 (28.1)	9 (100)	<0.001	15 (32.6)	12 (44.4)	0.372	6 (33.3)	21 (38.2)	0.505
Cannot be eliminated	29 (45.3)	0		18 (39.1)	11 (40.7)		6 (33.3)	23 (41.8)	
Does not require	17 (26.6)	0		13 (28.3)	4 (14.9)		6 (33.3)	11 (20.0)	

BTM -> SMI: simple medical intervention

## DISCUSSION

Since forensic reports are of great importance for the functionality of law, utmost care and attention must be paid when preparing these reports.<sup>6</sup> All physicians have forensic medicine duties, but since physicians working in emergency departments encounter forensic cases more frequently, forensic medicine duties are much more important for this group of physicians.<sup>2,7</sup>

Similar to studies in the literature, the rate of male participants in our study is higher.<sup>8,9</sup> Similar to the study conducted by Kumral et al.<sup>10</sup> to evaluate the views of

physicians in Tekirdağ province on malpractice, the majority of the participants in our study are general practitioners. Since only physicians working in emergency departments were included in our study and the number of specialist doctors working in emergencies is less in the Cappadocia region where the study was conducted, the majority of the participants are general practitioners. Unlike studies in the literature, the average length of service of the participants in our study was found to be lower.<sup>8,9</sup> The reason for this is; The reason may be that only physicians working in the emergency department were included in our study and most of them were young general practitioners.

Similar to Yavuz et al.<sup>11</sup> study, in which they evaluated the knowledge and attitudes of physicians working in emergency departments regarding forensic reports, the majority of physicians in our study reported that they did not receive adequate forensic medicine training. Many studies in the literature have shown that participants found the forensic medicine education they received inadequate.<sup>8,9,12-14</sup> Again, the participants who answered forensic medicine education as insufficient; 'Do you get nervous when the forensic case comes?' It was determined that the answer to the question was 'partially and yes' at a higher rate. It is thought that when adequate forensic training is not received, physicians become uneasy about forensic cases due to the fear of making mistakes.

Participants were asked: 'Do you know which cases are considered judicial cases?' When the question was compared in terms of service period, a statistically significant difference was found ( $p=0.036$ ). Participants with more than 5 years of service answered yes to this question at a higher rate. It is thought that this rate is high due to the increase in the experience of physicians as the length of service increases.

While the type of forensic report prepared in our study was mostly determined as a definitive report, in the study conducted by Yavuz et al.<sup>11</sup> with participants working in the emergency departments of university hospitals, the type of temporary forensic report was higher. Since all emergency services in the provinces and districts of the Cappadocia region were included in our study, it is thought that the rate of final forensic reports is higher.

'Do you know the legal responsibility of forensic reports and their effects on the trial?' Most of the participants partially answered the questions. Similarly, in the literature, it is seen that the level of knowledge of the participants regarding legal liability and laws is insufficient.<sup>11,12,15,16</sup> Again, the rate of specialist physicians answering 'yes' to these questions is higher than general practitioners. It was thought that specialist physicians were more knowledgeable on these issues due to their experience and training.<sup>17-20</sup>

## CONCLUSION

Associated with more experience and education; It is thought that people are less anxious about judicial cases and these cases can be evaluated more clearly. Since most physicians consider the forensic medicine education they receive to be inadequate; It would be beneficial to organize in-service training in this field, especially after graduation. It has also been determined that most physicians do not have sufficient knowledge

about the legal liability of forensic cases and their effects on the trial. Providing training and information regarding this will make it easier for physicians to prepare forensic reports more properly.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Nevşehir Hacı Bektaş Veli University Ethics Committee (Date: 25.10.2021, Decision No: 2021.09.318).

### Informed Consent

All patients signed the free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.


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# Association between red blood cell transfusion and mortality in critically ill children: a single-center pediatric intensive care experience

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**Cite this article as:** Durak C, Şahin C. Association between red blood cell transfusion and mortality in critically ill children: a single-center pediatric intensive care experience. *Anatolian Curr Med J.* 2024;6(1):11-16.

Received: 24.08.2023

Accepted: 23.11.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** Our study aimed to evaluate the association of erythrocyte transfusion with mortality and morbidity in critically ill children and to emphasize the importance of the risk it carries.

**Methods:** A retrospective evaluation of 524 pediatric patients aged 1 month to 18 years who had been admitted between February 2022 to March 2023 at Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, were performed. Children with hemoglobinopathies, and chronic anemia (defined as the presence of anemia for more than 6 weeks) were excluded. Demographic data, clinical variables, and outcome data were analyzed.

**Results:** The median age was 36.5 (1.0-272.0) months, and 56.1% of the patients were male. The median duration of a pediatric intensive care unit stay was 5 (1-114) days. Respiratory diseases (44.7%) were the most common reasons for admission to the pediatric intensive care unit, followed by, neurological diseases (12.8%) and sepsis (11.3%). Mortality rate was 5.7%. The median baseline hemoglobin level upon admission was 10.5 g/dl (3.2-18.8). Severe anemia (hemoglobin < 7 g/dl) was present in 6.1% of all patients. One hundred and sixteen (22.1%) patients were transfused; 61 (11.6%) were transfused only once. A total of 292 packed red blood cells transfusions were administered. Transfused patients required prolonged hospital stays, support for inotropic agents, invasive mechanical ventilation, and extracorporeal treatment and had an excessive mortality rate ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ).

**Conclusion:** Clinicians should consider that the administration of packed red blood cells transfusions in critically ill patients may have the potential to both raise mortality and provide life-saving benefits during their pediatric intensive care unit stay. As with any treatment with potential side effects, it is essential to reduce the use of unnecessary blood products.

**Keywords:** Critical care, erythrocyte transfusion, mortality, pediatrics

## INTRODUCTION

Anemia is prevalent among critically ill pediatric patients at the time of admission and throughout their pediatric intensive care unit (PICU) stay, and these patients may have a lower tolerance for anemia. Transfusion of packed red blood cells (PRBCs) is widespread, occurring in 74% of PICU patients.<sup>1</sup>

PRBC transfusions may be medically required and even life-saving in certain situations, such as severe anemia, and active blood loss.<sup>2</sup> The sole method for promptly treating severe anemia is through the administration of PRBC transfusions. The primary objective of PRBC transfusion is to elevate the hemoglobin (Hb) concentration, with the aim of enhancing both oxygen supply and oxygen consumption.<sup>3,4</sup>

Nevertheless, red blood cell (RBC) storage can impair the capacity to supply oxygen over time. Observational studies have indicated a heightened mortality risk among critically ill patients who received PRBC transfusions.<sup>5</sup> PRBC infusions carry a multitude of risks, encompassing infections, immunosuppression, transfusion reactions, fluid overload, and medical errors.<sup>2</sup> Hence, in light of the potential risks and elevated mortality rates linked to transfusions, healthcare professionals must exercise cautious discernment when assessing the requirement for PRBC transfusion.

Our study aimed to evaluate the association of erythrocyte transfusion with mortality and morbidity in critically ill children and to emphasize the importance of the risk it carries.

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## METHODS

A retrospective cohort study was performed in the PICU at Şehit Prof. Dr. İlhan Varank Training and Research Hospital, University of Health Science, throughout February 2022 to March 2023. Healthcare provision for children aged from 1 month to 18 years is provided in our PICU, which is equipped with 12 beds, 12 ventilators, 5 Prismaflex™ hemofiltration machines (Baxter, USA), and 9 isolation rooms.

The study was conducted in accordance with the Declaration of Helsinki. The study's protocol was approved by Ethics Committee of Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Date: 17.02.23 Decision No: E-46059653-050.99-209549220), and all study-related anonymized data are available upon reasonable request.

Demographic data (age, gender), clinical variables (diagnosis at the admission, Pediatric Risk of Mortality III score, length of PICU stay, requirement of invasive mechanical ventilation, inotropic agents, extracorporeal therapy, requirement of PRBC transfusion, number of PRBC transfusions, and outcome data (alive/expired) of 524 patients were collected. Pediatric Risk of Mortality III (PRISM III) scores corresponding to the first 24 hours of hospitalization were calculated according to the equation described by Pollack et al.<sup>6</sup> PRBC transfusion is classified as none, 1 time, and  $\geq 2$  times. Children with hemoglobinopathies, and chronic anemia (defined as the presence of anemia for more than 6 weeks) were excluded. Our unit did not have a transfusion guideline. The decision to transfuse a patient was made by the attending clinician. Routinely, the quantity per erythrocyte transfusion amounts to 15 ml/kg.

Statistical Package for the Social Sciences (IBM Corp SPSS Statistics for Windows, Version 20.0. Armonk, NY) was used for statistical analyses. Numbers, frequencies [%], ratios, medians, and ranges were used in the descriptive statistics of the data. Continuous variables were tested for normal distribution by Kolmogorov-Smirnov or Shapiro-Wilk test. For analysis of continuous data, a t-test or Mann-Whitney U test was performed to detect differences between the groups, depending on the distribution. Relationships between categorical variables were analyzed by the Chi-square test. When Chi-square assumptions were not met, Fisher's exact test was used. A one-way analysis of variance (ANOVA) test is used for three or more groups of data, to gain information about the relationship between the dependent and independent variables.

## RESULTS

The study included 524 patients who met the research criteria out of the total number of patients admitted to our PICU. The median age was 36.5 (1-272) months. The majority of the patients were male (56.1%). The most frequent diagnoses of admission to the PICU were respiratory diseases (44.7%), such as pneumonia and asthma attacks, followed by neurological diseases, such as epilepsy and encephalitis (12.8%), and sepsis (11.3%). The median length of stay in the PICU was 5 days, ranging from 1 to 114 days, and the median PRISM III score was 2 (0-40). The mortality rate was 5.7% (**Table 1**).

**Table 1.** Clinical characteristics of patients admitted to pediatric intensive care unit

Gender, n (%)	
Male	294 (56.1)
Female	230 (43.9)
Age (month), median (min-max)	36.5 (1.0-272.0)
Etiologies of admission, n (%)	
Respiratory diseases	234 (44.7%)
Neurological diseases	67 (12.8%)
Sepsis	59 (11.3%)
Intoxication	44 (8.4%)
Trauma	37 (7.1%)
Endocrinological diseases	24 (4.6%)
Acute renal failure	12 (2.3%)
Postoperative admissions	10 (1.9%)
Cardiological diseases	9 (1.7%)
Hematology-oncological diseases	7 (1.3%)
Others	21 (4%)
PRISM III score	2 (0-40)
Length of stay (day), median (min-max)	5 (1-114)
Requirement of IMV, n (%)	142 (27.2%)
Length of stay on IMV (day), median (min-max)	6 (1-102)
Requirement of CRRT, n (%)	41 (7.8%)
Requirement of inotropic agents, n (%)	69 (13.2%)
Requirement of TPE, n (%)	49 (9.4%)
Mortality, n (%)	30 (5.7%)
CRRT : Continuous renal replacement therapy, IMV : Invasive mechanical ventilation, PRISM III : Pediatric Risk of Mortality, TPE : Therapeutic plasma exchange	

A total of 142 patients (27.2%) required invasive mechanical ventilation (IMV), with a median duration of 6 (1-102) days. Inotropic drugs were used in 69 patients (13.2%). While therapeutic plasma exchange (TPE) was performed on 49 patients (9.4%), continuous renal replacement therapy (CRRT) was performed on 41 patients (7.8%) (**Table 1**).

The median baseline hemoglobin level upon PICU admission was 10.5 g/dl (3.2-18.8). Severe anemia (Hb <7 g/dl) was present in 6.1% of all patients. One hundred and sixteen (22.1%) patients were transfused; 61 (11.6%) were transfused only once. A total of 292 PRBC transfusions were administered (**Table 2**).

**Table 2.** Hemoglobin values and transfusion requirements of patients admitted to the pediatric intensive care unit

Hemoglobin (g/dl) at admission	10.5 (3.2-18.8)
Hemoglobin ranges	
≥8 g/dl	454 (86.6%)
7-8 g/dl	38 (7.3%)
≤7 g/dl	32 (6.1%)
PRBC transfusion	
None	408 (77.9%)
One time	61 (%11.6)
≥2 times	55 (10.5%)
Total PRBC transfusion count	292

PRBC: Packed red blood cell

Differences in demographic and clinical variables between patients who received one or more PRBC transfusions and those who were not transfused were examined. Between the three groups, there were statistically significant differences in age and gender

(p=0.031 p=0.022). Upon comparing the etiology, it was noted that patients hospitalized for sepsis, hemato-oncological diseases, acute renal failure, and cardiological disorders had a much greater requirement for red blood cell transfusion (p<0,001). We found a significantly higher median PRISM III score in transfused patients, indicating that they were more critically ill (p<0.001) (**Table 3**).

Baseline hemoglobin levels were found to be statistically lower among people who required multiple transfusions (p<0.001). Transfused patients also required prolonged stays in the PICU and had a greater need for inotropic agents, IMV, and extracorporeal treatment(p<0.001, p<0.001, p<0.001, p<0.001). We observed an excessive mortality rate, especially among children who received multiple transfusions (p<0.001) (**Table 4, 5**).

**Table 3.** Comparison of PRBC transfusion requirements and clinical characteristics of patients

	PRBC transfusion			p
	None	One time	≥2 times	
Gender/ Male, n(%)	237 (80.6%)	32 (10.8%)	25 (8.5%)	0.022
Age (month), median (min-max)	38 (1-272)	25 (1-214)	48 (1.33-20-08)	0.031
Etiologies of admission				<0.001
Respiratory diseases	206 (88.0%)	19 (8.1%)	9 (3.8%)	
Neurological diseases	58 (86.6%)	6 (9.0%)	3 (4.5%)	
Sepsis	20 (33.9%)	19 (32.2%)	20 (33.9%)	
Intoxication	43 (97.7%)	1 (2.3%)	0 (0%)	
Trauma	25 (67.6%)	5 (13.5%)	7 (18.9%)	
Endocrinological diseases	24 (100%)	0 (0%)	0 (0%)	
Acute renal failure	2 (16.7%)	4 (33.3%)	6 (50.0%)	
Postoperative admissions	8 (80%)	2 (20%)	0 (0%)	
Cardiological diseases	5 (55.6%)	1(11.1%)	3 (33.3%)	
Hematology-oncological diseases	1 (14.3%)	2 (28.6%)	4 (57.1%)	
Others	15 (71.4%)	4 (19.0%)	2 (9.5%)	
PRISM III score, median (min-max)	2 (0-30)	7 (0-40)	11 (0-39)	<0.001
Length of stay, median (min-max)	4 (1-62)	7.5 (1-77)	19 (1-114)	<0.001
Mortality, n (%)	8 (%26.7)	7 (23.3%)	15 (50.0%)	<0.001
Hemoglobin (g/dl) at admission	10.8 (6.5-18.8)	8.35(5.1-14.3)	8.9 (3.2-13.2)	<0.001
Hemoglobin ranges				<0.001
≥8 g/dl	386 (85.0%)	34 (7.5%)	34 (7.5%)	
7-8 g/dl	20 (52.6%)	11 (28.9%)	7 (18.4%)	
≤7 g/dl	1 (3.1%)	17 (53.1%)	14 (43.8%)	

PRISM III : Pediatric Risk of Mortality, PRBC: Packed red blood cell

**Table 4.** Comparison of PRBC transfusion requirements and supportive therapies, and outcomes of patients

	PRBC transfusion			p
	None	One time	≥2 times	
Requirement of IMV, n (%)	66 (46.5%)	35 (24.6%)	41 (28.9%)	<0.001
Requirement of inotropic agents, n (%)	18 (26.1%)	16 (23.2%)	35 (50.7%)	<0.001
Requirement of CRRT, n (%)	10 (24.4%)	4 (9.8%)	27 (65.9%)	<0.001
Requirement of TPE, n (%)	12 (%24.5)	8 (16.3%)	29 (59.2%)	<0.001

CRRT : Continuous renal replacement therapy IMV : Invasive mechanical ventilation TPE : Therapeutic plasma Exchange PRBC: Packed red blood cell

	Hemoglobin (g/dl) at admission			p
	≤7 g/dl	7-8 g/dl	≥8 g/dl	
Gender/ Male, n(%)	12 (4.0%)	23 (7.8%)	259 (88.0%)	<0.001
Age (month), median (min-max)	37 (1-202)	12.5 (1-198)	39 (1-272)	0.001
Etiologies of admission				<0.001
Respiratory diseases	5 (2.1%)	23 (9.8%)	206 (88.0%)	
Neurological diseases	1 (1.5%)	2 (3.0%)	64 (95.5%)	
Sepsis	12 (20.3%)	3 (5.1%)	44 (74.6%)	
Intoxication	0 (0%)	0 (0%)	44 (100%)	
Trauma	3 (8.1%)	3 (8.1%)	31 (83.8%)	
Endocrinological diseases	0 (0%)	0 (0%)	24 (100%)	
Acute renal failure	6 (50.0%)	2 (16.7%)	4 (33.3%)	
Postoperative admissions	0 (0%)	0 (0%)	10 (100%)	
Cardiological diseases	0 (0%)	1(11.1%)	7 (77.8%)	
Hematology-oncological diseases	3 (42.9%)	2 (28.6%)	2 (28.6%)	
Others	2 (9.5%)	1 (4.8%)	18 (85.7%)	
PRISM III score, median (min-max)	9 (0-27)	2 (0-29)	2 (0-40)	<0.001
Length of stay, median (min-max)	7 (1-46)	5.5 (3-45)	4 (1-114)	0.018
Mortality, n (%)	6 (%20.0)	3 (10.0%)	21 (70.0%)	0.003
PRBC transfusion				<0.001
None	1 (0.2%)	20 (4.9%)	386 (94.8%)	
One time	17 (27.4%)	11 (17.7%)	34 (54.8%)	
≥2 times	14 (25.5%)	7 (12.7%)	34 (61.8%)	

PRISM III : Pediatric Risk of Mortality PRBC: Packed red blood cell

## DISCUSSION

There are many causes of anemia in critically ill pediatric patients. First off, active bleeding and iatrogenic blood loss due to laboratory tests are frequent in the PICU. Patients receive a lot of intravenous fluids, which causes further hemodilution. In addition, critically ill patients are prone to anemia as a result of abnormal iron metabolism, nutritional deficiencies, decreased amount of erythropoietin, and inhibited bone marrow.<sup>2</sup> Due to these factors, numerous children will develop anemia at a certain point during their treatment in the intensive care unit.

A total of 22.1% of our patients received at least one PRBC transfusion. The median Hb values for patients who underwent one-time and numerous transfusions were 8.35 g/dl and 8.9 g/dl, respectively. These rates are consistent with retrospective studies in PICUs.<sup>7-9</sup> According to a study by Rafique et al.<sup>13</sup> PRBC were the most commonly incorrectly transfused blood product (20%). Confusion between the more recent restriction RBC transfusion strategy and the more established liberal RBC transfusion strategy is the most likely explanation for this.<sup>10</sup> Nevertheless, a definitive threshold for hemoglobin (Hb) levels that necessitate transfusion in severely ill patients has yet to be established. In 2019, the Pediatric Critical Care Transfusion and Anemia Expertise Initiative recommended transfusion of critically ill children with Hb below 5 g/dl and avoidance of transfusion in children above 7 g/dl if they are hemodynamically stable. In Hb values between 5-7 g/dl, they recommend

deciding according to the patient's condition. However, it should be kept in mind that these patients are in critical condition and their oxygenation may be poor. Therefore, the decision should not be made based on the Hb value alone, and the clinical condition of the patient should also be evaluated, such as hemodynamics.<sup>5</sup>

The study revealed elevated transfusion rates among patients admitted for sepsis, hemato-oncological illnesses, and acute renal failure. However, Armano et al.<sup>8</sup> demonstrated the requirement of PRBS transfusion in patients hospitalized for respiratory failure or elective surgery. The primary factor contributing to this difference can be attributed to the larger sample size of sepsis patients included in our research. Additionally, it is worth noting that cardiac surgery comprised the majority of elective procedures in the study conducted by Doctor et al.<sup>8</sup> On the other hand, in the study conducted by Muszynski et al.<sup>11</sup> in patients with sepsis, PRBC transfusion rates were shown to increase to 50%. The most frequent hospitalization diagnoses for patients requiring transfusions were respiratory failure, cardiac failure, and sepsis, according to a survey carried out in our nation.<sup>12</sup>

Our analysis identified several risk factors associated with PRBC transfusion, as evidenced by numerous previous studies. A higher PRISM III score, prolonged PICU stay, requirement of IMV, and extracorporeal treatments were found to be independently associated with a PRBC transfusion.<sup>7,13,14</sup> The likelihood of these risks is further amplified in cases involving several transfusions.

Interestingly, our study found no correlation between Hb levels below 7 g/dl and mortality. In contrast, mortality was more prevalent among patients with Hb levels above 8 g/dl. Upon careful examination of the data, it was observed that a total of 11 patients, constituting 36.7% of the non-survivors, were admitted to the PICU with a confirmed diagnosis of sepsis. Sepsis is one of the leading global causes of pediatric mortality. The potential explanation for the increased mortality observed in patients with hemoglobin (Hb) levels over 8 g/dl, may be attributed to efforts aimed at maintaining higher hemoglobin values which is intended to optimize tissue oxygenation.

While the presence of severe anemia can result in more adverse consequences, it is important to acknowledge that transfusions also have inherent dangers. Numerous studies have investigated the correlation between transfusions of PRBC and morbidity and mortality. The association between PRBC transfusion and mortality risk was investigated in a study conducted by Kneyber et al.<sup>7</sup> which included a sample of patients with anemia (Hb<9.6 g/dl) from PICU. The study revealed that children who received PRBC transfusion showed increased mortality, longer stays in PICU, and prolonged use of IMV, and inotropic agents. In another study, early transfusion within the first 2 days was found to be associated with mortality.<sup>11</sup> With mortality rates as high as 15%–30%, the main causes are hemolytic transfusion responses, acute lung injury from transfusions, and acute circulatory overload from transfusions.<sup>15</sup> However, pre-transfusion Hb level was not significantly associated with mortality.<sup>7</sup> In another study by Bateman et al.<sup>17</sup> it was found that PRBC transfusion was significantly associated with increased risk of mortality, cardiac arrest, nosocomial infections, and longer PICU stay and requirement of IMV, considering other factors such as age at presentation and severity of disease. Consistent with the literature, in our study, PRBC transfusions had a notable impact on death rates. Furthermore, this association was found to be more pronounced as the frequency of transfusions increased. Therefore, not only the benefits but also the risks of RBC transfusion should be considered when making the transfusion decision.

### Study Limitations

The main limitation of our study was the inclusion of only one tertiary center. Research conducted across multiple centers has the potential to yield supplementary information. In addition, we could not provide complete data on transfusion-related complications. Multicenter studies on transfusion-related complications will provide insights to clinicians to determine the advantage/disadvantage ratio of PRBC transfusion and how much erythrocyte suspension should be given to which patient.

## CONCLUSION

Clinicians should consider that the administration of PRBC transfusions in critically ill patients may have the potential to both raise mortality and provide life-saving benefits during their stay in PICU. As with any treatment with potential side effects, it is essential to reduce the use of unnecessary blood products.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ethical Committee of Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Date:17.02.2023, Decision No: E-46059653-050.99-209549220).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# The relationship between physical activity and self-esteem among Turkish university students: a gender perspective; a multidisciplinary and multi-center study

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**Cite this article as:** Doymaz F, Çakır Ö, Telli Atalay O, Özkeskin M, Şenol H. The relationship between physical activity and self-esteem among Turkish university students: a gender perspective; a multidisciplinary and multi-center study. *Anatolian Curr Med J.* 2024;6(1):17-22.

Received: 17.08.2023

Accepted: 25.11.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** The current study aimed to examine the associations between physical exercise and self-esteem as well as other social-cognitive variables including self-efficacy and body image among Turkish university students.

**Methods:** Sociodemographic Information Form, short form of the International Physical Activity Questionnaire, Rosenberg Self-Esteem Scale, Body Cathexis Scale, and General Self-Efficacy Scale were administered to 1167 students.

**Results:** There were significant gender differences in total, vigorous, moderate activity, and walking scores as well as body image scores in favor of male participants; while female participants had significantly higher self-efficacy scores. There were significant differences between sedentary, active, and very active participants in terms of self-esteem, and body image and between all groups in terms of self-efficacy. Also, there were significant and positive correlations between physical activity and self-esteem, and between body image and self-efficacy in university students.

**Conclusion:** Level of physical activity increased with age. This increased level of physical activity showed positive correlations with self-esteem, body image, and self-efficacy.

**Keywords:** Gender, student, body image, exercise, self-efficacy

## INTRODUCTION

Physical activity and exercise improve various elements of well-being. Regular physical activity restores body composition; improves lipid-lipoprotein profile; regulates glucose balance and insulin sensitivity; decreases blood pressure, systemic inflammation and coagulation; and regulates coronary blood flow and cardiac functions. Regular physical activity is also associated with psychological well-being. Decreased levels of anxiety, stress, and depression are important for preventing cardiovascular diseases and treating chronic diseases such as diabetes, cancer, and hypertension by positively affecting mental health.<sup>1</sup>

Self-esteem is regarded as an important indicator of mental health. According to Rosenberg,<sup>2</sup> self-esteem is a favorable or unfavorable attitude toward the self. Self-esteem is an important aspect of psychological well-being and includes emotional and evaluative

components of one's self-concept. Increased self-esteem leads to feelings of worthiness and strength.<sup>3</sup> Low self-esteem is related to negative health behaviors including lack of exercise.<sup>4</sup> According to the authors, participation in physical exercise leads to an increase in self-esteem regardless of the type of physical activity. Today, many researchers think that self-esteem is a variable that has the potential of reflecting the psychological benefits of regular exercise.<sup>5</sup> Previous research provided support for this model by demonstrating that self-esteem and exercise are positively associated. Other studies also suggested that regular physical activity positively affects self-esteem among male and female university students.<sup>3,5</sup> High perceived stress reduces cognitive functioning in students, especially during exam times, stress levels increase considerably. Physical activity positively affects both cognitive performance and mental health. Thus, the learning and academic

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success of university students increases.<sup>6</sup> On the other hand, Hubbs et al.<sup>7</sup> found a significant correlation between perceived stress and self-esteem but could not determine a significant relationship between self-esteem and physical activity.

According to Bandura, self-efficacy is one's judgment regarding one's capability to organize and perform certain acts that are needed to achieve designated types of performances.<sup>8</sup> High self-efficacy motivates performing behavior and is effective in achieving such behavior with satisfactory results.<sup>9</sup> In another study, self-efficacy was found to contribute to the level of physical activity in an adult sample, however, its effect size was found to be small.<sup>10</sup>

The term "body image" corresponds to body-related self-perceptions and attitudes. Women tend to have more negative body image and their self-esteem is more significantly related to body image compared to men.<sup>11</sup> Body image is linked to self-esteem and exercise behaviors.<sup>12</sup>

In our large population study, the relationship between self-esteem, self-efficacy, body image, and physical activity level was investigated. It was hypothesized that physical activity is positively associated with self-esteem, self-efficacy, and body image.

## METHODS

This study was performed in Türkiye as a cross-sectional, multi-centered, and multidisciplinary study. The study was conducted with 1167 students from four different universities. The inclusion criteria for this study were being a university student between 18-30 years of age. The exclusion criteria were having a orthopedic, neurological, psychiatric or systemic disease, being pregnant, having a BMI over 29.9 kg/m<sup>2</sup>, being in psychiatric treatment and refusing to participate in the study.

Prior to conducting the study, ethical permissions were obtained from İzmir University Faculty of Medicine Non-invasive Researches Ethics Committee (Date: 17.12.2015 Decision No: 2015/49). The paper was held according to the Helsinki Declaration. The students were informed about the study aim and they signed informed consent forms. Participation in the study was voluntary. A sociodemographic information form; which included questions about age, gender, height, weight, body mass index (BMI), education, and employment status; the International Physical Activity Questionnaire, the Rosenberg Self-Esteem Scale, the Body Cathexis Scale, and the General Self Efficacy Scale were administered to the students in a classroom setting by the researchers.

## Instruments

**International physical activity questionnaire:** The physical activity levels of the participants were measured by the short form of the International Physical Activity Questionnaire (IPAQ). This short form consists of seven questions and provides information about the time spent sitting, walking, and engaging in moderately intense activity and vigorous activities during the last seven days. The total score of the short form is calculated as the sum of data obtained multiplied by the activity type coefficient, duration of the activity, and the number of days that the activity had been performed. In the evaluation of all activities, performing each activity for at least 10 minutes at one time was taken into consideration. A score of "MET-minute/ week" is obtained by multiplying minutes, days, and MET (folds resting oxygen consumption). In the calculation of the walking score, the duration of walking (minutes) was multiplied by 3.3 METs. Four METs for moderately intense activity and 8 METs for vigorous activity were used in the calculation. The levels of physical activity were classified as not being physically active (<600 MET-min/week), low level of physical activity (600-3000 MET-min/week), and adequate level of physical activity (beneficial for health) (>3000 MET-min/week).<sup>13</sup>

**Rosenberg self-esteem scale:** Rosenberg Self-Esteem Scale examines the level of self-esteem both in medical patients and healthy individuals. The scale was developed by Rosenberg in 1965. It is a Likert-type scale including 10 items with responses ranging from 0 (strongly agree) to 3 (strongly disagree). Higher scores indicate higher levels of self-esteem. The validity and reliability of the Rosenberg Self-esteem Scale were shown in different ethnic groups. The Turkish validity and reliability study of the scale was conducted in 1985 by Cuhadaroglu.<sup>14</sup>

**Body cathexis scale:** The Body Cathexis Scale (BCS), evaluates the level of body image satisfaction. BCS assesses how individuals perceive all body parts in detail. The scale has 40 items. Each item describes a body part (such as arms, legs, or face). Responses are expressed as "I do not like it at all-I do not like it-Neutral-I like it -I like it so much". Each item is given a score between 1-5 points. A total score of 40-200 points can be obtained and higher scores indicate an increase in the positive direction. The Cronbach's alpha internal consistency coefficient of the scale was found to be 0.91 (p<0.01) in the Turkish adaptation study, which was conducted by Hovardaoglu in 1990.<sup>15</sup>

**The general self-efficacy scale:** The General Self-Efficacy Scale (GSE) is a 4-point Likert type scale including 10 items. Total scores range from 10 to 40. The validity and reliability study of the Turkish version of the GSE was conducted by Aypay.<sup>16</sup>

### Statistical Analysis

Data were analyzed using the SPSS 21.0 software. Continuous variables were expressed as mean±standard deviation and categorical variables as number and percent. Kruskal Wallis Variance Analysis was used to compare independent groups. For post-hoc analysis, the Mann-Whitney U test with Bonferroni Correction was used when the Kruskal Wallis test indicated significant differences between groups. The Spearman Correlation Coefficient was used for determining the correlation between continuous variables. Linear regression analysis was used to analyze the factors that had an effect on the Rosenberg Self-Esteem scale, Body Cathexis Scale and General Perceived Self-Efficacy Scale scores, which were examined as the dependent variable.

### RESULTS

A total of 1235 participants were included in this study. However, 68 of them were excluded due to missing data, and the analysis was completed with 1167 participants. Thirty-three of these 68 excluded participants were because of obesity. Data obtained from participants whose BMI was 29.9 kg/m<sup>2</sup> were excluded from the sample since obesity may have negative effects on physical activity levels and self-esteem. The BMI of our participants was found to be between 20.00-29.99 kg/m<sup>2</sup>, which is accepted as normal or overweight. This situation may be considered as a limitation of our study. The demographic characteristics of the participants were provided in **Table 1**. In order to analyze the difference between groups, the participants were defined as sedentary (0-600), active (601-3000), and very active (≥3001) according to the results of the IPAQ (**Table 1**).

When the differences according to the genders are examined; In all physical activity examinations, male participants levels were found to be significantly

higher than female participants. Rosenberg values did not show statistically significant difference according to gender. Body Cathexis Scale values were found to be significantly higher in male participants according to female participants and General Perceived Self-Efficacy Scale values were found to be significantly higher in female participants according to male participants (**Table 2**).

Considering the results of Kruskal Wallis Analysis of Variance, which was conducted to examine the differences between physical activity level groups; for Rosenberg Self-Esteem Scale and Body Cathexis Scale values, it was observed that the values of the participants with Sedentary and active groups were significantly lower than very active group. In the General Perceived Self-Efficacy Scale, the values of the participants with Sedentary and active groups were significantly lower than very active group, moreover sedentary group have significantly lower values than active group (**Table 3**).

**Table 1.** Demographic characteristics and activity levels of the participants

Variable	N	% ratio
Gender; female	722	61.9
Male	445	38.1
Marital status; single	1155	99
Married	12	1
<b>mean±SD</b>		
Age (years)	21.11±1.91	
BMI (kg/m <sup>2</sup> )	22.78±5.45	
Cigarette use number/day (n=206)	12.64±7.95	
Years of cigarette smoking (n=169)	4.19±3.17	
<b>Groups</b>	<b>N</b>	<b>%</b>
Sedentary (0-600)	241	24.2
Active (601-3000)	513	51.6
Very active (≥3001)	241	24.2
Mean±SD: Mean±Standard Deviation		

**Table 2.** Physical activity levels of of the study participants according to the gender

	Total	Female	Male	P
	mean±SD	mean±SD	mean±SD	
Vigorous physical activity	669.18±1709.67	510.98±69.25	1189.81±98.60	<0.0001*
Moderate intensity physical activity	283.39±1045.70	255.53±25.90	435.67±82.15	<0.0001*
Walking	1115.71±1873.97	1197.91±92.12	1306.65±72.76	0.007*
IPAQ-total	2068.28±3042.11	1964.43±126.22	2932.15±166.10	<0.0001*
Rosenberg self-esteem scale	21.53±5.14	21.61±0.21	21.34±0.26	0.387
Body cathexis scale	150.06±21.06	148.48±0.84	154.70±0.95	<0.0001*
General perceived self-efficacy scale	28.20±5.54	62.16±1.57	46.87±2.07	<0.0001*

\*p<0.05 statistically significant; Mean±SD: Mean±Standard Deviation; Mann Whitney U test

**Table 3.** Self-esteem levels of the participants according to the physical activity levels

Variable	Sedentary	Active	Very active	P
	mean±SD	mean±SD	mean±SD	
Rosenberg Self-Esteem Scale	21.23±5.15	21.11±5.23	22.93±4.68	<0.0001* <sup>bc</sup>
Body Cathexis Scale	147.62±22.57	148.72±20.26	156.84±19.18	<0.0001* <sup>bc</sup>
General Perceived Self-Efficacy Scale	26.99±5.27	28.29±5.69	29.79±5.20	<0.0001* <sup>abc</sup>

\*p<0.05 statistically significant; Mean±SD: Mean±Standard Deviation; Kruskal Wallis Variance Analysis; a: Statistically significant difference between Sedentary and Active; b: Statistically significant difference between Sedentary and Very Active; c: Statistically significant difference between Active and Very Active

All differences in self-esteem, body image, and self-efficacy parameters were derived from the active and very active groups, and from the sedentary and very active groups.

In order to test the correlation between physical activity and self-esteem, Spearman's correlation analysis was conducted. According to the results, there were significant and positive correlations between IPAQ total scores and self-esteem, body image, and self-efficacy. On the other hand, vigorous physical activity had significant and positive correlations with body image and self-efficacy. Moderate physical activity had significant and positive correlations with Self-Esteem Scale and self-efficacy. Also, walking scores had significant and positive correlations with self-esteem, body image, and self-efficacy (Table 4).

Moreover, the relationships between physical activity and psychological variables were examined based on gender. In female participants, vigorous exercise was significantly and positively associated with body image and self-efficacy; whereas moderate exercise was significantly and positively related to body image. In addition, walking scores were significantly and positively associated with body image and self-efficacy; while the IPAQ total scores were significantly and positively correlated with body image and self-efficacy (Table 4).

The relationships between physical activity and psychological variables were also examined in male participants. Vigorous

activity significantly and positively correlated with GSE. Moderate activity significantly and positively correlated with self-esteem and self-efficacy; while walking scores were significantly associated with self-esteem and GSE. Finally, the IPAQ total scores were significantly and positively correlated with self-esteem and GSE (Table 4).

When examining the factors affecting scale scores, it was observed that moderate intensity physical activity values and total physical activity values have statistically significant and enhancing effects on Rosenberg scale scores. Additionally, body mass index (BMI) and years of smoking were found to have statistically significant and decreasing effects on Rosenberg scores. It was observed that high intensity physical activity values, walking activity values, total physical activity values, and male gender have statistically significant and enhancing effects on BİÖ scale scores. It was observed that high intensity physical activity values, moderate intensity physical activity values, walking activity values, total physical activity values, and the number of cigarettes smoked per day have statistically significant and enhancing effects on GAÖÖ scale scores (Table 5).

**Table 4:** Correlations between physical activity and self-esteem, body image, and self-efficacy

		Rosenberg Self-Esteem Scale_Total	Body Cathexis Scale_Total	General Perceived Self-Efficacy Scale_Total
<b>Overall</b>				
Vigorous physical activity	r	0.036	0.110*	0.117*
	p	0.246	0.000	0.000
Moderate intensity physical activity	r	0.096*	0.056	0.126*
	p	0.002	0.074	0.000
Walking	r	0.083*	0.118*	0.149*
	p	0.006	0.000	0.000
IPAQ-total	r	0.079*	0.161*	0.197*
	p	0.007	0.000	0.000
<b>Female participants</b>				
Vigorous physical activity	r	0.007	0.099*	0.083*
	p	0.862	0.012	0.035
Moderate intensity physical activity	r	0.053	0.104*	0.063
	p	0.183	0.009	0.117
Walking	r	0.066	0.143*	0.125*
	p	0.083	0.000	0.001
IPAQ-total	r	0.030	0.174*	0.172*
	p	0.421	0.000	0.000
<b>male participants</b>				
Vigorous physical activity	r	0.089	0.036	0.133*
	p	0.070	0.473	0.007
Moderate intensity physical activity	r	0.168*	-0.055	0.208*
	p	0.001	0.275	0.000
Walking	r	0.112*	0.041	0.183*
	p	0.022	0.399	0.000
IPAQ-total	r	0.164*	0.069	0.215*
	p	0.001	0.148	0.000

\*p<0.05 statistically significant correlation; r: Spearman Correlation Coefficient

**Table 5.**

Dependent/Independent	Std. Beta	t	P	95% C.I Lower	95% C.I upper
<b>Rosenberg Self-Esteem Scale_Total</b>					
IPAQ_vigorous	0.044	1.433	0.152	0.000	0.000
IPAQ_moderate	0.081	2.602	0.009*	0.000	0.001
IPAQ_walking	0.049	1.625	0.105	0.000	0.000
IPAQ_total	0.077	2.648	0.008*	0.000	0.000
BMI	-0.133	-4.594	0.0001*	-0.18	-0.072
Gender	-0.025	-0.841	0.401	-0.869	0.348
Marital status	-0.042	-1.428	0.154	-5.058	0.797
Cigarette number/day	0.051	0.727	0.468	-0.058	0.125
Cigarette-year	-0.16	-2.095	0.038*	-0.533	-0.016
<b>Body Cathexis Scale_Total</b>					
IPAQ_vigorous	0.132	4.314	0.0001*	0.001	0.002
IPAQ_moderate	0.058	1.859	0.063	0.000	0.002
IPAQ_walking	0.063	2.097	0.036*	0.000	0.001
IPAQ_total	0.134	4.604	0.0001*	0.001	0.001
BMI	-0.016	-0.535	0.593	-0.283	0.162
Gender	0.158	5.468	0.0001*	4.397	9.318
Marital status	0.05	1.697	0.09	-1.621	22.347
Cigarette number/day	0.114	1.643	0.102	-0.068	0.746
Cigarette-year	0.1	1.295	0.197	-0.383	1.841
<b>General Perceived Self-Efficacy Scale_Total</b>					
IPAQ_vigorous	0.115	3.753	0.0001*	0.000	0.001
IPAQ_moderate	0.092	2.956	0.003*	0.000	0.001
IPAQ_walking	0.074	2.459	0.014*	0.000	0.000
IPAQ_total	0.151	5.214	0.0001*	0.000	0.000
BMI	-0.025	-0.855	0.393	-0.084	0.033
Gender	0.049	1.673	0.095	-0.097	1.214
Marital status	0.049	1.664	0.096	-0.479	5.82
Cigarette number/day	0.181	2.63	0.009*	0.036	0.249
Cigarette-year	0.043	0.556	0.579	-0.222	0.395

\*p<0.05 statistically significant; Std. Beta: Standardized Beta Coefficient; 95% C.I: 95% Confidence Interval; Linear Regression Analysis

## DISCUSSION

The aim of this study is to examine the relationship between self-esteem, self-efficacy, body image and physical activity level. We sought to determine the existence of significant differences between the means of the physically active and non-exercising groups, for the variables body image, self-esteem and self-efficacy. In the current study, the relationships between physical activity level and self-esteem, self-efficacy, and body image were assessed, and while highly significant relationships between total physical activity score and body image and self-efficacy were found, there was no relationship between physical activity and self-esteem in female participants.

The comparative report of the World Health Organization showed that 54.6% of the population aged above 15 years was insufficiently active. In the current study, 1167 university students with a mean age of  $21.10 \pm 0.05$  and an average BMI value of  $22.78 \pm 5.45$  were assessed. In the evaluation of physical activity levels, it was found that 20.7% of the students were sedentary, 44% were active and 20.7% were very active. In the present study, participants with a normal BMI were included, therefore the physical activity level of the sample was deemed satisfactory. In the groups which had been classified according to the level of physical activity, mean ages were  $20.61 \pm 0.09$  in the sedentary group,  $21.31 \pm 0.08$  in the active group, and  $21.36 \pm 0.11$  in the very active group. As the ages of the participants increased, the level of physical activity also raised. This raise may be linked to the fact that health-related awareness improves with age. This increased level of physical activity showed positive correlations with self-esteem, body image, and self-efficacy.

In a study investigating self-efficacy in participants doing regular sports and those not doing regular sports activities, it was reported that female university students doing regular sports had higher levels of positive self-perception.<sup>17</sup> In the current study, self-esteem also significantly increased with higher levels of physical activity.

Hubbs et al.<sup>7</sup> assessed the perceived stress, self-esteem, and physical activity levels among university students  $\geq 18$  years old and found that there was a significant correlation between perceived stress and self-esteem but the level of physical activity did not have any relationship with these two variables. According to the literature, the association between physical exercise and self-esteem is particularly significant in people with low self-esteem. The reason for not being able to find a significant association between exercise and self-esteem may be that the female participants in the present study had moderate levels of self-esteem. In addition, the difference between female and male students regarding

the relationship between self-esteem and physical exercise may be due to their reasons for exercise. Women tend to engage in exercise to achieve weight control and attractiveness compared to men, who exercise for health-related purposes. Exercising for health-related outcomes was linked to increased self-esteem, whereas exercising for weight control was not related to self-esteem.<sup>18</sup> We found significant relationships between exercise and self-esteem across the whole sample and male participants. This finding is in line with previous research.<sup>3</sup>

Fox<sup>19</sup> and reviewed research on the effects of exercise on self-esteem and demonstrated that there is an inconsistent association between physical activity and global self-esteem. Self-esteem is a stable construct and cannot be easily changed. A study<sup>7</sup> provided support for this view by demonstrating that increases in self-esteem are not maintained after the termination of an exercise-related intervention program. In a systematic review, it was also indicated that physical exercise has short-term benefits in terms of self-esteem among children and youth.<sup>20</sup> Moreover, self-esteem is a multifaceted construct and studies examining the link between exercise and self-esteem need to focus on the physical self rather than global self-esteem in order to establish significant associations with physical exercise. Thus, in line with the findings of the current study, it can be presumed that physical exercise influences one's physical self-perceptions and body image rather than global self-esteem.

There were significant correlations between total physical activity scores and self-esteem, and self-efficacy and body image but there was no correlation between total physical activity level and body image in males. The difference between female and male participants was thought to be associated with gender-based priorities. Contemporary Turkish culture and media overtly emphasize the need for women to look good and be thin but men are not a participant to such pressure. This double standard may have influenced our findings, leading to an insignificant association between physical activity and body image in male students. Similarly, Lowery et al.<sup>21</sup> found that women had a more negative body image compared to men albeit they consistently exercised. The study of Pauline et al.<sup>22</sup> in which they investigated the motivation and physical activity behaviors among college students, revealed that females were motivated for weight gain and physical appearance more, whereas males were motivated for performance-related matters like strength and endurance. In the current study, while there was a significant relationship between total physical activity level and body image in female students, the values of males did not show any relationship in this way and this was thought to be associated with gender based differences.

## Limitations

Most previous studies made a distinction between global self-esteem and physical self-esteem. In the current study, a global measure rather than a physical measure of self-esteem was used. Further studies investigating the associations between exercise and physical self-esteem in Turkish college students are needed.

## CONCLUSION

In the current study, the level of physical activity increased with age. This increased level of physical activity showed positive correlations with self-esteem, body image, and self-efficacy. There were significant relationships between exercise and self-esteem across the whole sample and male participants. In the current study, while there was a significant relationship between total physical activity level and body image in female students, the values of males did not show any relationship in this way and this was thought to be associated with gender-based differences.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

permission of the İzmir University Faculty of Medicine Non-invasive Researches Ethics Committee (Date: 17.12.2015, Decision No: 2015/49).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Investigation of the treatment and follow-up approaches of pregnant with asthma

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**Cite this article as:** Ayhan Albayrak G, Bardakçı Mİ. Investigation of the treatment and follow-up approaches of pregnant with asthma. *Anatolian Curr Med J.* 2024;6(1):23-28.

Received: 13.09.2023

Accepted: 06.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** Uncontrolled asthma during pregnancy can lead to complications for both the mother and the fetus. In this study; It was aimed to evaluate the follow-up and treatment of pregnant women with asthma, their knowledge about asthma triggers, their use of inhaler therapy, and their compliance with pulmonologist controls for asthma.

**Methods:** In this study; 64 pregnant patients with asthma who applied to our clinic between 01.01.2022 and 31.07.2022 were reviewed. Demographic patients (mean age, age groups, smoking history, comorbidities), recommended treatment information, and birth information, whether they used asthma treatment or not, were recorded and evaluated according to patient groups.

**Results:** There was a statistically significant difference between drug use during pregnancy according to the age groups of pregnant women with asthma (Chi-square test;  $\chi^2=6.684$ ;  $p=0.035$ ). As the age of the pregnant women increased, the rate of drug use during the pregnancy increased, and there was a correlation between drug use during pregnancy and whether the patients were regularly checked by a pulmonologist (Chi-square test;  $\chi^2=12.835$ ;  $p=0.0001$ ). While 68% of those who were not under the control of a pulmonologist did not use medication, 60.8% of those under the control of a pulmonologist used medication during their pregnancy.

**Conclusion:** Pregnant women with asthma must be followed by a gynecologist and a pulmonologist. Using inhaler therapy in asthma treatment in pregnant women can keep asthma under control and reduce the number and severity of exacerbations.

**Keywords:** Pregnancy, asthma therapy, inhaler therapy, asthma triggers

## INTRODUCTION

Asthma is one of the most common chronic diseases in pregnancy. Epidemiological studies showed that approximately 4% of all pregnancies are complicated by asthma. In addition, life-threatening asthma or status asthmaticus has been reported in 0.05% to 2% of all pregnancies. Uncontrolled asthma during pregnancy can lead to both maternal and fetal complications. The relationship between asthma and pregnancy is not one-sided because not only does uncontrolled asthma cause morbidity in the mother and the baby, but pregnancy also increases bronchial inflammation, impairing asthma control and making attacks more frequent. As a classical knowledge, asthma shows a variable course during pregnancy. In 1/3 of asthmatics, asthma worsens with pregnancy, remains stable in 1/3, and may improve in 1/3. A study showed that the disease worsened in 52-65% of pregnant women with severe asthma, and worsening occurred in only 8-13% of pregnant women with mild asthma.<sup>1</sup>

The effect of pregnancy on asthma can have variable results. Deterioration in asthma control usually begins in the second trimester of pregnancy. It manifests as wheezing, decreased sleep quality, and difficulty in daily activities. Exacerbations also usually increase in the second trimester. Drug use increases compared to the first trimester and is at the highest level in the third trimester. In 60% of consecutive pregnancies, asthma progresses during the first pregnancy. It is stated that allergen exposure does not cause a different worsening in pregnant asthmatics. It has been reported that diseases accompanying asthma, such as allergic rhinitis, have a similar course at a rate of 50% during pregnancy.<sup>2</sup>

Viral infections can cause uncontrolled asthma in pregnant asthmatics. Preventing upper respiratory tract viral infections in pregnant women is very important for asthma control. Smoking and addiction to inhaled steroids are other factors that complicate asthma control during pregnancy.<sup>3</sup>

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Prolonged pregnancy, preterm delivery, preeclampsia, high perinatal mortality, elective cesarean section, low birth weight, and risk of congenital malformations are common potential complications. Low birth weight babies increase by 46%, preterm birth by 22%, and preeclampsia by 54% in pregnant women with asthma. The incidence of cleft lip with or without cleft palate increases compared to pregnant women without asthma. While there is almost no maternal or fetal impact in pregnant women with mild or moderate asthma, the risk is higher in severe asthma.<sup>2,3</sup>

Asthma is a fairly common health problem for pregnant women and a potentially serious medical condition that can complicate pregnancy. Many complications are related to the lack of disease control, which can negatively affect the mother's quality of life and perinatal outcomes. The course of asthma symptoms during pregnancy is unpredictable, but exacerbations are more common in the second trimester. The causes are multifactorial, and the asthma phenotype may play a role. It has been suggested that CARAT (Allergic Rhinitis and Asthma Test Control) and pulmonary function tests can be used to monitor and adjust treatment during pregnancy in patients with asthma. Uncontrolled asthma causes many maternal and fetal complications, such as hyperemesis, hypertension, pre-eclampsia, antepartum or postpartum vaginal bleeding, placenta previa, cesarean delivery, delivery complications, intrauterine growth retardation, premature birth, low birth weight, increased perinatal mortality, and neonatal hypoxia.<sup>2</sup>

Within the scope of this research, we aimed to elucidate the follow-up treatments for pregnant women with asthma and to evaluate the effects of the drugs used on the fetus and the mother, the factors that trigger asthma, and the use of the correct inhaler. Asthma during pregnancy must be kept under control to prevent both maternal and fetal complications. For control, the pregnant woman must know the treatment and follow-ups of asthma, the triggering factors of asthma, and the correct use of inhaler medications used in treatment.

## METHODS

The sample size was determined as 102 pregnant women with asthma who applied to outpatient our clinic of Şişli Hamidiye Etfal Training & Research Hospital between 01.01.2022 and 31.07.2022. 102 patients were randomly selected for the study, but only the data of 64 of the patients could be reached completely and these patients were included in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was initiated with the approval

of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.09.2022, Decision No: 3669). As this was a retrospective analysis, no informed consent has been obtained from participants.

Demographics (age, smoking history), comorbidities, asthma diagnosis information (old diagnosis or diagnosis made during pregnancy), treatment information used before and during pregnancy, patients' information about asthma triggers during pregnancy, and information on whether patients use their inhalers correctly during pregnancy. Whether the pregnant women were under the control of a pulmonologist or not and the birth information of the patients were obtained from hospital records.

### Inclusion Criteria

Pregnant individuals  $\geq 18$  years old, who were diagnosed with asthma have been included in this analysis.

### Exclusion Criteria

Women under the age of 18 who do not have any respiratory symptoms, those who have a psychiatric disease that prevents them from using inhalers, and pregnant women who are not diagnosed with asthma.

### Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the "Independent Sample T-test" was used for two groups, and the "Pearson Chi-Square Test" was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05. Considering the difference in the medium effect size (effect size=0.5) between the groups, the sample size was calculated as 102 patients for the alpha significance level 0.05 and 80% Power (Sample size was calculated with the G\*Power Version 3.1.6 program).

## RESULTS

38 (59.37%) were in the age group of 19 – 29, 21 (32.81%) were in the age group of 30 – 39, and 5 (7.82%) were 40 and over. 12 (18.75%) of the patients are smokers, 24 (37.5%) are ex-smokers and 28 (43.75%) are non-smokers. 53 (82.82%) patients had a previous diagnosis, and 11 (17.18%) patients had a new diagnosis. 27 (42.18%) had allergic rhinitis, 6 (9.37%) had obesity, 7 (10.93%) had diabetes mellitus (DM), 5 (7.18%) had a cardiovascular disease, 3 (4.68%) had hypertension, 1 (1.56%) had epilepsy and 15 (24.10 %) (**Table 1**).

**Table 1.** Demographic characteristics of patients (age, smoking status, comorbidities, asthma diagnosis status)

Variables	n	%
Age		
19-29 Years	38	59.37
30-39 Years	21	32.81
40≤	5	7.82
Smoking status		
Smoker	12	18.75
Ex-smoker	24	37.50
Non-smoker	28	43.75
Comorbidities		
Allergic Rhinitis	6	9.37
Obesity	7	10.93
Diabetes Mellitus		
Cardiovascular Disease	5	7.18
Hypertension	3	4.68
Epilepsy	1	1.56
None	15	23.43
Asthma Diagnosis		
New	11	17.18
Old	53	82.82

62.50% used salbutamol, 39.06% used antihistamines, and 26.56% used long-acting beta-agonists (LABA) in combination with inhaled corticosteroid (ICS). 25.0% of patients had an episiotomy, 43.75% had a cesarean section, 1.56% had a breech delivery, and 29.68% experienced a normal vaginal birth. 42.18% of patients were followed by a pulmonologist, while the remaining 57.82% were not. Among the patients, 35.94% used an inhaler, while 64.06% did not. 14.06% of patients did not attend their follow-up appointments and instead relied solely on their asthma medications. 39.06% of patients used medication for allergic rhinitis (Table 2).

**Table 2.** The characteristics of the type of birth and drug use during pregnancy

Variables	n	%
Medications used		
Antihistaminic drug	25	39.06
Salbutamol	40	62.50
LABA+ICS	17	26.56
Delivery Mode		
Episiotomy	16	25
Cesarean section	28	43.75
Normally birth	19	29.68
Breech birth	1	1.56
Pulmonologist follow-up		
No	37	57.81
Yes	27	42.19
Medication use during pregnancy		
No	41	64.06
Yes	23	35.94

LABA: long affective beta-2 mimetic agonist, ICS: Inhaler corticosteroid

32 (50%) patients had allergies and/or were aware of their triggers. These patients 3 (4.68%) had a prick test (+) (Table 3). Significant differences in drug use patients based

on their age groups were observed ( $\chi^2=6,684$ ;  $p=0.035$ ) (Table 4). 27 (42.12%) were controlled by a pulmonologist and 23 (35.88%) were using medications in pregnancy. There was a significant difference in the medication use of pregnant women with asthma depending on whether they were treated by a pulmonologist or not. (Chi-square test;  $\chi^2=12.835$ ;  $p=0.0001$ ). While 68% of those who were not controlled by a pulmonologist did not use a drug, 60.8% of those who followed a pulmonologist were used in pregnancy (Table 5). 23 patients who used inhaler therapy, 18 used it correctly (Table 6).

**Table 3.** Understanding asthma triggers based on age in pregnant women with asthma

Understanding asthma triggers during pregnancy	No	Yes	no attention
Age			
19-29	21 (55.3%)	17 (44.7%)	24 (63.1%)
30-39	10 (47.6%)	11 (52.4%)	10 (47.6%)
40≤	1 (20%)	4 (80%)	2 (40%)
Total	32 (50%)	32 (50%)	36 (56.2%)

**Table 4.** Examining drug use during pregnancy among pregnant women with asthma across different age groups

Medication use during pregnancy	No	Yes	Total
Age			
19-29	19 (61.3%)	2 (22.2%)	21 (52.5%)
30-39	12 (38.7%)	6 (66.7%)	18 (45%)
40≤	0 (0%)	1 (11.1%)	1 (2.5%)
Total	31	9	40

Chi-square test;  $\chi^2=6.684$ ;  $p=0.035$

**Table 5:** Whether pregnant women are under the care of a pulmonologist affects their drug use.

Pulmonologist follow-up	No	Yes	Total
Medication use during pregnancy	No	21 (100%)	10 (52.6%)
	Yes	0 (0%)	9 (47.4%)
Total	21	19	40

Chi-square test;  $\chi^2=12.835$ ;  $p=0.0001$

**Table 6:** According to prenatal Pulmonologist consultation, the correct use of inhalers according to the age groups of pregnant women

Inhaler use during pregnancy	Inhaler using	Correct inhaler using
Age		
19-29	10 (15.6%)	9 (14.1%)
30-39	9 (14.1%)	7 (10.9%)
40≤	4 (6.2%)	2 (3.1%)
Total	23 (35.9%)	18 (28.1%)

## DISCUSSION

We retrospectively evaluated the files of 64 pregnant women with asthma aged 19-47 who gave birth in our hospital. Over half of them were under 30, and 18.75% of them continued to smoke during pregnancy. Women over 30 with asthma face high-risk pregnancies, and if not managed properly, it can lead to premature birth and low birth weight.<sup>2,3</sup> 27 (42.18%) of patients had allergic rhinitis and asthma. 7 (10.93%) patients had diabetes



mellitus (DM) as a common comorbidity. Up to 65% of pregnant women may experience nasal symptoms that can vary in control. Vasomotor rhinitis of pregnancy is likely if symptoms occur in the second or third trimester and resolve within 5 days after giving birth.<sup>1,2-4</sup>

In the study, 25% had an episiotomy, 43.75% had a cesarean section, 1.56% had a breech delivery, and 29.68% had a normal vaginal birth. Severe asthma attacks occur between the 24<sup>th</sup> and 36<sup>th</sup> weeks of pregnancy, but 90% of asthmatics have no complications during delivery. Emergency visits are reported in 11-18% of pregnant women with asthma, and hospitalization in 62%. It is crucial to control asthma during pregnancy for the health of both the mother and baby. Hypoxia can affect the baby's growth, so managing asthma carefully during pregnancy is important.<sup>2,6</sup>

Our study found that 82.82% of patients had asthma prior to pregnancy, while 17.18% were diagnosed during pregnancy. Asthma causes coughing, wheezing, chest tightness, and shortness of breath. Symptoms can worsen at night and be triggered by allergens, infections, smoke, exercise, and irritants. A physical examination and detailed medical history can help diagnose asthma. Pregnant women can experience similar symptoms due to body changes, which can decrease lung function. Therefore, a careful diagnosis is necessary to differentiate between pregnancy-related symptoms and asthma.<sup>7,8</sup>

Our study found that 42% of patients were under the care of a pulmonologist, while 36% used inhalers. 14% of patients did not attend follow-up appointments but still used their asthma medications. 39% of patients used medication for allergic rhinitis during pregnancy. Most pregnant patients used short-acting beta 2-agonist (SABA) salbutamol. Recent studies have shown that a fixed combination of LABA and low-dose ICS can be used as first-line therapy for mild asthma. This combination can be used as both maintenance and reliever therapy (MART) if necessary to control asthma symptoms. MART has been proven to be effective in managing asthma and can lead to lower overall use of ICS and fewer exacerbations. SABA can be used as a reliever therapy, but only in combination with maintenance ICS and LABA if needed.<sup>3</sup>

There is a low chance of fetal malformation caused by inhaled SABA. During delivery, systemic SABA may have a tocolytic effect. It is important to note that LABA should never be prescribed as a reliever or maintenance therapy without ICS. If LABA is needed to control asthma, it should be used in combination with ICS. The available data on the effects of LABA on the fetus is limited, but it is encouraging. The use of low and moderate doses of ICS during pregnancy has not been linked to an increased risk of malformations, preterm birth, low birth weight,

or SGA. However, it is hard to determine if higher doses are associated with adverse events or if these events are due to the severity of the underlying disease and/or the frequency of exacerbations. On the other hand, some studies suggest that the use of systemic steroids in pregnant women during the first trimester may increase the risk of cleft lip, cleft palate, premature birth, low birth weight, and preeclampsia.<sup>3</sup>

Salmeterol has the longest safety record and can be utilized in conjunction with ICS (ICS/LABA) as a maintenance therapy, along with SABA as required. Other LABAs in combination with ICS can also be considered, particularly in situations where adherence may be a concern.<sup>3</sup>

What do pregnant women know about asthma triggers according to their age groups? Half of the patients with asthma, allergies, and drug allergy reactions were aware of the triggers that caused their symptoms. Specific immunoglobulin E (IgE) levels in the patient's peripheral blood can help determine which allergens are causing symptoms. To manage symptoms, patients should avoid known allergens by using dust mite covers, removing pets, and exterminating cockroaches. While subcutaneous immunotherapy is not usually started during pregnancy, it may be continued at the same dose as before pregnancy if the patient was already at maintenance dosing. However, sublingual immunotherapy is not recommended during pregnancy.<sup>9</sup>

Pregnant women with asthma tend to use more drugs during pregnancy as they age. To have a safe pregnancy, they should avoid triggers and tobacco exposure, and take their asthma medication properly. Induction of labor is not commonly recommended due to asthma, as moderate to severe asthmatic patients tend to have a higher planned cesarean section rate. Obstetricians and respiratory physicians have teamed up to prevent serious complications during labor for pregnant women with asthma. This collaboration reduced severe respiratory issues during labor from 72 to 14 per 10,000 deliveries with asthma between 2000 and 2018. However, women with asthma who attempt vaginal delivery may have a higher risk of emergency caesarean section deliveries (OR 1.29) due to increased respiratory symptoms and complications related to maternal asthma.<sup>3</sup>

A study on 27 pregnant women with asthma found that medication use was significantly higher among those who were monitored by a pulmonologist. Asthma during pregnancy has been linked to severe maternal morbidity. In a prospective study, 23% of women with asthma improved, while 30% worsened. Among women with mild asthma, 12.6% had exacerbations and 2.3% required hospitalization.

Asthma during pregnancy has been linked to severe maternal morbidity. Among pregnant women with

asthma, 23% improved and 30% worsened. Women with asthma had an increased risk of low-birth-weight babies, pre-eclampsia, and preterm birth, compared to those without asthma. A meta-analysis revealed a statistically significant increase in the risk of non-major congenital malformations in women with asthma.<sup>10</sup> Asthmatic pregnant women have a higher rate of perinatal mortality. Proper asthma treatment before pregnancy is crucial to prevent spontaneous abortion. Women who experienced an asthma attack during pregnancy had a higher rate of low-birth-weight babies and were three times more likely to have a baby with low birth weight compared to those who did not have an attack. Enrolling in an asthma management program and monitoring disease activity during pregnancy can lead to better adherence with ICS. Asthmatics under optimal control during pregnancy did not experience ante-natal complications. Pregnant women with asthma are high-risk patients. Uncontrolled asthma can harm the mother and fetus. Proper asthma management ensures a good prognosis. Asthma exacerbations during pregnancy can cause harmful hypoxia for the fetus. Administer the lowest possible dose of medication to minimize fetal risk. Avoid multiple drug administration, especially in the first trimester.<sup>16</sup> In addition to the general pharmacological treatment principles for the treatment of asthma in pregnant women, the following points should be considered: 1) maternal symptoms and fetal development should be monitored objectively 2) environmental asthma-inducing factors should be well controlled, 3) patient education should be as little as drug therapy. great importance should be given.<sup>17,18</sup>

## CONCLUSION

Asthma treatment in pregnant women is still difficult due to the physiological conditions of asthma and pregnancy. Pregnant asthmatics should be followed up with a gynecologist and chest disease specialist. Treatment aims to keep asthma under control and reduce the number and severity of exacerbations. In this way, possible fetal risks can be prevented. The education of the pregnant, the rescue and therapeutic drugs to be used at home, the way of use should be taught, and preparation for birth should be ensured with regular controls.

Managing asthma during pregnancy can be challenging due to the unique physiological conditions of both asthma and gestation. The study suggests a collaborative approach between gynecologists and pulmonologists to achieve optimal asthma control during pregnancy. Education, proper medication usage, and regular follow-up appointments are vital components of successful asthma management in pregnant women.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was initiated with the approval of the University Şişli Hamidiye Etfal Training and Research Hospital University Medical Faculty Clinical Researches Ethics Committee (Date: 20.09.2022, Decision No: 3669).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Clinical profiles in pediatric systemic lupus erythematosus: a retrospective study

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**Cite this article as:** Kılınç Uğurlu A, Gülfem Özlü S, Kargın Çakıcı E, et al. Clinical profiles in pediatric systemic lupus erythematosus: a retrospective study. *Anatolian Curr Med J.* 2024;6(1):29-37.

Received: 22.10.2023

Accepted: 06.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** This study aimed to analyse clinical and laboratory findings, prognosis, and survival of systemic lupus erythematosus (SLE) patients, differentiating according to gender, pubertal status, and renal involvement.

**Methods:** Ninety-six pediatric SLE patients, diagnosed using ACR criteria, were retrospectively analyzed. Inclusion criteria comprised age under 18, meeting at least four ACR criteria, and six months of monitoring. Data encompassed demographics, symptoms, diagnosis, organ involvement, autoantibodies, treatment, prognosis, and survival. Categorization was based on gender and pubertal status. Renal biopsies followed WHO-ISN classification, with asymptomatic findings termed “silent lupus nephritis.” Biopsied patients were divided into proliferative and non-proliferative lupus nephritis categories, excluding irreversible damage cases. Outcomes studied included remission, relapse, end-stage renal failure, and mortality.

**Results:** Among 96 participants, females constituted 82.3%, males 17.7%, resulting in a female-to-male ratio of 4.6:1. Mean age at diagnosis was 11.9 years, with 37 prepubertal (38.5%) and 59 pubertal (61.5%) cases. Oral-nasal ulcers ( $p=0.01$ ) were more prevalent in males related to system involvement. Nephrotic syndrome prevalence increased from 21.6% in prepubertal to 44.1% in pubertal cases ( $p=0.025$ ). Positive Anticardiolipin IgM antibodies decreased from 56.2% in prepubertal to 25.9% in pubertal cases ( $p=0.047$ ). Type IV lupus nephritis was predominant, followed by Type II, in prepubertal and pubertal groups and both genders. Proliferative lupus nephritis showed higher rates of renal involvement (95.7% vs. 65.6%), nephrotic syndrome (46.8% vs. 21.9%), proteinuria (89.4% vs. 62.5%), hematuria (57.4% vs. 28.1%), elevated creatinine (43.5% vs. 9.7%), and low albumin (67.4% vs. 23.3%). Cases with proliferative lupus nephritis had higher neuropsychiatric involvement (36.2% vs. 12.5%), seizures (25.5% vs. 3.1%,  $p=0.008$ ), and increased hemolytic anemia rates (78.7% vs. 56.2%,  $p=0.033$ ). Thirteen had silent lupus nephritis, revealing various types through biopsy. All reported deaths occurred within the first five years, resulting in stable 91% survival rates at 5, 10, and 15 years.

**Conclusion:** This study provides insights into the clinical, prognostic, and survival characteristics of pediatric systemic lupus erythematosus (SLE), revealing notable patterns related to gender, pubertal development, and renal involvement. There is an association between proliferative lupus nephritis and renal involvement, nephrotic syndrome, and neuropsychiatric symptoms. Significantly, silent lupus nephritis highlights the complex renal implications, necessitating diligent surveillance for prompt intervention.

**Keywords:** Pediatric systemic lupus erythematosus (SLE), gender, pubertal status, renal involvement, proliferative lupus nephritis, silent lupus nephritis

This study was presented orally at the 8. Erciyes Pediatri Akademisi Kongresi. The congress took place between 12<sup>th</sup> and 14<sup>th</sup> May 2022, with our presentation being held on 13<sup>th</sup> May 2022.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by inflammation that affects multiple systems of the body. Although the exact cause of SLE is unknown, it is believed that autoimmunity is triggered by genetic, hormonal, or environmental factors that stimulate the immune system. The incidence of SLE varies in different populations. In children, the annual incidence is generally reported to range from 0.36 to 0.9 per 100,000.<sup>1</sup> In adults, it has been reported that the annual incidence is in the region of 3%.<sup>1</sup> SLE occurs in 10–17% of cases during childhood<sup>2</sup> and is more common in females and in Asians,

African Americans, Hispanics, and Native Americans. The disease typically manifests after puberty. It is rare in children under five years of age. In both childhood and adulthood, the disease incidence is higher in females. The prevalence of SLE is higher in prepubertal girls than in boys, with a ratio of 4:1. However, during the pubertal period, this ratio increases significantly to 8:1.<sup>3</sup> SLE has a variable prognosis and severity. While some cases present with mild generalized symptoms, others may have a severe course with multiple organ involvement. There needs to be more research on how the clinical findings of SLE vary with age, mainly comparing children and adults and insufficient

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studies on the evaluation of disease progression in childhood groups.<sup>4</sup> This study aims to evaluate the clinical and laboratory findings, prognosis, and long-term outcome of childhood SLE cases followed up in our clinic, and to analyze disease characteristics according to sex (male-female), pubertal status (pubertal-prepubertal) and renal biopsy results (proliferative-nonproliferative nephritis).

## METHODS

The study was derived from the thesis on “Evaluation of epidemiological characteristics, clinical and laboratory findings, and prognosis of patients with systemic lupus erythematosus observed between 1990 and 2013: a retrospective study” dated 2014 in Ankara Dr Sami Ulus Pediatrics Training and Research Hospital. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study retrospectively analyzed the data of 96 patients diagnosed with systemic lupus erythematosus (SLE) according to the American College of Rheumatology (ACR) criteria,<sup>5</sup> who were monitored for a minimum of 6 months at the Department of Pediatric Nephrology of Dr. Sami Ulus Maternity, Gynecology, Pediatrics Training and Research Hospital. Inclusion criteria comprised patients diagnosed under the age of 18, with at least four of the 11 ACR SLE criteria positive, monitoring for at least six months, and having sufficient records that permit analysis. A uniform form was used to record the gender, age, origin of symptoms, diagnosis date, the ACR SLE criteria at the time of diagnosis, organ involvement, autoantibody and laboratory profiles, treatment received, follow-up, prognosis, causes of death, and survival times of each patient; this form was completed by only one clinician using files and computerized medical records.

This study compared patients based on gender. Patients were segregated based on pubertal status into two categories: prepubertal and pubertal. Prepubertal patients were categorized as Tanner stage 1 upon pubertal examination, whereas pubertal patients were identified as Tanner stage 2 or higher.<sup>6</sup>

Renal biopsy results were classified according to the WHO-International Society of Nephrology revised criteria for lupus nephritis.<sup>7</sup> Cases without clinical evidence of renal involvement but with nephritic findings on biopsy were defined as silent lupus nephritis.

Patients who underwent renal biopsy were classified as having either proliferative or non-proliferative lupus nephritis.<sup>8</sup> Patients with type III and IV lupus nephritis were classified as proliferative, whereas patients with type I, II and V lupus nephritis were classified as non-proliferative. Patients with type VI lupus nephritis and irreversible renal damage were excluded.

The patients had four prognoses: remission, relapse, end-stage renal failure (ESRD), and death. Remission was defined as the stabilization and improvement of renal function for at least 6 months, the disappearance of urinary sediment abnormalities such as hematuria and cellular cilia, a reduction in proteinuria (protein/creatinine ratio of less than 0.2 or protein positive), and the normalization of C3 levels. Relapse was defined as an increase in proteinuria (>960 mg/m<sup>2</sup>/day) and/or activation of sediment findings in the urine and/or an increase in creatinine levels after responding to treatment.<sup>9,10</sup> ESRD was defined as the requirement for permanent dialysis.<sup>9,10</sup>

## Statistical Analysis

In this study, statistical analysis were performed using SPSS 20.0 software. Kolmogorov Smirnov normality test was used to analyse the conformity to normal distribution and Levene's test statistics was used for the conformity of homogeneous variance assumption. Descriptive statistics of continuous variables were presented as mean  $\pm$  standard deviation and categorical variables were presented as number of patients (N) and percentage (%). Mann Whitney U test was used to analyse continuous variables for two groups. In the comparison of categorical variables between groups, chi-square test or Fisher exact test was used. In addition, Kaplan-Meier curve was used to investigate the effect of survival and renal survival of the patients and renal biopsy classification on the presence of ESRD. Test results were evaluated at a significance level of  $p < 0.05$ .

## RESULTS

Out of 96 participants enrolled in this research, 79 (82.3% of the total) were identified as female, while 17 (17.7% of the total) were classified as male. The ratio between female and male participants was determined to be 4.6:1. The mean age of the patients at the time of diagnosis was  $11.9 \pm 3.4$  years. The follow-up period was 5.7 (0.5-13) years. Of the patients, 37 (38.5%) were prepubertal, out of which 27 (73%) were girls and 10 (27%) were boys (F/M:2.7:1). Whereas 59 (61.5%) were pubertal, among whom 52 (88.1%) were girls and 7 (11.9%) were boys (F/M: 7.4:1). **Table 1** presents numerical and percentage data on the clinical and laboratory findings, systemic involvement, laboratory results according to the ACR SLE diagnostic criteria, and prognosis of the patients included in the study.

Among the patients in the study, the malar rash was present in 50 (52.1%) individuals, renal involvement in 76 (79.2%), hematologic involvement in 72 (75%), ANA positivity in 87 (90.6%), and anti-dsDNA positivity in 69 (71.9%), based on the ACR SLE diagnostic criteria for clinical and laboratory findings. Patients with cardiac

involvement were most diagnosed with pericarditis, while patients with neuropsychiatric involvement were most diagnosed with seizures. Furthermore, it was observed that individuals exhibiting hematologic involvement were predominantly diagnosed with hemolytic anemia. The clinical presentation indicated a comparatively lower incidence of oral-nasal ulcers. Following our analysis of the patients' prognosis, we found that 63 patients (63.6%) were in remission, 18 (18.2%) had relapsed, 7 (7.1%) had exited, while 11 (11.1%) had developed ESRD.

**Table 1. System involvement, laboratory findings and prognosis of patients with SLE**

	Total n (%) n: 96 (100%)
Malar rash	50 (52.1%)
Discoid rash	15 (15.6%)
Photosensitivity	13 (13.5%)
Oral-nasal ulcer	11 (11.5%)
Joint involvement	45 (46.9%)
Renal involvement	76 (79.2%)
Proteinuria	71 (74%)
Hematuria	43 (44.8%)
Nephritic syndrome	22 (22.9%)
Nephrotic syndrome	34 (35.4%)
Cellular cylinder	17 (17.7%)
Neuropsychiatric involvement	24 (25%)
Seizure	15 (15.6%)
Psychosis	4 (4.2%)
Headache	5 (5.2%)
Cardiac involvement	16 (16.6%)
Endocarditis	3 (18.8%)
Myocarditis	1 (6.2%)
Pericarditis	12 (75%)
Pleuritis	12 (12%)
Hematologic involvement	72 (75%)
Hemolytic anemia	70 (72.9%)
Leukopenia	30 (31.2%)
Lymphopenia	35 (36.8%)
Thrombocytopenia	16 (16.8%)
ANA	87 (90.6%)
Anti-dsDNA	69 (71.9%)
Anti-smith (n: 72)	6 (8.3%)
Anti-cardiolipin IgM (n: 43)	16 (37.2%)
Anti-cardiolipin IgG (n: 41)	11 (26.8%)
Lupus anticoagulant (n: 15)	6 (40%)
VDRL (n: 60)	4 (6.7%)
Prognosis	
Remission	63 (63.6%)
Relapse	18 (18.2%)
Exitus	7 (7.1%)
ESRD	11 (11.1%)

Male patients showed a higher frequency of oral-nasal ulcers (p=0.01) when compared to female patients, based on their system involvement. **Table 2** provides a comparison of patients' gender with regards to system involvement, laboratory findings, and prognosis.

**Table 2. System involvement, laboratory findings and prognosis by gender in patients with SLE**

	Total n: 96 (100%)	Male n: 17 (17.7%)	Female n: 79 (82,3%)	p value
Malar rash	50 (52.1%)	11 (64.7%)	39 (49.4%)	0.25
Discoid rash	15 (15.6%)	1 (5.9%)	14 (17.7%)	0.22
Photosensitivity	13 (13.5%)	1 (5.9%)	12 (15.2%)	0.30
Oral-nasal ulcer	11 (11.5%)	5 (29.4%)	6 (7.6%)	<b>0.010*</b>
Joint involvement	45 (46.9%)	9 (52.9%)	36 (45.6%)	0.58
Renal involvement	76 (79.2%)	14 (82.4%)	62 (78.5%)	0.72
Proteinuria	71 (74%)	14 (82.4%)	57 (72.2%)	0.38
Hematuria	43 (44.8%)	10 (58.8%)	33 (41.8%)	0.20
Nephritic syndrome	22 (22.9%)	3 (17.6%)	19 (24.1%)	0.56
Nephrotic syndrome	34 (35.4%)	7 (41.2%)	27 (34.2%)	0.58
Cellular cylinder	17 (17.7%)	3 (17.6%)	14 (17.7%)	0.99
Neuropsychiatric involvement	24 (25%)	4 (23.5%)	20 (25.3%)	0.87
Seizure	15 (15.6%)	4 (23.5%)	13 (16.4%)	0.32
Psychosis	4 (4.2%)	1 (5.9%)	3 (3.8%)	0.54
Headache	5 (5.2%)	1 (5.9%)	4 (5.1%)	0.63
Cardiac involvement	16 (16.6%)	3 (17.6%)	13 (16.4%)	0.90
Endocarditis	3 (3%)	0 (0.0%)	3 (3.7%)	0.20
Myocarditis	1 (1%)	0 (0.0%)	1 (1%)	0.56
Pericarditis	12 (12.5%)	3 (17.6%)	9 (11%)	0.57
Pleuritis	12 (12%)	4 (23.5%)	8 (10.1%)	0.13
Hematologic involvement	72 (75%)	14 (82.4%)	58 (73.4%)	0.44
Hemolytic anemia	70 (72.9%)	14 (82.4%)	56 (70.9%)	0.33
Leukopenia	30 (31.2%)	7 (41.2%)	23 (29.1%)	0.33
Lymphopenia	35 (36.8%)	7 (41.2%)	28 (35.9%)	0.68
Thrombocytopenia	16 (16.8%)	4 (23.5%)	12 (15.4%)	0.41
ANA	87 (90.6%)	15 (88.2%)	72 (91.1%)	0.70
Anti-dsDNA	69 (71.9%)	14 (82.4%)	55 (69.6%)	0.28
Anti-smith (n: 72)	6 (8.3%)	2 (16.7%)	4 (6.7%)	0.25
Anti-cardiolipin IgM (n: 43)	16 (37.2%)	4 (44.4%)	12 (35.3%)	0.61
Anti-cardiolipin IgG (n: 41)	11 (26.8%)	1 (11.1%)	10 (31.2%)	0.22
Lupus anticoagulant (n: 15)	6 (40%)	1 (50%)	5 (38.5%)	0.65
VDRL (n: 60)	4 (6.7%)	1 (9.1%)	3 (6.1%)	0.56
Prognosis				
Remission	63 (63.6%)	10 (55.6%)	53 (65.4%)	0.43
Relapse	18 (18.2%)	3 (16.7%)	15 (18.5%)	0.85
Exitus	7 (7.1%)	2 (11.1%)	5 (6.2%)	0.46
ESRD	11 (11.1%)	3 (16.7%)	8 (9.9%)	0.40

\*The values in bold represent p value < 0.05, ESRD: End-stage renal disease

Nephrotic syndrome was reported to be 21.6% in the prepubertal group, which increased to 44.1% in the pubertal group (p=0.025) when the cases were compared based on pubertal status. The prevalence of positive Anticardiolipin IgM antibodies decreased from 56.2% in the prepubertal group to 25.9% in the pubertal group (p=0.047), as compared based on the patient's pubertal status. A comparison of prognoses based on pubertal status revealed that prepubertal patients had a higher mortality rate, whereas pubertal patients had a higher

rate of end-stage renal disease ( $p>0.05$ ). The comparison of patients' pubertal status with system involvement, laboratory findings and prognosis are shown in **Table 3**.

**Table 3.** System involvement, laboratory findings and prognosis of prepubertal and pubertal cases in patients with SLE

	Total n:96 (100%)	Prepubertal n: 37 (38,5%)	Pubertal n: 59 (61,5%)	p value
Malar rash	50 (52.1%)	20 (54.1%)	30 (50.8%)	0.76
Discoid rash	15 (15.6%)	8 (21.6%)	7 (11.9%)	0.20
Photosensitivity	13 (13.5%)	8 (21.6%)	5 (8.5%)	0.06
Oral-nasal ulcer	11 (11.5%)	3 (8.1%)	8 (13.6%)	0.41
Joint involvement	45 (46.9%)	13 (35.1%)	32 (54.2%)	0.06
Renal involvement	76 (79.2%)	26 (70.3%)	50 (84.7%)	0.08
Proteinuria	71 (74%)	25 (67.6%)	46 (78.0%)	0.25
Hematuria	43 (44.8%)	13 (35.1%)	30 (50.8%)	0.13
Nephritic syndrome	22 (22.9%)	7 (18.9%)	15 (25.4%)	0.46
Nephrotic syndrome	34 (35.4%)	8 (21.6%)	26 (44.1%)	<b>0.025*</b>
Cellular cylinder	17 (17.7%)	5 (13.5%)	12 (20.3%)	0.39
Neuropsychiatric involvement	24 (25%)	10 (27.0%)	14 (23.7%)	0.71
Seizure	15 (15.6%)	8 (21.6%)	9 (15.3%)	0.89
Psychosis	4 (4.2%)	1 (2.7%)	3 (5.1%)	0.49
Headache	5 (5.2%)	1 (2.7%)	4 (6.8%)	0.35
Cardiac involvement	16 (16.6%)	6 (16%)	10 (16.9%)	0.92
Endocarditis	3 (3%)	2 (5.4%)	1 (1.6%)	0.76
Myocarditis	1 (1%)	1 (2.7%)	0 (0%)	0.20
Pericarditis	12 (12.5%)	3 (8%)	9 (15.2%)	0.16
Pleuritis	12 (12.5%)	3 (8.1%)	9 (15.3%)	0.13
Hematologic involvement	72 (75%)	27 (73%)	45 (76.3%)	0.71
Hemolytic anemia	70 (72.9%)	26 (70.3%)	44 (74.6%)	0.64
Leukopenia	30 (31.2%)	12 (32.4%)	18 (30.5%)	0.84
Lymphopenia	35 (36.8%)	13 (35.1%)	22 (37.9%)	0.78
Thrombocytopenia	16 (16.8%)	8 (21.6%)	8 (13.8%)	0.32
ANA	87 (90.6%)	33 (89.2%)	54 (91.5%)	0.70
Anti-dsDNA	69 (71.9%)	28 (75.7%)	41 (69.5%)	0.51
Anti-smith (n: 72)	6 (8.3%)	3 (9.7%)	3 (7.3%)	0.52
Anti-cardiolipin IgM (n: 43)	16 (37.2%)	9 (56.2%)	7 (25.9%)	<b>0.047*</b>
Anti-cardiolipin IgG (n: 41)	11 (26.8%)	4 (25%)	7 (28%)	0.83
Lupus anticoagulant (n: 15)	6 (40%)	3 (50%)	3 (33.3%)	0.45
VDRL (n: 60)	4 (6.7%)	2 (7.4%)	2 (6.1%)	0.61
Prognosis				
Remission	63 (63.6%)	23 (59%)	40 (66.7%)	0.43
Relapse	18 (18.2%)	9 (23.1%)	9 (15%)	0.30
Exitus	7 (7.1%)	4 (10.3%)	3 (5%)	0.27
ESRD	11 (11.1%)	3 (7.7%)	8 (13.3%)	0.38

\*The values in bold represent p value < 0.05, ESRD: End-stage renal disease

Ten out of the 96 patients involved in our study were not eligible for a biopsy for various reasons, such as a disorder in their bleeding profile. Only three of the 86 patients who underwent a biopsy had renal biopsy results reported as insufficient due to inadequate material. Of 83 patients, 51% were diagnosed with type IV lupus nephritis, followed by

30% with Type II, 7% with type V, 6% with Type III, 5% with type VI and 1% with Type I. In both prepubertal and pubertal groups and across both genders, type IV lupus nephritis was the most common Type, followed by Type II as the second most common Type.

Based on biopsy results, we divided our patients into those with proliferative lupus nephritis and those with nonproliferative lupus nephritis. We excluded four cases with lupus nephritis of type VI on biopsy. Among our patients (n:79), 59% (n:47) had proliferative lupus nephritis. 41% (n:32) had nonproliferative lupus nephritis. Within the proliferative group, 6% (n:5) had Type III, and 53% (n:42) had Type IV. Meanwhile, within the nonproliferative group, 1% (n:1) had Type I, 39% (n:25) had Type II, and 6% (n:6) had Type V lupus nephritis.

The rate of renal involvement in proliferative lupus nephritis was 95.7% compared to 65.6% in nonproliferative lupus nephritis ( $p=0.001$ ); the rate of nephrotic syndrome was 46.8% compared to 21.9% in nonproliferative lupus nephritis ( $p=0.024$ ); the rate of proteinuria was 89.4% compared to 62.5% in nonproliferative lupus nephritis ( $p=0.004$ ); hematuria was 57.4% compared to 28.1% in nonproliferative lupus nephritis ( $p=0.01$ ); elevated creatinine at first presentation was 43.5% compared to 9.7% in nonproliferative lupus nephritis ( $p=0.001$ ); low albumin at first presentation was 67.4% compared to 23.3% in nonproliferative lupus nephritis ( $p=0.001$ ) (**Table 4**).

The rate of neuropsychiatric involvement was 36.2% in the proliferative group compared to 12.5% in non-proliferative lupus nephritis ( $p=0.019$ ); the rate of seizures was 25.5% compared to 3.1% in non-proliferative lupus nephritis ( $p=0.008$ ). Neuropsychiatric involvement was present in 17 cases of proliferative lupus nephritis, with seizures in 12, psychosis in 3, and headache in 3. Neuropsychiatric involvement was present in 4 cases of nonproliferative lupus nephritis. Of these patients, 1 had a seizure, one had a central nervous system hemorrhage, 1 had a central nervous system infarction, and 1 had chorea. Cranial magnetic resonance imaging appeared compatible with vasculitis in 3 of our patients. The rate of hemolytic anemia was 78.7% in proliferative lupus nephritis and 56.2% in non-proliferative lupus nephritis ( $p=0.033$ ) (**Table 4**).

In our study, 66 out of 79 patients in this group had evidence of renal involvement. The remaining 13 (12%) patients had no clinical or laboratory evidence of renal involvement. However, when we analysed the biopsies of these patients, we found one patient each with type I, III and IV lupus nephritis and 10 (50%) patients with type II lupus nephritis. As a result, we found silent lupus nephritis in 13 patients. The comparison of proliferative and non-proliferative lupus nephritis and system involvement, laboratory findings, prognosis and hypertension is shown in **Table 4**.

**Table 4.** System involvement, laboratory findings, hypertension and prognosis in patients with proliferative and nonproliferative lupus nephritis

	Total n: 79 (100%)	Proliferative n: 47 (59%)	Non- proliferative n: 32(47%)	P value
<b>Gender</b>				
Male	14 (17.7%)	9 (19.2%)	5 (15.6%)	0.68
Female	65 (82.3%)	38 (80.8%)	27 (84.4%)	
Malar rash	43 (54.4%)	28 (59.6%)	15 (46.9%)	0.26
Discoid rash	14 (17.7%)	6 (12.8%)	8 (25%)	0.16
Photosensitivity	13 (16.5%)	7 (14.9%)	6 (18.8%)	0.65
Oral-nasal ulcer	10 (12.7%)	7 (14.9%)	3 (9.4%)	0.46
Joint involvement	40 (50.6%)	25 (53.2%)	15 (46.9%)	0.58
Renal involvement	66 (83.5%)	45 (95.7%)	21 (65.6%)	<b>0.001*</b>
Proteinuria	62 (78.5%)	42 (89.4%)	20 (62.5%)	<b>0.004*</b>
Hematuria	36 (45.6%)	27 (57.4%)	9 (28.1%)	<b>0.010*</b>
Nephritic syndrome	17 (21.5%)	12 (25.5%)	5 (15.6%)	0.29
Nephrotic syndrome	29 (36.7%)	22 (46.8%)	7 (21.9%)	<b>0.024*</b>
Cellular cylinder	15 (19%)	11 (23.4%)	4 (12.5%)	0.22
Neuropsychiatric involvement	21 (26.5%)	17 (36.2%)	4 (12.5%)	<b>0.019*</b>
Seizure	13 (16.4%)	12 (25.5%)	1 (3.1%)	<b>0.008*</b>
Psychosis	3 (3.7%)	3 (6.4%)	0 (0%)	0.20
Headache	3 (3.7%)	3 (6.4%)	0 (0%)	0.20
Cardiac involvement	16 (20.2%)	8 (17%)	10 (31%)	0.58
Endocarditis	2 (2%)	1 (2%)	1 (3%)	
Myocarditis	1 (1%)	1 (2%)	0 (0%)	
Pericarditis	9 (11.3%)	6 (12.7%)	3 (9.3%)	
Pleuritis	10 (12.7%)	8 (17%)	2 (6.3%)	0.15
Hematologic involvement	57 (72.2%)	37 (78.7%)	20 (62.5%)	0.11
Hemolytic anemia	55 (69.6%)	37 (78.7%)	18 (56.2%)	<b>0.033*</b>
Leukopenia	23 (29.1%)	14 (29.8%)	9 (28.1%)	0.87
Lymphopenia	27 (34.6%)	17 (37%)	10 (31.2%)	0.60
Thrombocytopenia	9 (11.5%)	6 (13%)	3 (9.4%)	0.61
ANA	71 (89.9%)	42 (89.4%)	29 (90.6%)	0.58
Anti-dsDNA	57 (72.2%)	37 (78.7%)	20 (62.5%)	0.11
Anti-smith (n: 59)	4 (6.8%)	2 (5.4%)	2 (9.1%)	0.47
Anti-cardiolipin IgM (n: 31)	12 (38.7%)	7 (33.3%)	5 (50%)	0.37
Anti-cardiolipin IgG (n: 29)	8 (27.6%)	5 (25%)	3 (33.3%)	0.64
Lupus anticoagulant (n: 7)	1 (14.3%)	1 (25%)	0 (0%)	0.57
VDRL (n: 52)	4 (7.7%)	3 (9.7%)	1 (4.8%)	0.46
<b>Prognosis</b>				
Remission	53 (53.5%)	32 (64%)	21 (65.6%)	0.88
Relapse	16 (16.2%)	8 (16%)	8 (25%)	0.31
Exitus	6 (6.1%)	5 (10%)	1 (3.1%)	0.23
ESRD	7 (7.1%)	5 (10%)	2 (6.3%)	0.43
Hypertension	24 (30.4%)	17 (36.2%)	7 (21.9%)	0.17
C3 impairment (n: 76)	52 (68.4%)	34 (75.6%)	18 (58%)	0.10
C4 impairment (n: 76)	53 (69.7%)	34 (75.6%)	19 (61.3%)	0.18
Creatinine (n: 77)	23 (29.9%)	20 (43.5%)	3 (9.7%)	<b>0.001*</b>
Albumin (n: 76)	38 (50%)	31 (67.4%)	7 (23.3%)	<b>0.001*</b>

\*The values in bold represent p value < 0.05, ESRD: End-stage renal disease

Among the 79 patients with renal involvement, three individuals were not evaluated for prognosis since they did not receive follow-up treatment at our clinic. Eleven out of 76 patients developed end-stage renal disease while under our care. The analysis of biopsies performed on 11 patients who developed end-stage renal failure, revealed that five of them had Type IV, two had Type V, and four had Type VI lupus nephritis (**Table 4**).

Our study found higher rates of ESRD and mortality in boys compared to girls (p>0.05). Although mortality was higher in the prepubertal period, our patients had a higher incidence of ESRD in the pubertal period (p>0.05). In the analysis of the prognosis of proliferative and nonproliferative lupus nephritis groups, it was found that mortality and end-stage renal disease rates were higher in proliferative lupus nephritis, while the relapse rate was higher in non-proliferative lupus nephritis (p>0.05).

During follow-up, seven patients died. After analyzing the causes of death, we found that one patient died due to macrophage activation syndrome, another patient died due to renal failure, one more patient died due to multiple organ failure, two patients died due to sepsis, and the remaining two patients died at their homes. All reported deaths occurred within the first five years. Consequently, the survival rates of our patients at 5, 10, and 15 years were 91%.

## DISCUSSION

Systemic lupus erythematosus is a chronic autoimmune disease that involves inflammation and affects multiple organ systems. Pathogenic autoantibodies and immune complexes are involved in its pathogenesis. The incidence of systemic lupus erythematosus is higher in females both in childhood and in adulthood. The onset of the disease typically occurs after puberty.<sup>11,12</sup> This study examines the complex clinical details, prognosis, and results of pediatric patients suffering from systemic lupus erythematosus (SLE). The research comprehensively evaluates the effect of gender, pubertal status, and renal biopsy outcomes on the symptoms of childhood SLE. The prominence of type IV and II lupus nephritis within the patient cohort is of paramount importance, highlighting their critical role in the course of the disease. The study highlights the critical importance of proliferative lupus nephritis, which is notably linked to renal involvement, nephrotic syndrome, and neuropsychiatric symptoms. A significant discovery has emerged in the diagnosis of lupus nephritis in 16% of individuals without any obvious clinical or laboratory symptoms - silent lupus nephritis. Notably, a significant number of cases with type II lupus nephritis have been detected among these individuals, highlighting the concealed renal impacts that require increased awareness. To mitigate the effects



of this concealed disease, the study emphasizes the need for sustained vigilance and careful monitoring. Prompt intervention and careful management strategies are crucial to effectively address the concealed dimensions of renal involvement in pediatric systemic lupus erythematosus cases.

Our study, consistent with the literature, found that the girl/boy ratio in favour of girls increased as the pubertal period progressed.<sup>13,14</sup> This is thought to be related to hormonal changes, such as an increase in estrogen and progesterone as the pubertal period progresses and the disease gradually acquires adult characteristics.<sup>15</sup>

Renal, hematological and malar rash were the most common systems involved in our patients. Patients with renal involvement were more likely to experience proteinuria, while those with hematological involvement often presented with haemolytic anaemia. Thabet et al.<sup>16</sup> (Tunisia) reported that anaemia was the most common presentation, followed by proteinuria and malar rash (67.6%). Lukic et al.<sup>17</sup> (Croatia) found that the musculoskeletal system was the most commonly involved (80%), while cases with renal involvement most commonly presented with hematuria (58%). Although different frequencies of involved organs/systems have been reported in studies from different countries, renal involvement is generally the most common finding in childhood.<sup>17</sup> These varying frequencies in clinical findings are thought to be the result of genetic, environmental, and racial factors.<sup>18</sup>

Wang's study<sup>19</sup> indicated a significantly higher prevalence of rash and alopecia among females, while our data showed that boys had a higher incidence of oral nasal ulcers compared to girls. Boys had more malar rash, joint involvement, renal involvement, pleuritis and hematological involvement than girls, but the differences were not statistically significant. A study conducted in India reported a higher occurrence of renal involvement in boys (78%) than in girls (46%).<sup>20</sup>

Our analysis of patients in pubertal and prepubertal periods showed a significantly higher probability of nephrotic syndrome during pubertal period and anticardiolipin IgM positivity during prepubertal period. The study conducted by Zhu et al.<sup>4</sup> analyzed SLE cases into 3 groups based on age: preschool (age 1-6 years), school age (age 7-11 years), and adolescent (age 12-18 years) periods. The study found that hepatosplenomegaly and arthritis were more frequent during the preschool period compared to the other age groups. However, there were no differences between the groups in terms of nephrotic syndrome and anticardiolipin antibody positivity. In a study by Chiang et al.<sup>21</sup> SLE cases were grouped into 3 categories according to age: prepubertal (< 8 years), pubertal (8-13 years), and postpubertal (13-

18 years) periods. The postpubertal period showed a significant increase in renal involvement, lymphopenia, and low c3 and c4 levels compared to the prepubertal period. Similar to our study, the pubertal period showed a higher frequency of renal involvement. This study did not find any difference in terms of anti-cardiolipin antibody positivity.

Lupus nephritis can present in a variety of forms, ranging from asymptomatic microscopic hematuria to severe proliferative glomerulonephritis, and the different rates of renal involvement found in studies may be related to the different severity of symptoms.<sup>22-24</sup> The most common histopathological subtype present in renal involvement is diffuse proliferative glomerulonephritis, which has the most rapid clinical course.<sup>25</sup> In our study, type IV lupus nephritis was the most frequently observed lupus nephritis, as is consistent with the literature.<sup>19,26-28</sup> Type IV lupus nephritis was observed most frequently in our study, followed by Type II, Type V, Type III, Type VI and Type I lupus nephritis, respectively. Studies conducted in Asia and America have reported that Type II and Type V lupus nephritis are the most common types after Type IV.<sup>26,27</sup>

Renal involvement, neuropsychiatric findings, hemolytic anaemia, elevated creatinine, and low albumin are more common in cases with proliferative lupus nephritis. Proteinuria, hematuria, and nephrotic syndrome are more frequent in the proliferative group of cases with renal involvement, while seizures are more common in cases with neuropsychiatric involvement. The study by Wu et al.<sup>29</sup> found hypertension, low glomerular filtration rate, proteinuria, hematuria, and sterile leukocyturia to be statistically significant in cases with proliferative lupus nephritis.

In a study from our country,<sup>30</sup> patients with proliferative lupus nephritis were found to have elevated basal creatinine levels, significant median daily proteinuria, anti-double-stranded DNA (dsDNA) positivity, reduced C3 and C4 complement levels, and the presence of active urinary sediment. Our findings further delineate the clinical picture, demonstrating that renal involvement, neuropsychiatric symptoms, hemolytic anemia, increased creatinine levels, and decreased serum albumin concentrations are more frequently observed in patients with proliferative forms of the disease. Moreover, proteinuria, hematuria, and nephrotic syndrome are more commonly encountered among those with renal manifestations, while seizures predominate in patients with neuropsychiatric complications. Complementing these observations, Wu et al.<sup>29</sup> identified hypertension, a lower glomerular filtration rate, proteinuria, hematuria, and sterile leukocyturia as significant clinical features in patients with proliferative lupus nephritis.

We analyzed biopsies from 13 patients who had no clinical or laboratory findings indicating renal involvement. We found one patient each with type I, III, and IV lupus nephritis and 10 (76%) patients with type II lupus nephritis. As a result, we found silent lupus nephritis in 16% of our patients with renal involvement, which is a significantly high rate.

In the study by Mannemuddhu<sup>31</sup> of 68 patients, 22 (32%) were identified with Silent Lupus Nephritis (SLN), with Class II Lupus Nephritis (LN) being the most frequently observed subtype in this group, representing 50% (n=11) of the SLN cases. Contrastingly, in our research, SLN was detected in 13 (12%) of our patients, and upon histopathological examination of their renal biopsies, a distribution of LN classes was discerned: one patient with Class I, one with Class III, one with Class IV, and a predominant 76% (n=10) with Class II LN, indicating a higher prevalence of Class II LN in our silent cases than reported in Mannemuddhu's cohort. In Gonzalez-Crespo et al.'s<sup>32</sup> study of 18 silent lupus nephritis cases, type I was found in 9, type II in 6, type IV in 1, and type V in 2. In both Gonzalez-Crespo's study<sup>32</sup> and ours, the majority of cases with silent lupus nephritis showed low-grade involvement according to biopsy results. Nevertheless, these patients can also be diagnosed with advanced lupus nephritis, which is significant in determining the prognosis of the disease. The involvement of the kidneys is a crucial factor in determining the prognosis and treatment of the disease. It is imperative to detect any renal involvement in both confirmed and suspected cases. Our study revealed that cases without any symptoms of kidney involvement may still display advanced histopathology biopsy results. Conversely, cases with kidney involvement may display low-grade lupus nephritis in the renal biopsies. The two above-mentioned scenarios play a crucial role in determining both the treatment protocol and prognosis of patients. These results highlight the need for performing a biopsy on patients diagnosed with SLE, even if renal involvement is not present.

According to Gonzalez-Crespo et al.<sup>32</sup> 3 patients died due to causes unrelated to renal involvement, while 3 patients died after developing ESRD. None of our patients with silent lupus nephritis developed ESRD. However, our analysis of biopsy results revealed cases of type III and IV lupus nephritis in our patients with silent lupus nephritis. It is known that ESRD is more common among patients with these types of nephritis.<sup>32</sup>

Our study found higher rates of ESRD and mortality in boys compared to girls. Although prepubertal mortality rate was higher, ESRD incidents were more frequent during pubertal period in our patients. Previous studies reported higher risk of ESRD in boys. Prognosis analysis revealed that death and ESRD incidence were higher in proliferative lupus nephritis cases, while nonproliferative

lupus nephritis cases showed higher relapse rate. Wu et al.<sup>29</sup> found higher death and ESRD incidence in proliferative lupus nephritis and higher renal exacerbation incidence in nonproliferative lupus nephritis, which is similar to our findings.

In our study, the mortality rate was 7.1%, with causes of death encompassing macrophage activation syndrome, renal failure, multiple organ failure, sepsis, and unattended home fatalities; this is in marked variance from Samantha et al.'s<sup>33</sup> findings of a 17.39% mortality rate, predominantly due to septicemia in patients with end-stage renal disease, and Listiyono's study<sup>34</sup>, which reported a 27% one-year post-diagnosis mortality, primarily due to infections in 8 (34%) out of 23 patients and renal failure in 7 (30%) out of 23 patients.

### Limitations

The most significant limitation of our study is that it was a retrospective study. Our study's strengths are that it evaluated the clinical, laboratory, and prognostic features of systemic lupus erythematosus (SLE) during childhood among pubertal status and genders - a topic that is rarely touched upon in the literature. This retrospective study provides a comprehensive insight into the clinical and laboratory characteristics, prognosis and survival of paediatric patients with systemic lupus erythematosus (SLE). The analysis focused on gender, pubertal status and renal involvement, shedding light on key patterns and outcomes. The investigation of lupus nephritis types revealed the predominance of type IV, followed by type II, across gender and pubertal categories. Proliferative lupus nephritis emerged as a significant determinant of clinical manifestations, including renal involvement, nephrotic syndrome, proteinuria and neuropsychiatric symptoms. This finding highlights the importance of identifying lupus nephritis subtypes based on renal biopsy in predicting disease severity and associated complications. Significantly, biopsy analysis revealed the emergence of silent lupus nephritis. This hidden condition encompassed occurrences of type I, III, and IV lupus nephritis, as well as a noteworthy incidence of type II lupus nephritis. These latent occurrences highlight the elusive nature of renal effects in systemic lupus erythematosus. Continued attentiveness and careful monitoring are crucial for prompt detection and management of these hidden processes.

### CONCLUSION

Our study has explored the complex realm of pediatric Systemic Lupus Erythematosus (SLE), providing insights into many different aspects of the disease's manifestation, prognosis, and outcomes. The results highlight the significant impact of gender and pubertal state on the progression of SLE, with a higher occurrence in females

and an increase in gender disparity during puberty. The presence of renal involvement, which frequently results in proteinuria, is a characteristic aspect of the condition, necessitating careful monitoring and immediate intervention. In addition, our research underscores the crucial significance of renal biopsy in the diagnosis of lupus nephritis and the classification of its subtypes. Notably, type IV and type II lupus nephritis have been identified as significant factors in the advancement of the disease. The predominance of “silent” lupus nephritis is a noteworthy finding, as it indicates the presence of advanced histological alterations in the absence of clinical symptoms. This discovery underscores the importance of maintaining diligent observation and implementing early management strategies.

Moreover, our study highlights the presence of gender inequalities in the outcomes of systemic lupus erythematosus (SLE), with male patients exhibiting a greater susceptibility to end-stage renal disease and mortality. Although death rates are higher during prepuberty, there is a notable increase in incidence of end-stage renal disease during the pubertal era. The presence of proliferative lupus nephritis has been found to be linked with elevated mortality rates and a greater likelihood of developing end-stage renal disease. Conversely, nonproliferative lupus nephritis has been associated with a higher probability of relapse.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was derived from the thesis on “Evaluation of epidemiological characteristics, clinical and laboratory findings, and prognosis of patients with systemic lupus erythematosus observed between 1990 and 2013: a retrospective study” dated 2014 in Ankara Dr Sami Ulus Pediatrics Training and Research Hospital.

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

## Acknowledgement

We thank all participants and their families for their involvement in our research.

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# Effect of different DMARD use on the frequency of urinary infection in patients with rheumatoid arthritis

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**Cite this article as:** Adar S, Taşgın MR, Dündar Ü, et al. Effect of different DMARD use on the frequency of urinary infection in patients with rheumatoid arthritis. *Anatolian Curr Med J.* 2024;6(1):38-43.

Received: 17.10.2023

Accepted: 08.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** It is known that the susceptibility to infection in general is increased in Rheumatoid Arthritis (RA) patients, but there is not enough information about whether urinary tract infections in particular differ according to different disease-modifying antirheumatic drugs (DMARDs) groups. The aim of this study was to compare the frequency of urinary infection attacks and pathogens in urine cultures of patients with RA treated with different groups of DMARDs.

**Methods:** In this retrospective study, 76 patients using biologic DMARDs (bDMARDs) and 74 patients using conventional synthetic DMARDs (csDMARDs) among patients followed with a diagnosis of RA for at least 5 years who came for regular follow-ups at our department's rheumatic diseases outpatient clinic were included. Patients with known immunodeficiency conditions, use of prednisolone (>7.5 mg), chronic renal failure, and renal pathologies were excluded from the study. The evaluation and follow-up records of the included patients between 01.01.2019 and 31.12.2022 were examined. Patients age, sex, medications, comorbidities, urine biochemistry, and urine culture results were recorded. Patients with pyuria detected by urine biochemistry were considered to have a urinary infection.

**Results:** The mean age of patients in the csDMARD group was  $61.39 \pm 11.41$  (37-87) and the mean age of patients in the bDMARD group was  $58.68 \pm 11.42$  (33-89) ( $p=0.149$ ). The number of urinary infection attacks during the follow-up period was similar in both the groups ( $p=0.090$ ). The positive culture rate was 23.21% in the bDMARD group and 7.5% in the csDMARD group ( $p=0.072$ ). *Escherichia coli* was detected in 81.8% and *Pseudomonas aeruginosa* was detected in 18.2% of the positive cultures in the bDMARD group. The pathogen in all positive cultures of the csDMARD group was *Escherichia coli*.

**Conclusion:** Although urinary infection and positive culture rates were higher in patients receiving bDMARDs, no statistically significant difference was observed between the groups.

**Keywords:** Rheumatoid arthritis, urinary tract infections, DMARD

## INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic autoimmune disease characterized by autoantibody production and chronic synovial inflammation.<sup>1</sup> Patients with RA have an increased risk of infection compared to the general population.<sup>2</sup> These infections are considered to be the main cause of morbidity and mortality in RA.<sup>3</sup>

As soon as patients are diagnosed with RA, disease-modifying antirheumatic drugs (DMARDs) should be started.<sup>4</sup> DMARDs are medications used to induce remission by suppressing autoimmune activity and slowing or preventing joint degeneration. These drugs are categorized as conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs).<sup>5</sup> Methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine are

examples of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) that constitute a diverse class of medications. They are typically recommended as the initial treatment for individuals with RA.<sup>4,5</sup> If the initial treatment is either intolerable or ineffective, the recommendation shifts towards biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs).<sup>5</sup> bDMARDs target key components of the host immune defense system, such as tumor necrosis factor- $\alpha$  (etanercept, infliximab, golimumab, adalimumab, and certolizumab pegol), Interleukin-1, Interleukin-6 (tocilizumab) B cells (rituximab), and T cells, explaining the increased susceptibility of patients to certain types of infections.<sup>6</sup> Glucocorticoids (GCs) can be used as a bridge therapy in the treatment of RA until the effects of DMARDs begin or

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as adjunctive therapy for active RA that persists despite the use of DMARDs.<sup>5</sup>

There is an increased risk of infection compared with csDMARDs due to the immunosuppressive nature of bDMARDs.<sup>6</sup> Respiratory, soft tissue, and urinary systems were the most frequent sites of infection.<sup>7</sup> A cohort study by Cipriani et al.<sup>9</sup> included 731 patients using bDMARDs for rheumatic disease, and the most common site of non-serious infection was the urinary tract.<sup>8</sup> Urinary tract infections, which affect 150 million people worldwide each year, are among the most common bacterial infections.<sup>9</sup> The presence of clinical findings and an inflammatory response in the urinary system due to a pathogenic bacterium is defined as a urinary tract infection. Urinary system infections can present with very different clinical presentations, ranging from acute cystitis to acute complicated pyelonephritis.<sup>10</sup>

Although it is known that susceptibility to infection is generally increased in patients with RA, there is not enough information about whether urinary tract infections in particular vary according to the DMARD group used. Based on the hypothesis that bDMARDs increase the risk of infection, this study aimed to examine the frequency of urinary infections and causative pathogens in patients diagnosed with RA based on the drugs used.

## METHODS

This study was approved by the Afyonkarahisar Health Sciences University (AFSU) Faculty of Medicine Clinical Researches Ethics Committee (Date: 07.04.2023, Decision No: 2023/164). In addition, prior to the study, permission to use the data was obtained from the Chief Physician of the Faculty of Medicine Health Application and Research Center (Hospital). Because the study was designed retrospectively, no written informed consent form was obtained from patients. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Patients who were followed up for at least 5 years at the Rheumatic Diseases Polyclinic of Afyonkarahisar Health Sciences University Faculty of Medicine Hospital, with a diagnosis of RA and using bDMARDs were evaluated. Patients with known immunodeficiency conditions, use of prednisolone (>7.5 mg), chronic renal failure, and renal pathologies were excluded from the study. 76 patients using bDMARDs and met the inclusion criteria were enrolled in this study. The control group included 74 patients using csDMARDs and meeting the inclusion criteria. The evaluation and follow-up records of the included patients between 01.01.2019 and 31.12.2022 were examined. Patients age, sex, medications, comorbidities, urine biochemistry, and urine culture

results were recorded. Patients with pyuria detected by urine biochemistry were considered to have a urinary infection.<sup>10</sup>

## Statistical Analysis

SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Descriptive statistics were used to summarize the data, with n representing the number of units, % indicating the percentage, and median (minimum–maximum) values reported. Chi-Square test was used to compare categorical variables. The t-test was used to compare the means of two independent groups with normally distributed data, whereas the Mann–Whitney U test was used to compare the medians of two independent groups with non-normally distributed data. The statistical significance level was set at  $p < 0.05$ .

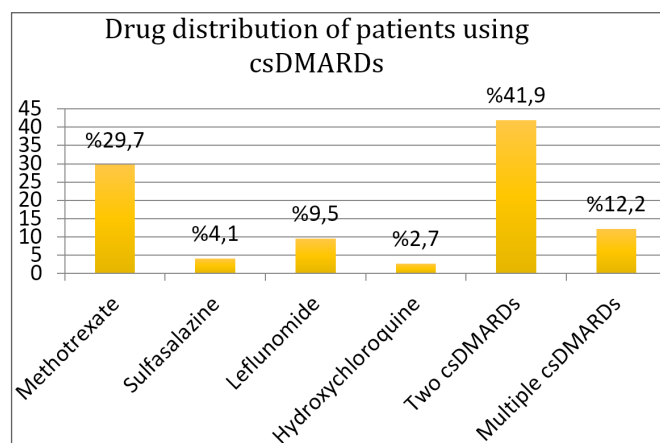
## RESULTS

The mean age of patients in the csDMARD group was  $61.39 \pm 11.41$  (37-87) and the mean age of patients in the bDMARD group was  $58.68 \pm 11.42$  (33-89). Groups were similar in terms of age ( $p = 0.149$ ). The mean duration of biological agent use in patients using bDMARDs was  $3.76 \pm 2.25$  (1-9) years. Other demographic and clinical data of the patients are shown in **Table 1**. The distribution of drugs used by the groups is shown in **Figures 1 and 2**.

**Table 1. Demographic and clinical characteristics of the groups**

	csDMARD group (n=74) % (n)	bDMARD group (n=76) % (n)	p*
Gender Female/Male	74.3 (55)/25.2 (19)	71.1(54)/28.9(22)	0.653
Presence of comorbidity	59.5(44)	51.3(39)	0.316
GC use	66.2 (49)	15.8 (12)	<0.001

csDMARD conventional synthetic disease-modifying antirheumatic drugs, bDMARD biological disease-modifying antirheumatic drugs, GC Glucocorticoid, \* Comparisons between groups chi square test



**Figure 1.** Drug distribution of patients using csDMARDs

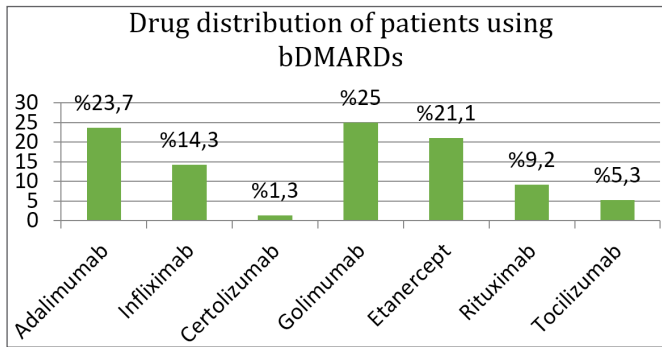


Figure 2. Drug distribution of patients using bDMARDs

Although a history of malignancy was more common in the csDMARD group (p=0.011), the groups were similar in terms of other comorbidities (p>0.05). The distribution of comorbidities in each group is shown in Figure 3.

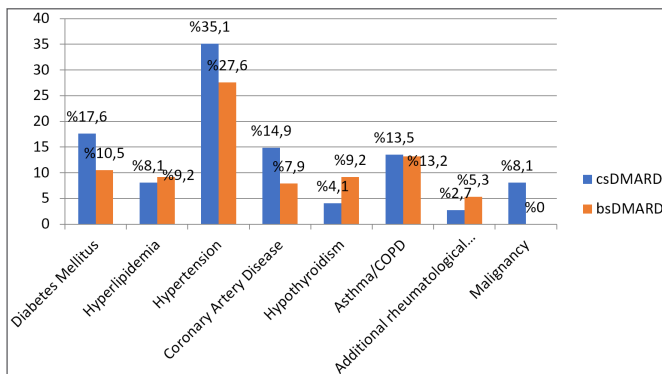


Figure 3. Comorbidities of the groups

Urine biochemistry analysis was performed at each admission during follow-up. The number of urine biochemistries analyzed in the 4-year follow-up in the csDMARD group was 6.96±4.53, while it was 8.97±8.18 in the bDMARD group (p=0,356). The number of urinary infection attacks during the follow-up period was similar (p = 0.090) (Table 2).

	csDMARD group (n=74)	bDMARD group (n=76)	P
Number of urinary infection attacks	1.50±2.16	2.42±4.15	0.090*
Mean±SD (min-max)	(0-9)	(0-22)	
Positive culture rate (%)	7.5	23.21	0.072**

csDMARD conventional synthetic disease-modifying antirheumatic drugs, bDMARD biological disease-modifying antirheumatic drugs, SD standard deviation, min-max minimum-maximum, \*\* Comparisons between groups independent samples t-test, \*\* Comparisons between groups independent samples Mann Whitney U test.

The number of urine cultures examined during the 4-year follow-up in the csDMARD group was 0.56±0.87, while it was 0.67±1.18 in the bDMARD group (p=0,891). The positive culture rate was 23.21% in the bDMARD group and 7.5% in the csDMARD group (p = 0.072) (Table 2).

*Escherichia coli* (*E. coli*) was detected in 81.8% and *Pseudomonas aeruginosa* was detected in 18.2% of the

positive cultures in the bDMARD group. The pathogen in all positive cultures of the csDMARD group was *E. coli*.

## DISCUSSION

In this study, the number of urinary infection attacks in patients treated with biological agents was compared with that in patients receiving csDMARDs during a 4-year follow-up period. Although urinary infection and positive culture rates were higher in patients taking bDMARDs, the difference was not statistically significant.

Urinary infections are the second most common infections in RA after respiratory tract infections, as in all systemic autoimmune diseases.<sup>11,12</sup> Patients with autoimmune disorders are at significant risk for serious infections. This heightened vulnerability stems from alterations in immune function resulting from the underlying disease, which can compromise both the cellular and humoral immune responses. Additionally, the impact of immunosuppressive therapies employed to manage disease activity further contributes to increased susceptibility to infections.<sup>13</sup>

Patients with rheumatoid arthritis (RA) have an increased risk of infections due to factors such as older age, extra-articular disease, high disease activity, presence of chronic obstructive pulmonary disease, interstitial lung disease, chronic kidney disease, lymphopenia, use of glucocorticoids (GC), and utilization of disease-modifying antirheumatic drugs (DMARDs).<sup>11</sup> In their cohort study by Cipriani et al.<sup>8</sup> 731 patients were examined using bDMARD for rheumatic disease, and disease duration, longer follow-up period, concurrent steroid treatment, and comorbidities were found to be significantly associated with non-serious infection.<sup>8</sup> In our study, risk factors such as follow-up periods and comorbidities of patients using bDMARDs and csDMARDs were similar; however, the rate of GC use was higher in the csDMARD group. This may have affected the results of our study and acted as an additional risk factor for patients using csDMARDs. Sharma et al.<sup>14</sup> reported that age and the duration of bDMARD use were significant factors associated with an increased risk of serious infections.<sup>14</sup>

The most commonly used bDMARDs are TNF-α inhibitors. TNF-α plays an important role in the pathogenesis of RA.<sup>15</sup> These drugs are used to treat RA, especially in patients whose disease does not respond to treatment with csDMARDs.<sup>16</sup> The prognosis of patients with RA has significantly improved with the use of TNF-α inhibitors, but these drugs, which target key molecules involved in the immune response to infectious agents, may also increase susceptibility to viruses and bacteria and cause adverse effects.<sup>17</sup>

In a review examining the infection profile in patients taking biologic drugs, lower respiratory tract, ear/nose/throat, and urinary infections were found to be moderately common and were particularly clustered in patients taking TNF $\alpha$  inhibitors.<sup>18</sup> Similar infection risks have been shown to exist with non-TNF $\alpha$  inhibitor bDMARDs such as rituximab and tocilizumab.<sup>18</sup> In a study by Quach et al.<sup>19</sup> infections occurred less frequently in patients receiving hydroxychloroquine in addition to sulfasalazine and methotrexate treatment than in patients receiving etanercept + methotrexate.<sup>19</sup> Analysis of real-world and clinical trial data from patients with RA has shown an increased risk of serious and non-serious infections in patients taking bDMARDs compared with csDMARDs.<sup>20</sup> In fact, etanercept, a TNF- $\alpha$  inhibitor, has been reported to have a lower risk of infection than other TNF- $\alpha$  inhibitor agents and the Janus kinase (JAK) inhibitor tofacitinib from the tsDMARD group.<sup>20</sup> Similarly, in a study by Yun et al.<sup>21</sup> among rheumatoid arthritis patients who had an infection in the hospital during TNF- $\alpha$  inhibitor treatment, abatacept and etanercept had the lowest risk of subsequent infection compared to other biologic treatments.<sup>21</sup>

In a prospective observational cohort study conducted by the British Society of Rheumatology Biological Rheumatoid Arthritis Register, several factors were associated with an increased risk of infection. These included advancing age, female gender, higher comorbidity burden, the use of glucocorticoid therapy, elevated Disease Activity Score in 28 joints, and a higher Health Assessment Questionnaire disability index. Notably, the study revealed a significant decrease in the risk of infection with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) compared to biological treatments. Within the biological treatment category, the study identified variations in infection risk. Tocilizumab and rituximab were associated with a higher risk of infection, while the csDMARD cohort showed a lower risk. Among the TNF- $\alpha$  inhibitors, adalimumab was linked to a higher risk of infection than etanercept. This information provides valuable insights into the factors influencing infection risk in patients with rheumatoid arthritis, helping to guide treatment decisions and patient management strategies.<sup>22</sup> Several recent studies have shown that the risk of infection differs between the top three TNF- $\alpha$  inhibitor agents: infliximab increases the risk compared with etanercept or adalimumab.<sup>23</sup> Based on these results, the fact that the majority of our patients were using golimumab, adalimumab, and etanercept may explain the lack of an increased risk compared with csDMARDs.

A meta-analysis of randomized controlled trials examining rituximab did not show a significant increase in the risk of infection. Similarly, in a separate meta-analysis that focused on tofacitinib, there was no elevated risk of infection associated with its use.<sup>23</sup>

Although there are studies in the literature showing that bDMARDs increase the risk of infection, some studies have shown that some biologics do not increase the risk. According to the results of this study, despite the small sample size, we can infer that bDMARDs do not significantly increase the risk of urinary infection compared with csDMARDs. The heterogeneity of the bDMARD molecules used in our patients may have affected our results. In addition, the higher GC use rates in our csDMARD group may explain why urinary infection rates in patients using csDMARDs were similar to those in patients using bDMARDs. Glucocorticoids have the potential to hinder phagocyte function and suppress cell-mediated immunity, thereby contributing to increased susceptibility to infections. A meta-analysis based on randomized clinical trials and observational studies showed an increased relative risk in patients with RA with a positive dose-response effect in GC users.<sup>23</sup> Although the use of csDMARDs seems to be more innocent in terms of infection compared to bDMARDs, it should be taken into consideration that GC use is more common in patients using csDMARDs, and caution should be taken in terms of urinary infections in patients using csDMARDs.

Urinary infections can be caused by both Gram-negative and Gram-positive bacteria as well as by some fungal agents. The most common cause of both uncomplicated and complicated urinary infections is uropathogenic *Escherichia coli*.<sup>24</sup> In addition, *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida* species may be the causative agents.<sup>9</sup> Eighty percent of tract infections in healthy women aged 18-39 are caused by *Escherichia coli*.<sup>21</sup> In a Spanish registry study, the National Drug Safety Registry of Patients with Rheumatic Diseases reported that cystitis was mainly caused by *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.<sup>25</sup> Similar to previous studies, the most common agent in our study was *Escherichia coli*.

### Limitations

Since our study was retrospective, other risk factors such as duration of bDMARD use, antimicrobial use, and hospitalization history were not investigated, and disease activities were not examined. In addition, the small sample size is another limitation because this was a single-center study.



## CONCLUSION

The findings of this study indicate that the incidence of urinary tract infections among patients receiving bDMARDs was similar to that of patients receiving csDMARDs over a four-year observation period. It is imperative to exercise caution regarding the potential for urinary tract infections when utilizing bDMARDs, as evidenced by the current body of literature. In addition, it is essential to closely monitor patients who are on csDMARDs for any signs of urinary tract infections, particularly when they are using additional GC.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This study was approved by the Afyonkarahisar Health Sciences University (AFSU) Faculty of Medicine Clinical Researches Ethics Committee (Date: 07.04.2023, Decision No: 2023/164). In addition, prior to the study, permission to use the data was obtained from the Chief Physician of the Faculty of Medicine Health Application and Research Center (Hospital).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Retrospective analysis of polyps detected in colonoscopy and investigation of the relationship with anemia

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**Cite this article as:** Güven İE, Doğan İ. Retrospective analysis of polyps detected in colonoscopy and investigation of the relationship with anemia. *Anatolian Curr Med J.* 2024;6(1):44-47.

Received: 10.10.2023

Accepted: 10.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** Patients with colonic polyps are generally asymptomatic. On the other hand, colon polyps are considered as colorectal cancer progenitors. In this study, we aimed to present the retrospective analysis of colon polyps detected in a gastroenterology unit within one year and the relationship between polyp features and anemia.

**Methods:** Patients with colon polyps who applied to our center between January 2015- January 2016 and underwent colonoscopy were included in the study. Polyps were grouped and compared as 1,2,3 and  $\geq 4$  according to their number; as hyperplastic, tubular, tubulovillous and villous according to their histopathological type; as  $\leq 6$  mm, 7-10 mm and  $\geq 11$  mm according to their size; as proximal, distal and proximal+distal according to their location.

**Results:** A total of 350 patients were recruited for the study, The median age of the study group was 60 years (54-65 years), of which 180 (51.4%) were male. The mean hemoglobin value was  $12.82 \pm 1.90$  g/dl. More than half of the patients (n=166, 52.5%) had single polyp. The most common type of polyp was tubular polyp (n=203, 55%). The majority of the polyps (63%) were smaller than 6 mm in size and the vast majority (47.2%) were located distally. When the polyp size and polyp types were compared, it was found that the incidence of tubulovillous pathology increased as the polyp size increased (p<0.001 for all comparisons). A positive, linear significant correlation was found between age and the number of polyps (r=0.209; p<0.001). There was a statistically significant difference between hemoglobin value according to polyp sizes (p<0.001).

**Conclusion:** We demonstrated that the number of polyps increased with age, and the incidence of tubulovillous pathology and the depth of anemia increased as the size of the polyp increased.

**Keywords:** Colon polyp, polypectomy, hemoglobin, colonoscopy

## INTRODUCTION

Colorectal polyps are lesions which develop secondary to the protrusion of the colorectal mucosal tissue into the lumen.<sup>1</sup> In clinical practice colon polyps don't cause any symptoms unless they reach large sizes and have an asymptomatic course.<sup>2</sup> However, although rare, depending on size, distributional and histopathological features, they can be associated with symptoms such as bleeding, intestinal obstruction and abdominal pain.<sup>3</sup>

Although colon polyps are generally asymptomatic, they can be precursor lesions for the development of colorectal cancer thus, several guidelines highlight the importance of colonoscopy for colorectal cancer screening.<sup>4,5</sup> Offered data showed that early detection and removal of colon polyps can significantly reduce the rate of colorectal cancer and related deaths.<sup>6</sup> In order to ensure successful

management of colon polyps' evaluation of the polyp characteristics is crucial.<sup>4</sup>

In the presented study, the aim is to analyze the colorectal polyps features detected by the colonoscopic examination in our gastroenterology unit retrospectively and evaluate the relationship between the polyp features and anemia.

## METHODS

The presented study was designed as a retrospective study conducted in gastroenterology department of Gazi University Faculty of Medicine. Approval for the study was obtained from the Ethical Committee of Gazi University Faculty of Medicine (Date: 08.02.2016, Decision No: 82). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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All eligible consecutive patients aged between 45 and 70 years who applied to our center between January 2015- January 2016 and underwent colonoscopy were retrospectively analyzed. Patients with polyps detected during colonoscopy procedure and underwent polypectomy and those with polypectomy material evaluated by the pathology department were enrolled for the study. Exclusion criteria encompassed the following: active malignancy, hematological diseases, inflammatory bowel disease and history of bowel surgery. Patients with inadequate colon preparation were also excluded since suboptimal colonoscopic examination may affect the polyp detection rate. The Boston bowel preparation scale was used in the assessment of the bowel preparation, and cases with segments score 3 were accepted as adequate bowel preparation.

Patients demographic data, hemoglobin levels and histopathological findings, sizes, numbers, and locations of the detected polyps were obtained from hospital records. Polyps were divided in sub-groups in order to compare on the basis of their number (as 1,2,3, and ≥4), histopathological type (as hyperplastic, tubular, villous and tubulovillous), size (as ≤ 6 mm, 7-10 mm, and ≥11 mm) and localization (as proximal, distal and proximal+distal). Polyps located in the splenic flexure, descending colon, sigmoid colon, and rectum were classified as distal.

**Statistical Analysis**

Statistical analysis was done by using the SPSS version 17 for Windows (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was assessed via the Kolmogorov-Smirnov test. Age was distributed non-normally so was given as median (interquartile range) and hemoglobin value was distributed normally and was given as mean±standard deviation. Categorical variables were given as frequency and percentages. The comparisons were done via the Chi-Square test for categorical variables, via the Oneway ANOVA test for hemoglobin value. Spearman correlation analyses were done to determine the relationship between age and the number of polyps and hemoglobin value. A p-value<0.05 was accepted as significant.

**RESULTS**

**Table 1** shows the characteristics of the patients. Three hundred and fifty patients were included in the study. The median age of the study group was 60 (54-65) years. More than fifty percent of the study group was male (n=180, 51.4 %). The mean hemoglobin value was 12.82±1.90 g/dl. A single polyp was detected in 166 (52.5%) patients. Tubular adenomatous polyp (n=203, 55%) was the most common polyp type, in addition most of the polyps (63%) were smaller than 6 mm in size. The polyps were located mostly distally (47.2%).

	<b>Whole study group (n=350)</b>
Age, years, median (interquartile range)	60 (54-65)
Gender, male, n (%)	180 (51.4%)
Hemoglobin (g/dL), mean±SD	12.82±1.90
Number of polyps, n (%)	
1	166 (52.5%)
2	94 (29.8%)
3	35 (11%)
≥4	21 (6.7%)
Polyp type, n (%)	
Hyperplastic	101 (27.4%)
Tubular	203 (55%)
Tubulovillous	50 (13.5%)
Villous	15 (4.1%)
Polyp size, n (%)	
≤6 mm	230 (63%)
7-10 mm	102 (28%)
≥11 mm	33 (9%)
Polyp localization, n (%)	
Proximal	95 (30%)
Distal	149 (47.2%)
Proximal+distal	72 (22.8%)

SD: Standard deviation

The comparisons of the relationship between the pathological sub-groups and polyp size revealed no statistically significant difference, except for tubulovillous pathology. In **Table 2** the comparisons between tubulovillous pathology and polyp size were given. A statistically significant relationship between polyp size and the presence of tubulovillous pathology was found (p=0.004), as polyp size increased, the incidence of tubulovillous pathology also increased (p<0.001 for all comparisons).

	<b>Polyp size</b>			<b>Total</b>	<b>p (total)</b>	<b>p (1-2)</b>	<b>p (1-3)</b>	<b>p (2-3)</b>
	<b>≤6 mm, n (%) (1)</b>	<b>7-10 mm, n (%) (2)</b>	<b>≥ 11 mm, n (%) (3)</b>					
Tubulovillous pathology					0.004	<0.001	<0.001	<0.001
No	181 (93.30)	71 (78.90)	15 (45.50)	267 (84.20)				
Yes	13 (6.70)	19 (21.10)	18 (54.50)	50 (15.80)				
<b>Total</b>	<b>194</b>	<b>90</b>	<b>33</b>	<b>317</b>				

**Table 3** summarizes the correlation analyses between age and the number of polyps, and a significant positive linear correlation was found between age and the number of polyps ( $r=0.209$ ;  $p<0.001$ ). **Table 4** provides the comparisons of the relationship between hemoglobin value and polyp size. There was a statistically significant difference in hemoglobin value according to polyp size ( $p<0.001$ ), as polyp size increased, statistically significant lower hemoglobin values were found ( $p<0.05$  for all comparisons).

	Number of polyps	Hemoglobin value
Age, years	$r=0.209$ ( $p<0.001$ )	$r=-0.006$ ( $p=0.922$ )

Polyp size	n	Hemoglobin mean±standard deviation	P (total)	P (1-2)	P (1-3)	P (2-3)
≤6 mm (1)	194	13.33±1.51				
7-10 mm (2)	90	12.79±1.81	<0.001	0.025	<0.001	<0.001
≥11 mm (3)	33	9.94±1.63				

## DISCUSSION

In this retrospective study, we found that tubular adenomatous polyp was the most detected histopathological subtype, most of the polyps were less than 6mm in size and located distally. In addition, a relationship was found between the presence of tubulovillous pathology and polyp size. Moreover, a positive linear significant correlation was demonstrated between the number of polyps and age. Notably, we have demonstrated that an increase in the polyp size is associated with lower hemoglobin values.

Colorectal cancers are the third most common cancer type in the world and take the second place in cancer-related deaths worldwide.<sup>7</sup> The high mortality rates of colorectal cancer highlight the importance of early diagnosis.<sup>8-10</sup> The majority of guidelines recommend screening with a colonoscopic examination after the age of 45 for the early diagnosis of colorectal cancer.<sup>11,12</sup> Since adenomatous polyps are associated with the risk of transformation into malignancy, it is recommended to remove colorectal polyps detected during screening.<sup>7,13,14</sup> According to the literature, the majority of colon polyps are located on the left side of the colon and smaller than 6 mm.<sup>15</sup> Our findings are consistent with the literature as we also found that the distal colon was the most common localization for the polyps and the majority were smaller than 6 mm. This finding draws attention to the fact that smaller polyps are difficult to detect during colonoscopy compared to larger polyps and may be easily missed. In addition, inadequate bowel preparation makes it more difficult to detect these types of polyps. Therefore, the

clinician should perform the examination carefully, being aware that the majority of polyps are smaller than 6mm, and pay attention to colon cleansing.

Another important finding of this study is that increased frequency of villous pathology was associated with increased polyp size. Tubulovillous adenomatous polyp, which are included under the title of adenomatous polyp, have a higher malignancy potential than tubular polyps.<sup>16,17</sup> Our findings highlight the importance of performing optimal resection of large-sized polyps, close follow-up of the pathology result, and additional resection if needed, since their higher malignant potential.

Several studies demonstrated that the incidence and number of polyps increase with age.<sup>14,18</sup> We also have demonstrated a positive linear correlation between age and the number of polyps. Considering their malignancy potential, colonoscopic screening of the geriatric population is becoming more important and prioritized and many guidelines emphasize the importance of screening this population, since the incidence of colorectal cancer increases with age.

Notably, we found statistically significant lower hemoglobin values as the polyp size increased. Although polyps are generally considered asymptomatic, it has been shown that, they can be associated with iron deficiency anemia.<sup>19-21</sup> However, based on these findings alone, it cannot be concluded that polyps may be associated with anemia. Thus, further prospective studies are needed to support this theory.

The major limitation of the current study was its retrospective design. Due to the nature of the study, the patients were not followed up. In addition, it was a single-centered study and had a relatively small sample size.

## CONCLUSION

We demonstrated that the number of polyps detected during colonoscopy increased with age. In addition, we found that the increase in the size of the polyp is associated with the frequency of tubulovillous pathological subgroup and the depth of anemia. Diagnosis and removal of colon polyps has a significant impact on reducing the incidence and mortality of colorectal cancer, and these findings highlight the importance of colonoscopic screening, especially in older ages and patients with anemia.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ethical Committee of Gazi University Faculty of Medicine (Date: 08.02.2016, Decision No: 82).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Pan-immune inflammation value as a biomarker in ankylosing spondylitis and associated with disease activity

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**Cite this article as:** Şen Uzeli Ü, Başaran PÖ. Pan-immune inflammation value as a biomarker in ankylosing spondylitis and associated with disease activity. *Anatolian Curr Med J.* 2024;6(1):48-54.

Received: 17.11.2023

Accepted: 10.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** Ankylosing spondylitis (AS) is the most common and characteristic form of Spondyloarthritis. The pan-immune inflammation value (PIV) is a marker obtained from complete blood count parameters, which has been used as an inflammatory and immune marker. In this study, we aimed to investigate the relationship between inflammation and disease activity in patients with AS and PIV.

**Methods:** In this prospective controlled study a total of 208 participants were included, consisting of 104 AS patients and 104 healthy controls. Complete blood count values, including neutrophils, monocytes, lymphocytes, platelets, and also C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were measured in all participants. In AS group disease activity was assessed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The AS group was divided into two subgroups based on BASDAI score: low disease activity (BASDAI score <4) and high disease activity (BASDAI score ≥4). The pan-immune inflammation value of patients and the control group was calculated as neutrophil count × monocyte count × platelet count/lymphocyte count. Comparative analysis was performed between the two groups, and these values were also compared based on the BASDAI.

**Results:** The AS group exhibited statistically higher values of CRP, monocytes, and PIV compared to the control group ( $p < 0.001$  for all). Patients with  $BASDAI \geq 4$  had a statistically lower disease duration ( $p < 0.001$ ) and lymphocyte count ( $p: 0.012$ ) compared to those with  $BASDAI < 4$ . Patients with  $BASDAI \geq 4$  had statistically higher values of CRP, ESR, neutrophils, platelets, and PIV compared to those with  $BASDAI < 4$  ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p: 0.008$ ,  $p < 0.001$  respectively). Strong positive correlation was found between PIV and BASDAI ( $\rho = 0.790$ ;  $p < 0.001$ ), moderate positive correlation with PIV and CRP ( $\rho = 0.467$ ;  $p < 0.001$ ) and also positive correlation was found between PIV and ESR ( $\rho = 0.326$ ;  $p < 0.001$ ). The specificity and sensitivity of PIV using a cutoff value of  $> 309,2$  were 80.0% and 86.0% respectively, for the active group.

**Conclusion:** Since the parameters comprising PIV are obtained from a complete blood count, it provides an advantage for its use as a simple and cost-effective marker in ankylosing spondylitis patients. In our study, we demonstrated that PIV is sensitive and specific in differentiating disease activity in patients with ankylosing spondylitis from healthy individuals and associated with disease activity.

**Keywords:** Ankylosing spondylitis, pan-immune-inflammation value, disease activity

## INTRODUCTION

Ankylosing spondylitis (AS) is the most common and characteristic form of Spondyloarthritis (SpA). AS is a common inflammatory disease that primarily affects the axial skeleton, sacroiliac joints and paraspinal soft tissues. It can also manifest with extra-articular symptoms such as anterior uveitis, inflammatory bowel disease, aortic valve disease, and osteoporosis, as well as peripheral joint involvement.<sup>1,2</sup>

While the exact pathogenesis of AS remains unclear, it is known that an inflammatory process initiated by certain environmental factors in individuals with genetic predisposition. Not only human leukocyte antigen B-27 (HLA B-27) but also the other HLA alleles like

HLA-B\*47:01, HLA-B\*51:01 plays an important role in the disease. The IL-23-IL-17 pathway plays a major role in the pathophysiology of ankylosing spondylitis. Under the influence of IL-6 and TGF- $\beta$ , which enhance IL-23R presentation on Th17 cells, CD4+ T cells transform into IL-17-producing Th17 cells, initiating a response to infections.<sup>3</sup>

It is important to diagnose the disease to prevent major complications and for early treatment. AS usually shows itself with chronic inflammatory lower back pain at the third decade of life. Along with clinical findings, a positive family history, and partially supportive laboratory tests accompanies.<sup>4</sup> Inflammatory lower back pain and morning stiffness are common symptoms of AS, which

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lead to activity limitation and increased pain during the active phase of the disease. Therefore, assessing disease activity in AS is crucial for better understanding the pathophysiology of AS and predicting disease prognosis. There is no specific laboratory test that can diagnose AS. Although acute phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been used at rheumatic diseases<sup>5</sup> CRP has been used as a useful parameter in the follow-up of the progression of the disease. In some studies, it has been found that an increase in CRP levels is associated with radiological progression.<sup>6</sup> At the same time, CRP has also been a useful parameter in making treatment decisions and monitoring the response to treatment. A decrease in CRP levels in patients undergoing Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) blocking therapy may indicate that the response is better.<sup>7</sup> However, they are not high in all patients and do not always show disease activity. At the same time, their use is limited due to their increase in other infectious and inflammatory diseases and their more pronounced increase in peripheral involvement compared to axial involvement. Recently, hemogram parameters have been investigated as a marker of inflammation in the follow-up of various inflammatory diseases. Such as lymphocyte monocyte ratio,<sup>8</sup> monocyte hdl ratio,<sup>9</sup> systemic immune inflammation index.<sup>10</sup> PIV is one of these markers. Unlike SII, monocytes, which are natural cells of the immune system, also participate in the calculation of PIV therefore we think that it will be more effective in showing disease activity. Imaging methods are of great importance in the diagnosis and classification of AS.<sup>11,12</sup>

The pan-immune inflammation value (PIV) is a marker calculated from complete blood count parameters and is used to assess the severity of inflammation. It is confirmed that PIV will be used to evaluate the prognosis in various oncological diseases.<sup>13</sup> It has been shown to be associated with clinical outcomes and lymphocytes infiltrating tumors in esophageal cancer.<sup>14</sup> Furthermore, PIV has been reported as a promising predictor of long-term outcomes in colorectal cancer patients.<sup>15</sup> In another study, it was shown to have prognostic potential in breast cancer patients treated with neoadjuvant chemotherapy.<sup>16</sup> In a different study evaluating the relationship between survival and PIV in operated breast cancer patients, PIV was found to be significant in predicting survival.<sup>17</sup>

Different outcome measures have been developed to evaluate the disease activity in patients with AS. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was the first of these measures and is a six-question scale that assesses fatigue, axial involvement, peripheral joint involvement, enthesopathy, and morning stiffness. The scale is a visual analog scale with response

options being “none” scored as 0 to “very severe,” scored as 10. According to the Assessment in SpondyloArthritis international Society (ASAS) criteria of the international spondyloarthritis assessment group, those with BASDAI $\geq$ 4 and above are considered active disease.<sup>18-20</sup>

In our study, we aimed to investigate the relationship between inflammation and disease activity in patients with AS and PIV

## METHODS

This study was approved by Hitit University Clinical Researches Ethics Committee (Date: 03.10.2023 Decision No: 2023-130), and all protocols involving human subjects were conducted in strict accordance with ethical guidelines outlined by the institutional and/or national research governing body, the 1964 Declaration of Helsinki, and its subsequent revisions or analogous ethical criteria.

A total of 208 participants, including 104 ankylosing spondylitis patients and 104 healthy individuals, were included in our prospective controlled study. Patients with acute infections, diabetes, a history of malignancy, those using medications that could alter hemogram parameters, and those whose ankylosing spondylitis treatment had changed in the last three months were excluded. Healthy participants were selected from individuals who attended routine check-up and did not have acute or chronic infections, a history of malignancy, a history of medication use affecting hemogram parameters, acquired immunodeficiency, or pregnancy. Demographic data was recorded. Laboratory results of patients with AS and healthy individuals were examined. Hemogram parameters including neutrophils ( $10^9/L$ ), monocytes ( $10^9/L$ ), lymphocytes ( $10^9/L$ ), platelets ( $10^9/L$ ), and also CRP (mg/L) and ESR (mm/h) levels were recorded. The pan-immune inflammatory index of patients and the control group was calculated as neutrophil count  $\times$  monocyte count  $\times$  platelet count/lymphocyte count. In AS group disease activity was assessed with BASDAI. It is a patient reported disease activity index. Higher scores indicates the severe disease. The patient group was divided into two subgroups according to the BASDAI scores. Low activity group (BASDAI score  $<$ 4) and high activity group (BASDAI score  $\geq$ 4). Comparative analysis was performed between AS and control group and also for the low activity and high activity groups.

Using the G\*Power program for sampling calculation, Kayhan et al.<sup>21</sup> calculated with the reference work of. The total number of samples was calculated with the parameters Effect size =0.51,  $\alpha$  error probability =0.05, Power (1- $\beta$  error probability) =0.95 and number of groups =2 (case/control ratio =1). According to the



results obtained, the total number of samples is 208. To calculate the minimum number of samples per group, the total number of samples was divided by the number of groups. According to this calculation, a minimum of 104 people per group will be included in the study.

**Statistical Analysis**

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as the number of units (n), percentages (%), means ± standard deviations, medians, and interquartile ranges. The normal distribution of data for numerical variables was assessed using the Shapiro-Wilk normality test. Variance homogeneity of groups was analyzed using the Levene test. The distribution of groups by gender was evaluated using the chi-square test. For numerical variables, two-group comparisons were conducted with independent samples t-tests if the data showed a normal distribution, and with Mann-Whitney U tests if the data did not exhibit a normal distribution. PIV values for control, BASDAI <4, and BASDAI ≥4 patients were compared using the Kruskal-Wallis H test. Post hoc comparisons were conducted using the Dunn-Bonferroni test. The relationship between BASDAI and the pan-immune-inflammation index was evaluated through Spearman correlation analysis.<sup>22</sup> The potential of the pan-immune-inflammation index to serve as a biomarker in AS groups was assessed using receiver operating characteristic (ROC) Curve analysis. A p-value of <0.05 was considered statistically significant.

**RESULTS**

In this study 102 patients with AS and 102 healthy controls were evaluated. The demographic and blood parameters are presented in **Table 1**. Groups are similar in age (p:0,109) and sex. The CRP, monocyte, and PIV values are statistically higher in AS group (p<0.001, p<0.001, p<0.001 respectively). There are no statistically significant differences in the other variable values between the groups.

When patients with AS divided into two subgroups according to BASDAI there is no statistically significant difference in age and sex between low activity group and high activity group. The disease duration and lymphocyte counts of patients in the BASDAI ≥ 4 group are statistically lower. The CRP, ESR, hemoglobin, neutrophil, platelet, and PIV values of patients in the BASDAI ≥ 4 group are statistically higher (p<0.001, p<0.001, p:0.028, p<0.001, p:0.008, p<0.001 respectively) (**Table 2**).

According to the correlation analysis between BASDAI and the PIV, a statistically significant strong positive correlation was found between the two variables (rho=0.790; p<0.001) (**Figure 1**)

**Table 1: Demographic and Laboratory findings of groups**

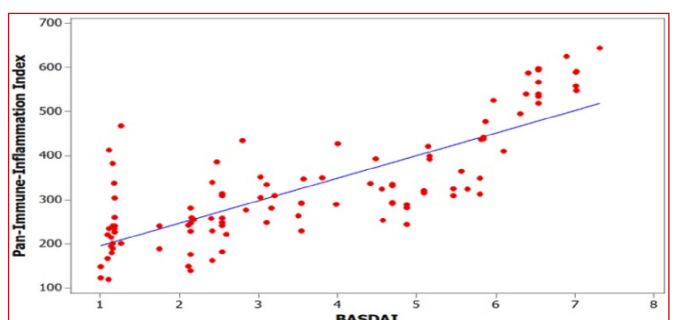
	Groups		Test statistics	
	AS n=104	control n=104	Test value	p value
Age, (year)	42.2±10.4	44.5±10.5	1.611	0.109†
Sex, n (%)				
Male	59 (56.7)	59 (56.7)	-	-
Female	45 (43.3)	45 (43.3)		
CRP	6.70 (13.04)	3.22 (0.89)	3.783	<0.001&
ESR	12.0 (16.0)	9.0 (11.8)	1.837	0.066&
Hemoglobin	13.85±1.65	14.10±1.63	1.097	0.274†
Neutrophil	4.55±1.18	4.26±1.41	1.593	0.113†
Monocyte	0.60±0.11	0.48±0.16	6.630	<0.001†
Lenfocyte	2.34±0.61	2.40±0.67	0.754	0.452†
Neutrophil (%)	57.12±9.01	54.40±8.44	1.840	0.068†
Lenfocyte (%)	31.51±8.11	34.38±8.06	2.094	0.038†
Platelet	273.5 (79.0)	262.5 (98.5)	1.205	0.228&
PIV	306.6 (127.6)	195.8 (180.4)	5.633	<0.001&

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PIV: Pan-immune inflammation value, n: Number of patients, %: Percentage of columns, numerical data are given as mean±standard deviation or median (interquartile range) values. †: T test in independent samples, &: Mann-Whitney U test

**Table 2. Comparison of variables according to BASDAI groups**

	BASDAI		Test statistics	
	<4 n=60	≥4 n=44	Test value	p value
Age, (year)	41.9±11.2	42.5±9.3	0.274	0.784†
Sex, n (%)				
Male	29 (48.3)	30 (68.2)	3.306	0.069‡
Female	31 (51.7)	14 (31.8)		
Disease duration, (month)	20.5 (15.2)	6.5 (6.2)	5.848	<0.001&
CRP	3.21 (2.90)	15.00 (18.50)	6.715	<0.001&
ESR	9.0 (13.7)	19.0 (25.0)	3.515	<0.001&
Hemoglobin	13.54±1.64	14.26±1.59	2.224	0.028†
Neutrophil	4.14±0.87	5.10±1.32	4.196	<0.001†
Monocyte	0.59±0.11	0.62±0.10	1.447	0.151†
Lenfocyte	2.46±0.58	2.16±0.60	2.560	0.012†
Neutrophil (%)	56.76±8.44	57.72±10.05	0.429	0.669†
Lenfocyte (%)	32.43±7.78	29.96±8.58	1.234	0.221†
Platelet	266.5 (78.7)	285.0 (77.5)	2.649	0.008&
PIV	247.3 (99.8)	415.4 (216.1)	6.895	<0.001&

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PIV: Pan-immune inflammation value n: Number of patients, %: Percentage of columns, numerical data are given as mean±standard deviation or median (interquartile range) values. †: T test in independent samples, &: Mann-Whitney U test, ‡: Kikare test



**Figure 1.** Graph of the relationship between BASDAI and pan-immune-inflammation value

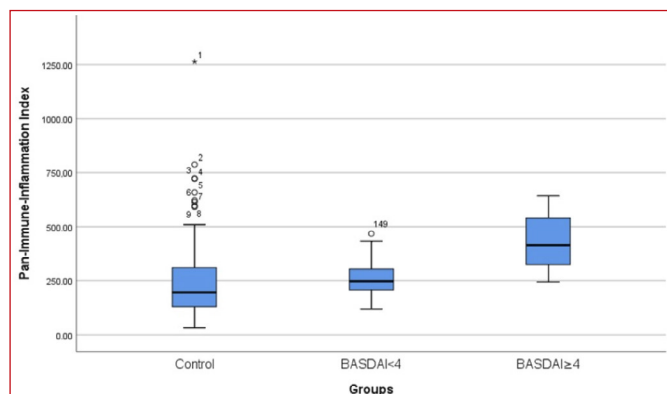


Figure 2. Pan-immune-inflammation value of the groups

There is a statistically significant difference in PIV between the control group, BASDAI <4 ( $p < 0.001$ ), and BASDAI  $\geq 4$  patients. The PIV of BASDAI  $\geq 4$  patients are statistically higher than those of the control group and BASDAI <4 patients ( $p < 0.001$ ). However, there is no statistically significant difference in PIV between the control group and BASDAI <4 patients ( $p: 0.097$ ) (Table 3).

According to the correlation analysis between CRP and PIV, a statistically significant moderate positive correlation was found between the two variables ( $\rho = 0.467$ ;  $p < 0.001$ ). Also there is a statistically significant weak positive correlation was found between PIV and ESR ( $\rho = 0.326$ ;  $p < 0.001$ ).

The performance of the PIV in predicting BASDAI groups was evaluated using ROC Curve analysis. According to the analysis, all areas under the curve are statistically significant, and the Pan-Immune-Inflammation Value reached the highest AUC value in the analysis for BASDAI <4 and BASDAI  $\geq 4$  groups. The obtained AUC value for distinguishing BASDAI <4 and BASDAI  $\geq 4$  patients is 0.897. When the PIV is  $> 309.2$ , a sensitivity of 86.0% and a specificity of 80.0% are achieved (Table 4).

## DISCUSSION

As our knowledge this is the first study which demonstrated that PIV levels were higher in patients with AS and correlated with disease activity. Also PIV was positively correlated with BASDAI, CRP and ESR. Ankylosing spondylitis (AS) is a common rheumatic disease characterized by chronic inflammation of the axial joints, primarily affecting the sacroiliac joints, spinal processes, and paraspinal soft tissues. The etiology of the disease is unknown. The first symptoms of the disease usually appear before the age of 30, and it predominantly affects men compared to women.<sup>23</sup> In our study, we also observed that the group with high disease activity had a higher number of male patients compared to female patients.

The immune system plays a crucial role in the pathophysiology of AS. Neutrophils play a role in the release of chemokines, cytokines, and growth factors, while platelets are involved in the increased levels of cytokines in inflammation. Inflammatory events lead to an increase in neutrophils, monocytes, and platelets, while lymphocyte levels decrease.<sup>24</sup> Various markers have been used in AS from past to present. There is not yet a definitive marker to assess systemic inflammation in patient with AS. Previously, the neutrophil lenfocyte ratio, platellet lenfocyte ratio systemic immune inflammation index have been used to indicate prognosis and disease activity in AS.<sup>25-27</sup> PIV is a newly developed index and includes all four main parameters of the complete blood count together neutrophil, monocyte, platelet and lymphocyte counts. PIV may be superior in demonstrating systemic inflammation compared to NLR and PLR but more studies on this issue are needed.

In our study, when the AS patient group was compared with the healthy control group, it was observed that the patient group had higher platelet and neutrophil counts and lower lymphocyte counts. Studies shown that in AS, with increasing inflammation, neutrophil and platelet

	Groups			Test Statistics		Pairwise Comparisons		
	Control n=104	BASDAI <4 n=60	BASDAI $\geq 4$ n=44	H value	p value	Control vs BASDAI <4	Control vs BASDAI $\geq 4$	BASDAI <4 vs BASDAI $\geq 4$
PIV	195.8 (180.4)	247.3 (99.8)	415.4 (216.1)	58.490	<0.001	0.097	<0.001	<0.001

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index , PIV: Pan-immune inflammation value The numerical data are given as the median (interquartile range) values. H: Kruskal-Wallis test

	AUC (95.0% CI)	p	Cutoff	Sensitivity (95.0% CI)	Specificity (95.0% CI)
Control vs AS	0.726 (0.660-0.785)	<0.001	>225.8	82.7 (74.0-89.4)	65.4 (55.4-74.4)
Control vs BASDAI<4	0.643 (0.564-0.716)	<0.001	>219.3	73.3 (60.3-83.9)	62.5 (52.5-71.8)
Control vs BASDAI $\geq 4$	0.840 (0.771-0.895)	<0.001	>243.9	100 (92.0-100.0)	69.2 (59.4-77.9)
BASDAI<4 vs BASDAI $\geq 4$	0.897 (0.822-0.948)	<0.001	>309.2	86.0 (72.6-94.8)	80.0 (67.7-89.2)

AS: Ankylosing spondylitis BASDAI: Bath Ankylosing Spondylitis Disease Activity Index AUC: Area under the curve, CI: Confidence interval

levels increase, while lymphocyte numbers decrease, which is consistent with our findings.

In our study it was found that according to the disease activity in AS determined with BASDAI, neutrophil and platelet levels increased and lymphocyte numbers decreased in patients with increased inflammation, similar to the studies in the literature.<sup>28</sup> There is no clear relationship between the clinical and imaging findings of acute phase reactants such as CRP, ESR and the progression of the disease in the evaluation of disease activity in AS patients. A study conducted by Liu et al. found that neither CRP nor ESR were superior in evaluating disease activity in ankylosing spondylitis patients.<sup>29</sup> However, there are also studies in the literature that show a positive correlation between the disease activity of ankylosing spondylitis patients and CRP, ESR levels. In the literature review conducted by Ruof and colleagues, there are data that acute phase reactants correlate with the activity of ankylosing spondylitis patients.<sup>30</sup> We also observed that the CRP and ESR values of patients with high BASDAI in the patient group were higher compared to the control group.

PIV has been used mostly as a prognostic biomarker in cancer diseases in the literature obtained from complete blood count parameters.<sup>31,32</sup> In a meta-analysis conducted by Güven et al.<sup>33</sup> it was stated that PIV may be a prognostic biomarker in cancer. A study conducted with peritoneal dialysis patients found that the initial PIV was significantly associated with an increased risk of death due to all causes, cardiovascular diseases and infection.<sup>34</sup> In a retrospective study conducted in patients with membranous nephropathy, it was found that PIV is a reliable marker for predicting a non-remission state.<sup>35</sup> PIV was studied at some rheumatological diseases, rheumatoid arthritis,<sup>36</sup> antineutrophil cytoplasmic antibody-associated vasculitis (AAV), familial mediterranean fever (FMF). Tutan et al.<sup>37</sup> found an association between PIV and disease activity at romatoid arthritis. Lee et al.<sup>38</sup> found an association between worse prognosis and high PIV levels in patients with AAV. In the previous study in FMF, patients were grouped as FMF gene mutations PIV were found higher in all groups but they foun no difference between the groups.<sup>39</sup>

In our study, it was also found that the patients' PIV level was sensitive and specific when the disease activity of their patients was high (BASDAI  $\geq 4$ ). Again, we found in our study that PIV significantly correlated with increased CRP and ESR levels in ankylosing spondylitis patients during periods when their diseases are active.

Since PIV contains parameters that play a role in immunity and inflammation, we tried to show in our study that it can be a biomarker that can indicate inflammation in chronic diseases. We think that with

PIV we can get information about the disease activity of patients just by looking at the complete blood count. PIV is simple, low-cost and easy to access in routine clinical settings compared to the other serum markers.

The assessment of disease activity in AS is challenging, and also its is important because we decide on treatment according to disease activity and evaluate response to treatment. However, acute-phase reactants like CRP and ESR are often used to monitor the disease and treatment response. In our study, when looking at the BASDAI level of the patient group, it was observed that the CRP and ESR values of patients with high BASDAI were higher than those in the control group. And also PIV is associated with BASDAI, CRP and ESR levels.

Our results demonstrated that PIV levels were significantly higher in AS patients with high disease activity (BASDAI  $\geq 4$ ). PIV showed high sensitivity and specificity in distinguishing AS patients with high disease activity from those with low disease activity. This suggests that PIV can be a valuable marker for assessing disease activity in AS. In the previous study in patients with RA, PIV is associated with disease activity as our study.

### Limitations

The medications used by patients with AS and their effect on PIV were not evaluated in our study. In addition, patients were evaluated once and the relationship between disease activity and PIV was not investigated in long-term follow-up.

### CONCLUSION

One of the key advantages of PIV is that the parameters used to calculate are obtained from a simple and inexpensive complete blood count. According to our study, PIV can be a useful marker for assessing disease activity in ankylosing spondylitis, especially in patients with high disease activity and those who may not have access to more specialized tests. PIV may provide a valuable tool for clinicians to monitor and manage AS patients more effectively. However, further research and validation in larger and diverse populations are needed to confirm its clinical utility.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

Ethics committee approval was obtained from Hitit University Clinical Researches Ethics Committee (Date: 03.10.2023 Decision No: 2023-130).

#### Informed Consent

Written consent was obtained from the patient participating in this study.

**Referee Evaluation Process**

Externally peer-reviewed.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Financial Disclosure**

The authors declared that this study has received no financial support.

**Author Contributions**

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Adolescent patients presenting to the emergency department due to falls from heights: a comparative analysis of suicidal and non-suicidal cases

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**Cite this article as:** Özel M, Çetinkaya R, Tatlıparmak AC, Yılmaz S, Ak R. Adolescent patients presenting to the emergency department due to falls from heights: a comparative analysis of suicidal and non-suicidal cases. *Anatolian Curr Med J.* 2024;6(1):55-58.

Received: 25.10.2023

Accepted: 11.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** This study aims to categorize adolescent patients presenting to the hospital due to falls from heights into two groups: suicidal and non-suicidal. It seeks to compare the clinical characteristics, trauma patterns, and outcomes between these groups.

**Methods:** A total of 69 patients were included in the study. The demographic features, trauma patterns, imaging methods, medical interventions, and clinical outcomes of the patients were retrospectively assessed.

**Results:** 63.8% (n=44) of the patients were categorized in the suicidal group, while 36.2% (n=25) were in the non-suicidal group. There was no statistically significant difference observed between the mean age of the suicidal group (16.27±2.52) and the non-suicidal group (15.96±2.85) (p=0.638). In the suicidal group, the incidence rates of maxillofacial trauma, pelvic trauma, and thoracic trauma were statistically significantly higher compared to the non-suicidal group (respectively; p=0.041, p=0.014, p<0.001). The in-hospital mortality rate in the suicidal group (22.7%, n=10) was statistically significantly higher than in the non-suicidal group (0%, n=0) (p=0.007).

**Conclusion:** Cases of falls from heights due to suicide attempts result in more severe outcomes compared to accidental falls. These patients require a more comprehensive medical assessment and intervention.

**Keywords:** adolescent, suicide, fall from height

## INTRODUCTION

A fall from a height can be defined as an individual descending to a lower level without experiencing syncope or stroke.<sup>1</sup> In Türkiye, falls from heights rank as the second most common cause of trauma, following traffic accidents.<sup>2</sup> According to the World Health Organization (WHO), accidental descents, whether from heights or on the same level, stand as the second leading cause of unintentional death worldwide. Each year, approximately 646,000 individuals succumb to injuries sustained from these falls.<sup>3</sup> Moreover, the WHO indicates that around 37.7 million falls are severe enough to require hospital admission annually. Concurrently, the global annual mortality rate attributed to suicide is approximated at 800,000 individuals.<sup>4</sup>

Adolescence is delineated by pronounced physical, biological, and emotional evolutions, coupled with the attainment of both sexual and social maturity. As defined by the WHO, this developmental phase spans the ages of

10 to 19, marking a period characterized by augmented independence and societal contribution. The prevalence of suicide attempts within this demographic is garnering increasing attention as a salient public health issue, ranking as the second leading cause of death among those aged 10 to 24.<sup>5,6</sup>

Globally, falls from heights account for a significant proportion of traumatic injuries and fatalities.<sup>7-9</sup> However, not all such incidents occur inadvertently. While a subset of these cases can be attributed to intentional suicide attempts, numerous incidents result from various unintentional circumstances leading to the fall.<sup>10,11</sup> Understanding the demographic, clinical, and prognostic disparities between suicidal and non-suicidal falls from heights holds critical implications for optimizing patient treatment and follow-up processes.

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In this study, the objective was to analyze and compare the suicidal and non-suicidal cases of patients presenting to the emergency department due to falls from heights, with the aim of elucidating the differences and similarities between the two groups.

## METHODS

This retrospective study was conducted under the approval of the Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 05.05.2023, Decision No: 383). All procedures performed adhered to the ethical standards and were in alignment with the principles of the Declaration of Helsinki. This research was undertaken at the emergency department of Gazi Yaşargil Training and Research Hospital, focusing on adolescent patients who presented due to falls from heights between January 1, 2020, and January 1, 2023.

All patients aged 10-19 who presented to the emergency department due to high falls within the specified dates were included in the study. Prior to the investigation, patients were assessed based on their medical history (anamnesis) and existing clinical documentation to determine whether their falls were suicidal or non-suicidal in nature. Methods of distinguishing suicidal cases from accidental falls in this study were based on [include specific criteria and methods used, such as psychological evaluations, witness statements, and circumstantial evidence]. Demographic information of the patients, such as age, gender, and residence characteristics (urban vs. non-urban), was collected. Additionally, details regarding the height of the fall, examinations conducted in the emergency department (including whole-body Computed Tomography [pan-CT], abdominal Computed Tomography [abdomen CT], and Focused Assessment with Sonography for Trauma [FAST ultrasound]), severity of injuries (cranial, maxillofacial, spinal, pelvic, thoracic, abdominal, extremity, and the total number of affected anatomical regions), and emergency department outcomes (including intubation, the application of Cardiopulmonary Resuscitation [CPR] within the emergency department, surgical requirements, intensive care monitoring, and in-hospital mortality) were retrospectively retrieved from hospital records.

### Statistical Analysis

The statistical evaluation was conducted using the SPSS software for Windows (Version 29, Chicago, IL, USA). Normality of the group distributions was verified using histograms and the Shapiro-Wilk test. Data were summarized using descriptive statistics: categorical variables were presented as frequencies

and percentages, while continuous variables were described using mean  $\pm$  standard deviation or median with interquartile range (IQR, 25<sup>th</sup>-75<sup>th</sup> percentile). For categorical data, the chi-square test or Fisher's exact test was used for group comparisons when appropriate. Continuous data comparisons between the groups were executed using the Student's t-test for normally distributed datasets and the Mann-Whitney U test for non-normally distributed datasets. A p-value of  $<0.05$  was set as the threshold for statistical significance, and all tests were two-tailed.

## RESULTS

The study included 69 patients. Of these, 63.8% (n=44) were categorized under the suicide group, and 36.2% (n=25) were in the non-suicide group. The age average in the suicide group ( $16.27 \pm 2.52$ ) did not show a statistically significant difference compared to the non-suicide group ( $15.96 \pm 2.85$ ) ( $p=0.638$ ). There was no statistically significant difference observed in the male gender distribution between the suicide group (56.8%, n=21) and the non-suicide group (43.2%, n=16) ( $p=0.193$ ). It was noted that 86.4% (n=38) of the suicides occurred in the city center, while this rate was 68% (n=17) in the non-suicide group, though the difference was not statistically significant ( $p=0.068$ ). The median number of floors fallen in the suicide group (4 [IQR 3 – 5]) was statistically significantly higher compared to the non-suicide group (2 [IQR 1.5 – 2]) ( $p<0.001$ ).

For the patients in the suicide group, 97.7% (n=43) underwent a pan-CT scan, a rate statistically significantly higher than the 64% (n=16) in the non-suicide group ( $p<0.001$ ). The rate of IV contrast abdominal CT scans in the suicide group (95.5%, n=42) was statistically significantly higher than the non-suicide group (64%, n=16) ( $p<0.001$ ). There was no statistically significant difference observed in pathology detection rates using Fast USG between the suicide (13.6%, n=6) and non-suicide groups (20%, n=5) ( $p=0.241$ ).

No statistically significant differences were detected between the suicide and non-suicide groups regarding rates of cranial trauma, spinal trauma, abdominal trauma, and extremity injuries (respectively,  $p=0.286$ ,  $p=0.145$ ,  $p=0.075$ ,  $p=0.663$ ). However, the occurrences of maxillofacial trauma, pelvic trauma, and thoracic trauma were statistically significantly more frequent in the suicide group compared to the non-suicide group (respectively;  $p=0.041$ ,  $p=0.014$ ,  $p<0.001$ ). The median number of affected anatomical regions in the suicide group (3 [IQR 2 – 4.75]) was statistically significantly higher compared to the non-suicide group (2 [IQR 1.5 – 2]) ( $p<0.001$ ).

The rate of emergency intubation in the suicide group (29.5%, n=13) was statistically significantly higher compared to the non-suicide group (0%, n=0) (p<0.001). In the suicide group, CPR was administered to 6 patients (13.6%), while none of the patients in the non-suicide group required CPR in the emergency department. 54.5% (n=24) of the patients in the suicide group underwent surgical intervention, while this rate was 48% (n=12) in the non-suicide group, with no statistically significant difference between the groups (p=0.601). The admission rate to the intensive care unit for the suicide group (86.4%, n=38) was statistically significantly higher compared to the non-suicide group (28%, n=7) (p<0.001). The in-hospital mortality rate in the suicide group (22.7%, n=10) was statistically significantly higher compared to the non-suicide group (0%, n=0) (p=0.007).

**Table 1. Demographic characteristics of the groups**

	Suicide (n=44)	Accidental Fall (n=25)	p value
Age	16.27±2.52	15.96±2.85	0.638
Gender (Male)	21 (56.8%)	16 (43.2%)	0.193
Incident Location (Urban)	38 (86.4%)	17 (68%)	0.068
Number of Floors Fallen	4 (3-5)	2 (1.5-2)	<0.001
PAN-CT*	43 (97.7%)	16 (64%)	<0.001
IV contrast abdominal CT**	42 (95.5%)	16 (64%)	<0.001
FAST Ultrasound***	6 (13.6%)	5 (20%)	0.241

\*PAN-CT: Whole Body Computed Tomography, \*\*IV contrast abdomen CT: Abdominal CT scan with intravenous contrast, \*\*\*FAST Ultrasound: Focused Assessment with Sonography for Trauma procedure

**Table 2. Comparison of groups based on trauma data**

	Suicide (n=44)	Accidental Fall (n=25)	p
Cranial	12 (27.3%)	4 (16%)	0.286
Maxillofacial	10 (22.7%)	1 (4%)	0.041
Spinal	29 (65.9%)	12 (48%)	0.145
Pelvis	22 (50%)	5 (20%)	0.014
Thoracic	40 (90.9%)	10 (40%)	<0.001
Abdominal	11 (25%)	2 (8%)	0.075
Extremity	27 (61.4%)	14 (56%)	0.663
Number of affected anatomical regions	3 (2-4.75)	2 (1.5-2)	<0.001

**Table 3. Comparison of groups based on outcome data**

	Suicide (n=44)	Accidental Fall (n=25)	p value
Emergency department intubation	13 (29.5%)	0 (0%)	<0.001
Emergency department CPR	6 (13.6%)	0 (0%)	----*
Surgical intervention	24 (54.5%)	12 (48%)	0.601
ICU (intensive care unit)	38 (86.4%)	7 (28%)	<0.001
In-hospital mortality	10 (22.7%)	0 (0%)	0.007

\*Statistical analysis was not conducted for this variable as the conditions for Chi-square testing were not met.

## DISCUSSION

This study aims to comparatively assess the clinical characteristics and outcomes of adolescent age group patients who presented to the emergency department

due to falls from heights, distinguishing between suicidal and non-suicidal incidents.

In this investigation, no statistically significant differences were identified between the suicidal and non-suicidal groups concerning age and gender. This finding indicates a homogeneous distribution in the demographic characteristics of patients presenting to the Emergency Department (ED) due to falls. However, when reviewing the literature, it is evident that while males predominantly represent accidental falls, females are more common in suicidal falls. The limited number of patients included in our study might explain this discrepancy.<sup>12-14</sup>

Our analysis revealed that the number of floors from which patients in the suicidal group fell was statistically significantly higher. This suggests that individuals in the suicidal category tend to fall from greater heights, leading to more severe injuries. In a study conducted by Choi et al.<sup>15</sup> various characteristics of 8,992 patients with accidental falls and 144 with suicidal falls were compared. It was emphasized that patients in the suicide group fell from significantly greater heights (4 meters or above).

Comparing the affected anatomical regions between the two groups, our study found that the prevalence of maxillofacial trauma, pelvic trauma, and thoracic trauma was statistically significantly higher in the suicidal group. This suggests that suicidal incidents involve high-energy trauma, affecting a broader range of anatomical areas. A study by Papadakis et al.<sup>14</sup> reported higher rates of pelvic and thoracic injuries in the suicidal group, while the non-suicidal group predominantly presented with upper extremity injuries.<sup>15</sup>

It is well-established that suicidal incidents generally result in more severe trauma outcomes and necessitate more intensive medical interventions.<sup>16-18</sup> Consistently, our study observed that patients in the suicidal group exhibited significantly higher rates of intensive care requirements, intubation, CPR, and in-hospital mortality.

In a study comparing the injury pattern between suicidal and accidental falls from height in Northern Tunisia, it was reported that head injuries were more common in the accidental falls group, whereas in our study there was no difference between the groups. However, while the aforementioned study covers a period of sixteen years, our study covers a period of three years.<sup>19</sup>

A comprehensive meta-analysis study reported that there was an increase in emergency department visits due to suicide attempts during the COVID-19 pandemic. Although our study coincided with the pandemic period, it is not possible to compare our results with this study since we did not make a comparison with the pre-pandemic period.<sup>20</sup>



## Limitations

There are certain limitations to this study. Firstly, the research was conducted in a single center, implying that the findings may not be wholly generalizable to other clinical settings or geographical regions. The use of a retrospective design suggests that data related to some potentially critical variables might be missing or may be misleading. Additionally, the inclusion of a relatively small number of patients limits the study's statistical power. This study lacks information on prior medication history and any medication taken before the fall in cases of suicidal intent, which is a factor that could potentially affect our mortality predictions.

## CONCLUSION

In this study, suicidal and non-suicidal high-fall cases were compared. It was determined that patients in the suicidal group typically experienced more severe traumas, necessitating more comprehensive medical interventions. Furthermore, the suicidal group exhibited higher mortality rates. In conclusion, cases of falls from heights due to suicide attempts result in more severe outcomes compared to accidental falls, and these patients require a more thorough medical assessment and intervention.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 05.05.2023, Decision No: 383).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Asymptomatic COVID-19 and structural changes in the brain

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**Cite this article as:** Eliaçık S, Büyüksireci M. Asymptomatic COVID-19 and structural changes in the brain. *Anatolian Curr Med J.* 2024;6(1):59-64.

Received: 06.11.2023

Accepted: 14.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** Neurological symptoms are the most prevalent extrapulmonary complications of coronavirus disease 2019 (COVID-19). In this context, the objective of this study is to assess the brain magnetic resonance imaging (MRI) parameters of asymptomatic COVID-19 individuals one year after diagnosed with COVID-19 in comparison with healthy control subjects.

**Methods:** The population of this prospective study consisted of individuals who have not developed olfactory impairment or other complications within one year after diagnosed with COVID-19. For the study, 8 male, 25 female, 4 male and 23 female individuals were accepted for PCG and CG, respectively, according to the inclusion and exclusion criteria. The mean age was found to be  $37.75 \pm 11.56$  and  $37.11 \pm 10.67$ , respectively. All participants included in the study underwent olfactory sulcus (OS) depth, olfactory bulb (OB) volume, hippocampal sclerosis (HS), insular gyrus area, and corpus amygdala area measurements.

**Results:** The bilateral OB volume, insular gyrus area and corpus amygdala area were significantly lower in the post-COVID-19 group (PCG) than in the control group (CG) ( $p < 0.05$ ). On the other hand, the bilateral OS depth was significantly higher in PCG than in CG ( $p < 0.05$ ). In the PCG, the insular gyrus area and corpus amygdala area values of the right side were significantly higher than those of the left side ( $p < 0.05$ ). In addition, bilateral HS was detected in five patients in the PCG, right-sided HS in two patients, and left-sided HS in one patient.

**Conclusion:** The findings of this study have shown that COVID-19 infection, albeit asymptomatic, can trigger neurodegeneration. We believe that in the future COVID-19 infection will play a role in the etiopathogenesis of many neurodegenerative diseases.

**Keywords:** Olfactory bulb, insular cortex, hippocampal sclerosis, COVID-19, amygdala, prefrontal cortex

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) that broke out in the Wuhan City of China in December, 2019, was declared a pandemic by the World Health Organization (WHO) on March 11<sup>th</sup>, 2020, and caused numerous morbidity and mortality worldwide since then. Although the pandemic has slowed down since 2022, extensive studies are needed to determine the long-term complications that may be caused by COVID-19.<sup>1,2</sup> Previous studies have demonstrated potential late complications of COVID-19 including lung fibrosis, venous and arterial thromboembolism, cardiac thrombosis, stroke, brain fog, dermatological complications, and mood dysfunctions.<sup>3-5</sup> Although the exact mechanisms responsible for long-term complications of COVID-19 remain unknown, it has been speculated that several pathophysiological mechanisms of the coronavirus that causes COVID-19, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might account for COVID-19's longer-term complications and sequelae.<sup>1</sup> Neurological

symptoms are the most prevalent extrapulmonary complications of COVID-19.<sup>6</sup>

In view of the foregoing, this study was carried out to assess the brain MRI parameters of asymptomatic COVID-19 individuals one year after diagnosed with COVID-19 in comparison with healthy control subjects.

## METHODS

### Study Design

The protocol of this study was approved by the Hitit University Faculty of Medicine Ethics Committee (Date: 31.03.2022 Decision No: 2022-17). This study was carried out in accordance with the ethical principles set forth in the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. Informed consent was obtained from all participants included in this study.

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## Population and Sample

The population of this prospective study consisted of individuals who have not developed olfactory impairment or other complications within one year after diagnosed with COVID-19. All participants included in the study underwent OS depth, OB volume, HS, insular gyrus area, and corpus amygdala area measurements.

None of the participants included in the study had olfactory disturbances during viral infection. The individuals who had asymptomatic COVID-19 had been diagnosed with COVID-19 using the reverse transcription-polymerase chain reaction (RT-PCR) test via nasopharyngeal swab specimens. They were infected by contact and did not have acute and/or chronic complaints during the follow-up period.

The study inclusion criteria were as follows; having been diagnosed with asymptomatic COVID-19 without complications and having had COVID-19 at least one year ago. On the other hand, the study exclusion criteria were as follows; having a trauma history, sinonasal cerebrospinal fluid leak or sinonasal surgery, sinonasal polyposis, facial and/or nasal septal deformity, Parkinson's and/or Alzheimer's disease, multiple sclerosis, epilepsy or another neurodegenerative disease.

## Data Collection Procedure

The individuals in both the PCG and the CG underwent a detailed neurological examination, and were administered the Hamilton Rating Scale for Depression (HRSD) and Hamilton Anxiety Rating Scale (HARS), as well as the Montreal Cognitive Assessment (MoCA) and Mini-Mental Status Examination (MMSE). All participants were evaluated by electroencephalography (EEG). The Brief Smell Identification Test was administered to all participants.

## Brain MRI Protocols

Participants' MRI images were obtained using a 1.5-Tesla MRI device at a single center. The sequences performed were axial T1-weighted spin-echo (T1W SE) MRI with and without contrast enhancement, diffusion-weighted imaging, axial and coronal T2-weighted fast-spin-echo (T2W FSE) MRI, and 2D fluid attenuated inversion recovery (FLAIR).

The measurement data from coronal T2W FSE images for OB volume and OS depth and axial FLAIR images for the insular gyrus area and axial T1W SE images for the corpus amygdala area were evaluated by a single radiologist with 12-year experience who was blinded to the study groups.

OB volume was manually measured first with an electronic cursor from the slice, where the OB image was most clearly seen on coronal T2W images, in square

millimeters, and secondly, this resulting value was multiplied by the slice thickness to obtain the volume in cubic millimeters. In order to measure the OS depth, a virtual tangent line was drawn in the posterior plane of the orbit connecting the inferior orbital gyrus and the lower edges of the gyrus recti on coronal T2W images. The OS depth was calculated by measuring a new line drawn from this tangent line to the deepest point of the OS. The area of the insular gyrus in square millimeters was measured at the level where the head of the caudate nucleus and putamen were observed and in the section where it was maximum. corpus amygdala area was measured in square millimeters in the sections where it was observed to be the largest.

## Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package licensed by Hitit University. Independent samples t-test, paired samples t-test, chi-square test, Pearson's correlation test, and Spearman's correlation rho efficient were used in the statistical analyses. The probability (p) statistics of <0.05 were deemed to indicate statistical significance.

## RESULTS

For the study, (24%) 8 male, (76%) 25 female, (15%) 4 male and (85%) 23 female individuals were accepted for PCG and CG, respectively, according to the inclusion and exclusion criteria. The mean age of the PCG was  $37.75 \pm 11.56$  years, and the mean age of the CG was  $37.11 \pm 10.67$  years. There was no significant difference between the groups in terms age ( $p=0,748$ ). The bilateral OB volume was significantly lower in the PCG than in the CG ( $p=0,033$ ). The bilateral OS depth was significantly higher in the PCG than in the CG ( $p=0,041$ ). The comparison of the OB volume or OS depth values within the groups did not reveal any significant difference between the left and right sides ( $p=0.637$ ). The bilateral insular gyrus area was significantly lower in the PCG than in the CG ( $p=0,0347$ ). The bilateral corpus amygdala area was significantly lower in the PCG than in the CG ( $p=0,026$ ). In the PCG, the insular gyrus area and corpus amygdala area of the right side were significantly higher than those of the left side ( $p=0,023$ ). In the CG, there was no significant difference between the left and right sides in insular gyrus area and corpus amygdala area volumes of ( $p=0,482$ ). The measurement results for the peripheral and central smell regions are shown in **Table**. Bilateral HS was detected in five patients in the PCG, right-sided HS in two patients (**Figure**), and left-sided HS in one patient. In the CG, bilateral HS was detected in only one patient. Epileptic activity and/or slow wave activity were

not observed on the EEG of any participant included in CG. Theta form slow wave activity was observed in bilateral centroparietal regions in three patients who were diagnosed with bilateral HS among the participants included in PCG. Neither group had a participant with a history of epileptic seizures. Cognitive functions were within normal limits in both groups. Participants who did not have depression or anxiety also had no olfactory impairment.

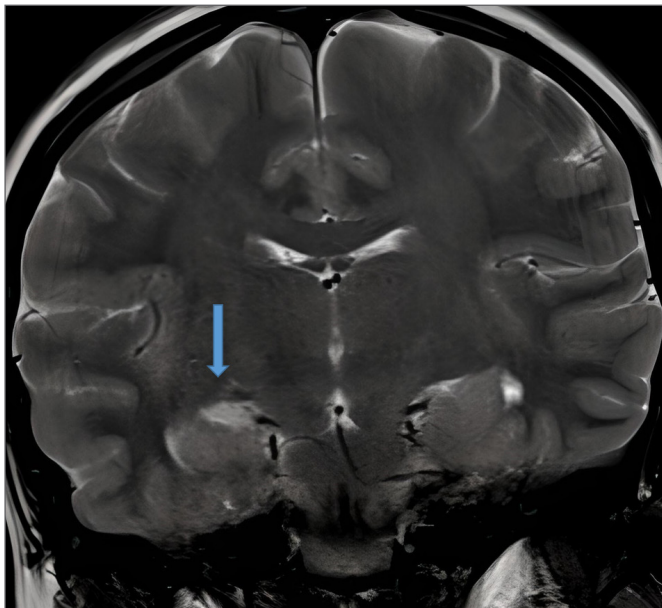


Figure. Right-sided hippocampal sclerosis

**DISCUSSION**

The exact mechanisms responsible for long-term complications of COVID-19 remain unknown. Nevertheless, it has been speculated that several pathophysiological mechanisms of SARS-CoV-2 virus might account for COVID-19’s longer-term complications and sequelae.<sup>1</sup> Among these are; the entry receptor for SARS-CoV-2 angiotensin-converting enzyme 2 (ACE2), which allows the virus to enter target cells through activation of its spike protein by transmembrane serine protease 2.<sup>7,8</sup> These receptors are expressed in epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, pancreatic β-cells, and renal podocytes, suggesting that direct tissue damage may be the primary mechanism of COVID-19 infection as well as its longer-term complications.<sup>9-11</sup> In addition to direct cellular infection, there are several other mechanisms which may explain the pathophysiology

leading to COVID-19-related multiorgan systemic disorder, including endothelial injury, immune system dysregulation, and hypercoagulability often leading to thrombosis.<sup>12</sup> The autoimmune reactions reported by a study evaluating the autopsies of individuals who died due to COVID-19 provided evidence for the hypothesis of cluster of differentiation 8-positive T lymphocytes (CD8+ T cell)-mediated cytotoxicity.<sup>13</sup>

Various COVID-19-related neurological and psychiatric long-term complications have been reported in the literature. Long-term symptom data from different sources indicated ongoing neurological findings in COVID-19 patients two months after acute infection, including fatigue, muscle weakness, sleep difficulties, myalgia, and headache.<sup>14,15</sup> In contrast, in this study, none of the participants included in PCG had such complaints.

SARS-CoV-2 reportedly may also cause neuroinvasion. As a matter of fact, postmortem brain studies reported symptoms including edema, hemorrhage, hydrocephalus, atrophy, encephalitis, infarcts, swollen axons, myelin loss, gliosis, neuronal satellitosis, hypoxic-ischemic damage, arteriolosclerosis, leptomenigeal inflammation, neuronal loss, and axon degeneration.<sup>16</sup> As the COVID-19 pandemic progressed, a growing body of evidence indicated that SARS-CoV-2 can cause neuroinvasion and affect the central nervous system (CNS) in multiple ways.<sup>17,18</sup> Neurotropism is another feature of SARS-CoV-2, and it has been reported that the endothelium, glial cells, and neurons express ACE2, which makes them a target for SARS-CoV-2.<sup>19</sup> Also, neurological manifestations during COVID-19 infection can be caused directly by the SARS-CoV-2 in the CNS or by the host’s immune response and systemic complications. After gaining access to the CNS, SARS-CoV-2 can cause immune cell infiltration and activate inflammatory pathways through the secretion of chemokines, and cytokines activate thrombotic pathways, contributing to tissue damage and causing microangiopathy.<sup>17,20</sup> Brain atrophy has been reported in long COVID-19 syndrome patients. In contrast the patients included in this study survived COVID-19 asymptotically without any complications during and after the COVID-19 process. Atrophy in the orbitofrontal and parahippocampal regions has been reported in the literature in patients with cognitive impairment who have had COVID-19. In one of these studies, Crunfli et al.<sup>21</sup> reported that, consistent with a model in which SARS-CoV-2 involved the CNS

Table. Measurement results in both groups								
	OS depth		OB volume		Insular gyrus area		Corpus amygdala area	
	R	L	R	L	R	L	R	L
PCG	10.95±1.13	10.68±1.24	31.20±2.83	34.75±3.23	254.90±53.03	241.23±29.6	136.0±17.33	124.90±19.15
CG	8.18±0.64	8.78±0.79	44.01±2.08	44.46±3.05	303.3±42.40	300.1±21.8	149.9±14.27	149±16.9

R right, L left, PCG post covid-19 group, CG control group, OB olfactory bulb, OS Olfactory sulcus

of COVID-19 patients, SARS-CoV-2 primarily infected astrocytes via neuropilin-1 interaction, and secondarily impaired neuronal function and viability. Accordingly, it was speculated that neuroinvasion mechanisms that play a role in fatal COVID-19 may also be effective in mild COVID-19, and therefore, interventions to treat COVID-19 should also foresee ways to prevent invasion of the CNS by SARS-CoV-2 and/or replication of SARS-CoV-2 in astrocytes. Although the cases included in this study were asymptomatic, an increase was detected in HS in addition to significant changes in the olfactory bulb, cingular, and amygdala areas. In a case series featuring two patients with normal MRIs who complained of cognitive symptoms, the hypothesis that these cognitive symptoms might be associated with the dysfunction of the cingulate cortex was supported by brain and 18-F-fluorodeoxyglucose positron emission tomography (FDG PET).<sup>22</sup> Experimental histological studies conducted on the olfactory bulb have demonstrated that synaptogenesis and neuroplasticity are likely to persist throughout life in this anatomical formation.<sup>23-25</sup> In an imaging study conducted with 25 patients with cognitive impairment, a significant positive correlation was determined between the total Fear of Coronavirus Disease 2019 Scale score and a decrease in volume at the right posterior cingulate cortex.<sup>26</sup> In another retrospective study including 14 relapsing-remitting multiple sclerosis patients, the 113 longitudinal MRI images of the patients revealed the decrease in parahippocampal gyrus' volume, suggesting accelerated atrophy during or after COVID-19.<sup>27</sup> In addition, weakening in the sense of smell is reportedly an early sign of Alzheimer's disease (AD) and a predictor of the conversion from mild cognitive impairment to AD.<sup>28</sup> Al-Otaibi et al.<sup>29</sup> reported significantly smaller olfactory cortex volume in patients with AD compared to healthy older control subjects. In comparison, this study's findings supports the hypothesis that COVID-19 may be a precursor of neurodegeneration.

Recently published studies have provided evidence for the etiology of memory deficit caused by COVID-19.<sup>30,31</sup> One of these studies reported a reduction in the gray matter volume such as the frontal lobe, which is responsible for working memory capacity, in certain COVID-19 patients.<sup>20,32</sup> In another study, COVID-19 reportedly caused silent brain hypoxia, also contributing to hippocampal damage.<sup>33,34</sup>

Previous studies speculated that a decrease in hippocampal volume in COVID-19 patients may cause cognitive deficits in memory,<sup>35,36</sup> suggesting that COVID-19 patients are much more likely to experience short-term memory deficits compared to long-term memory. As a matter of fact, 50% of the MRI scans of COVID-19

patients revealed white matter hyperintensities in the frontal and parietal lobes and significant reductions in gray matter thickness bilaterally especially in the parahippocampal gyrus, anterior cingulate cortex, and temporal pole compared to healthy control subjects. In comparison, in this study, the insular gyrus area and corpus amygdala area of the left side were significantly decreased in post-COVID-19 patients compared to the right side. All participants included in this study were right-handed, that is, atrophy in both areas was in the dominant hemisphere. The literature data, including the case studies and case series, suggest that COVID-19 patients could suffer memory problems after the onset of COVID-19 even if they do not have significant past medical or neuropsychiatric condition.<sup>37</sup> The EEG studies indicated that diffuse pathological slowing, intermittent rhythmic delta-activity, and low delta band at baseline were associated with memory impairment in COVID-19 patients.<sup>38-40</sup> In comparison, in this study, slow wave activity was detected on EEG in three patients with bilateral hippocampal sclerosis. Previous studies indicate that either structural abnormalities, e.g., cortical atrophy and white matter hyperintensities or functional abnormalities, e.g., hypometabolism in widespread brain regions may exist in COVID-19 patients with memory impairment compared to healthy control subjects. These brain abnormalities and memory dysfunction are likely to reverse over time in most cases. The direction, i.e. increase vs. decrease, of the anatomical and metabolic alterations initially was in line with imaging findings in patients with comparable memory impairments such as dementia and AD,<sup>37,41</sup> and studies have shown that COVID-19 severity was independent of patients' memory impairments.<sup>34</sup> Structural MRI and 18F-FDG PET were the most frequently utilized imaging tools in the previous studies on the brain changes associated with memory impairment. Nonetheless, the findings of these studies are contradictory.<sup>42,43</sup> Tian et al.<sup>44</sup> pointed out that COVID-19 patients without the manifestations of memory deficits could still have brain pathological changes such as declined global cortical thickness. Hence, decreased cortical thickness, i.e. brain atrophy, might not be necessarily a direct cause of memory impairments in COVID-19 patients. This study's findings are in line with the findings of the said two studies. Evidence from both animal and postmortem showed that elevated inflammatory chemokines, especially C-C motif chemokine ligand 11 (CCL11), found in long COVID-19 syndrome patients with cognitive symptoms, directly contributed to the increased white matter microglial reactivity particularly in the hippocampus, an area highly responsible for learning and memory. These neuroinflammatory-related changes might be directly associated with early and transient

memory impairment in COVID-19 patients.<sup>45</sup> Although the relationship between COVID-19 infection and neurodegenerative diseases remains unclear, a genetic relationship between Alzheimer's and COVID-19 has been found. We can think that COVID-19 will have a greater place in both etiopathogenesis and treatment in future neurodegenerative disease studies.<sup>46,47</sup> Remdesivir was approved for the treatment of COVID-19 infection in 2020, but we only know that antiviral agents are not enough for treatment. Which treatments will be more effective, especially in long-term complications, still protects the dark side of the disease.<sup>4</sup> Current treatments for COVID-19, using antivirals, target pathological mechanisms by reducing inflammation. Therefore, from laboratory and clinical studies in the literature, when the pathophysiological pathways underlying the neurological symptoms of long COVID-19 become more understandable, new treatment modalities will also be on the agenda.<sup>48</sup>

### Limitations

The primary limitation of this study was its relatively small sample size, which was partly due to the difficulty of finding asymptomatic COVID-19 cases who tested positive for COVID-19 during the pandemic process. In addition, another limitation is that our study does not include the parameters of neurodegeneration (cerebrospinal fluid (CSF) analysis or PET). Therefore, future studies that preferably employ 18F-FDG PET or CSF are needed to corroborate the findings of this study.

### CONCLUSION

There is sufficient evidence suggesting that memory impairment is a prominent symptom of COVID-19, and likely associated with COVID-19-induced brain dysfunction. Long-term histopathological studies will help us understand the pathophysiology of COVID-19-related memory impairment. Hypometabolism, increased white matter hyperintensities, and decreased cerebral gray matter volume may be effective indicators of memory dysfunction in COVID-19 patients, but the causal relationships between these phenomena have yet to be elucidated, as have the complications caused by asymptomatic COVID-19 infection involving multiple mechanisms in the acute period. Our knowledge on the etiopathogenesis and clinical findings of long-term COVID-19 complications will increase over time. In sum, the findings of this study suggest that COVID-19 infection, even if asymptomatic, may trigger neurodegeneration, we believe that in the future COVID-19 infection will play a role in the etiopathogenesis of many neurodegenerative diseases.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was initiated with the approval of the Hitit University Faculty of Medicine Ethics Committee (Date: 31.03.2022 Decision No: 2022-17).

#### Informed Consent

Written consent was obtained from all participants before starting the study.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Financial Disclosure

The authors declared that this study has received no financial support.

#### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Attention deficit hyperactivity disorder in the diabetic population: relationship with metabolic syndrome and atherogenic index of plasma

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**Cite this article as:** Çiftel S, Gürbüzler N. Attention deficit hyperactivity disorder in the diabetic population: relationship with metabolic syndrome and atherogenic index of plasma. *Anatolian Curr Med J.* 2024;6(1):65-72.

Received: 19.10.2023

Accepted: 15.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** The objective of the current study is to investigate the prevalence of Attention Deficit/Hyperactivity Disorder (ADHD) among individuals diagnosed with diabetes mellitus (DM). Additionally, this study aims to evaluate the potential association between ADHD and metabolic syndrome (MetS), atherogenic index of plasma (AIP), and other lipid parameters, considering the different types of DM.

**Methods:** The study comprised 213 adult patients diagnosed with diabetes mellitus, consisting of 120 females and 93 males. Participants completed the Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) as a screening tool for symptoms. The study assessed many physiological indicators, including body mass index, waist circumference, blood pressure, glucose levels, cholesterol levels, high-density lipoprotein levels, low-density lipoprotein levels, triglyceride levels, uric acid levels, and glycated hemoglobin levels.

**Results:** The study yielded a prevalence rate of 10.7% for ADHD among diabetes individuals. The prevalence of ADHD was found to be more common in individuals diagnosed with type 1 diabetes mellitus (T1DM) compared to those with type 2 diabetes mellitus (T2DM), with rates of 15.4% and 9.8% respectively. The study revealed that individuals diagnosed with T2DM who also had MetS, organ involvement, concurrent disorders, and stress-related eating had significantly higher scores on the ASRS/T scale. There was a correlation observed between the ASRS-HI and AIP levels in individuals diagnosed with T2DM. The statistical analysis revealed that ADHD-HI and T scores significantly influenced the severity of MetS. A progressive increase in ASRS/T and ASRS/I scores was observed with the duration of DM.

**Conclusion:** In conclusion, by recognizing and treating accompanying neuropsychiatric conditions such as ADHD symptoms in diabetic patients, individuals may exhibit improved adherence to lifestyle modifications and antidiabetic therapies. This approach potentially reduces the risks of acute and chronic complications, including cardiovascular risk, through the enhanced management of DM.

**Keywords:** Diabetes mellitus, attention deficit hyperactivity disorder, metabolic syndrome, atherogenic index of plasma

## INTRODUCTION

Diabetes mellitus (DM), one of the most significant public health diseases of the 21st century, impacting millions of individuals worldwide, is the most common endocrine disorder. The estimated prevalence of the condition is approximately 463 million, with projections indicating a potential increase to 700 million by 2045.<sup>1</sup> This chronic illness substantially impacts individuals' quality of life, necessitating a considerable allocation of medical and economic resources.

In recent studies, it has been demonstrated that DM affects glucose metabolism and other physiological

systems. The effects of diabetes on metabolic health, both acute and chronic organ complications, are well known. For instance, metabolic syndrome (MetS) accompanying DM may indicate a more complex and severe clinical course for patients. In addition, it is reported that diabetes may also affect neurological and psychiatric functions. In this context, investigation of neurological and psychiatric comorbidities associated with DM is becoming increasingly important.

In recent studies, evidence has emerged indicating a potential correlation between DM and behavioral disorders, specifically attention deficit hyperactivity

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disorder (ADHD).<sup>2</sup> ADHD is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity incompatible with the development level, often leading to impairments in social, academic, and occupational functionality. The etiology of ADHD is not fully understood, but an essential etiological factor is that, as in diabetes, the genetic component predominates.<sup>3</sup> The likelihood of ADHD is increased by two to fourfold in first-degree relatives of children with ADHD.<sup>4</sup> Similarly, the likelihood of diabetes is increased by four to sixfold higher in first-degree relatives of individuals with Type 2 DM (T2DM).<sup>5</sup> ADHD affects 2.6% of the global population,<sup>6</sup> reported to be 4.2% in rich-resource countries and 1.9% in poor-resource countries, increasing over the years.<sup>7</sup> ADHD symptoms typically appear in early childhood, and about half of the disease persists into adulthood. With the adoption of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria in 2013, ADHD is now recognized not as a childhood disease but as a chronic disease that persists throughout life.<sup>8</sup> Hypoactivity of dopamine (DA) and norepinephrine in frontal-subcortical circuits in ADHD forms the basis of brain and functional dysfunction in ADHD.<sup>9</sup> DA and norepinephrine exhibit neuromodulatory effects on behavior and cognition via the fronto-striato-cerebellar circuit pathway.<sup>10</sup> Further research is needed to elucidate the molecular mechanisms linking DM-associated dopaminergic dysfunction and cognitive impairment and evaluate glucotoxicity's detrimental effects. Animal studies have reported that hyperglycemia and relative insulin deficiency promote neurodegeneration by impairing dopaminergic neurotransmission.<sup>11</sup> Recent reports suggest that advanced glycation end products and their precursor methylglyoxal are associated with cognitive impairment and changes in the dopaminergic system.<sup>12,13</sup> Considering the crucial role of insulin and glucose in DA homeostasis, it is not surprising that dopaminergic function is altered in DM.<sup>14</sup>

It is also known that individuals with T2DM have significant impairments in visual and verbal memory, attention and concentration, processing speed, executive function, and motor control.<sup>15</sup> ADHD has been found to be correlated with systemic inflammation, a significant factor in the pathogenesis of atherosclerosis, as observed in numerous diseases. The atherogenic index of plasma (AIP) is a parameter used as an indicator of cardiovascular risk calculated based on plasma triglyceride (TG) and high density lipoprotein (HDL) levels, assessing the possibility of atherogenic status with lipid profile. A recent large-scale study reported that plasma TG levels increased

while HDL levels decreased in individuals with ADHD.<sup>16</sup> These findings have led to the need to evaluate the potential cardiovascular risk of ADHD using the AIP. The prevalence of ADHD has been documented to be higher in patients diagnosed with T1DM and T2DM. However, the precise mechanisms of this relationship remain yet unknown. In a large-scale study, it was reported that adolescents and young adults with ADHD were approximately three times more susceptible to developing T2DM.<sup>17</sup> It is thought that ADHD might increase the risk of DM, and DM could exacerbate ADHD symptoms. Impulsive behaviors, self-regulation, and self-motivation problems may be risk factors for the development of abnormal eating, such as overeating, which can lead to DM and obesity. It has been demonstrated that individuals diagnosed with T1DM exhibit a heightened vulnerability to psychiatric disorders, such as ADHD.<sup>18,19</sup> The fact that T1DM is a neurodevelopmental disorder like ADHD, immune system damage, and inflammatory processes predispose to the development of ADHD. The management of T1DM requires more adequate cognitive and manual dexterity compared to T2DM in carbohydrate counting and calculation of insulin correction doses. Research has demonstrated that patients co-diagnosed with ADHD and T1DM have poorer metabolic control, and diabetic ketoacidosis is twice as common as those without ADHD.<sup>20</sup> Several studies have found a reduction in white matter volume, particularly in the frontal region, in individuals diagnosed with T2DM. This region is responsible for various cognitive tasks, including attention, cognition, and motor activity.<sup>21,22</sup> Therefore, this phenomenon may potentially increase the susceptibility of ADHD by eliciting symptoms of inattentiveness and impulsivity. The similarity of hereditary transmission rates and potential factors in pathogenesis- including dysfunction of the dopaminergic system, insulin resistance, obesity, abnormal eating patterns, predisposition to MetS, and neurodevelopmental characteristics are the common characteristics of DM and ADHD currently being investigated.

The objective of our research is to investigate and compare the prevalence and severity of ADHD in T1DM and T2DM and to evaluate the potential association between ADHD and MetS, AIP, and other lipid parameters, considering the being T1DM or T2DM. Ultimately, recognizing ADHD symptoms that negatively affect diabetes regulation and providing appropriate intervention may be crucial for diabetes treatment. In addition, early initiation of lifestyle changes that might reduce the risk of T2DM and MetS in patients with ADHD will form the basis of preventive and therapeutic holistic approaches.

## METHODS

Two hundred and thirteen patients with diabetes mellitus (120 females and 93 males) admitted to the outpatient clinic of Endocrinology and Metabolism Diseases, Erzurum Health Science University Training and Research Hospital between June 2023 and October 2023 were involved in this prospective cross-sectional study. Our study focused on the clinical characteristics and biochemical parameters of 213 adult participants with DM. The study protocol received approval from the Ethics Committee of Erzurum Training and Research Hospital, with a decision number 02/16, dated 14.06.2023. All participants provided written and verbal informed consent. The research was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki. The patients filled out the sociodemographic, clinical data form and the Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) to screen ADHD symptoms. Participants' weight, height, waist circumference, and blood pressure were measured. The diagnostic criteria for Metabolic Syndrome (MetS) employed the guidelines established by the National Cholesterol Education Program Adults Treatment Panel-III.<sup>23</sup> The following formulas were used. The severity of MetS was calculated based on the number of positive criteria.

$$\text{BMI} = \text{Weight (kg)} / \text{Height (m)}^2$$

$$\text{AIP} = \log_{10} (\text{Triglyceride} / \text{HDL ratio}),$$

The criteria for inclusion in the present study were established as follows: individuals must have a confirmed diagnosis of diabetes mellitus, be within the ages of 18 to 65 years, have fundamental literacy skills, and not have any physical or mental disabilities that might impede their ability to complete the required assessments. Additionally, they should give their written consent to be involved in the study. Pregnant women, patients with renal failure, cancer, another cognitive disorder, major psychiatric diagnosis, receiving psychotropics, and alcohol or drug addiction were excluded from the study.

### Data Collection Tools

**Sociodemographic-clinical data form:** It is a form developed by researchers to document the characteristics of participants, including age, gender, body mass index (BMI), and waist circumference. (WC)

**Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS):** The screening tool for adult ADHD symptoms has been developed by the World Health Organization. The scale consists of nine items on Inattention (ASRS-I) and nine on hyperactivity/

impulsivity (ASRS-H/I). There are 18 questions that evaluate ADHD symptoms. The Likert-type scale employed in this study consists of five points, aiming to assess the frequency of occurrence for each symptom throughout the preceding six-month period. The study on validity and reliability in the Turkish context was conducted by Doğan et al.<sup>24</sup> The scale's internal consistency was determined to be 0.88 during the reliability investigation. The Cronbach's Alpha coefficients for the Inattention and Hyperactivity/Impulsivity subscale are 0.82 and 0.78, respectively. The study observed a test-retest consistency of 0.85 for total scores and 0.73 and 0.89 for subscales, respectively. Those who scored 24 or above from any of the subscales points were considered to have "highly likely ADHD," those who scored 17-23 points were supposed to have "possible ADHD," and those who scored 0-16 points were considered not to have ADHD.<sup>25</sup>

### Blood Samples

A series of biochemical tests were conducted. Blood samples were collected from the participants during the fasting period, specifically between the hours of 08:00 and 10:00. Following a period of rest in a seated position, the patients had measurement of routine biochemical parameters in the antecubital region using a vacutainer, administered by experienced health personnel. A sample of blood was collected into a biochemistry tube to measure the levels of glucose, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), uric acid, and glycated Hemoglobin (HbA1c). The spectrophotometric approach was used to investigate glucose, cholesterol, HDL, LDL, TG, and uric acid levels. This analysis was conducted using an Atelica clinical chemistry analyzer manufactured by Siemens in Germany. The HbA1c levels were measured by employing the high-performance liquid chromatography technique on the Lifotronic H9 HbA1c device (Lifotronic H9, China)

### Statistical Analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, the USA) Statistical software was used for all analyses. Before starting the analyses, a normality test was performed. Frequency analysis was performed to obtain descriptive information about the study's variables. The Student's t-test and the Mann-Whitney U Test were used to compare normally and non-normally distributed variables in comparisons of two independent groups. The ANOVA test was employed for comparing continuous variables across several independent groups, provided that the normal distribution assumption was met. Following the completion of the ANOVA test, subsequent post-hoc analyses were performed. Specifically, the Bonferroni test was employed when the

variances exhibited homogeneity, whereas Tamhane's T2 test was used in cases where the variances did not demonstrate homogeneity. The Pearson Chi-square test was employed for 2x2 comparisons, including categorical variables when the expected value > 5. Conversely, the Chi-square Yates test was used when the predicted value fell within the range of 3-5. Fisher's Exact test was employed if the anticipated value was <3. In comparing categorical variables with dimensions larger than 2x2, the Pearson Chi-square test was used when the expected value was > 5. In contrast, the Fisher-Freeman-Halton test was used when the predicted value was below 5. When comparing two quantitative variables, the Pearson correlation coefficient was employed when the assumption of normal distribution was met. Alternatively, the Spearman correlation coefficient test was utilized if this assumption was not met. In multivariate analysis, previous analyses used linear regression analysis to identify the estimated risk factors between groups. A significance level of p<0.05 was utilized for statistical analysis.

**RESULTS**

A total of 213 patients, 120 females (18 with T1DM, 102 with T2DM) and 93 males (21 with T1DM, 72 with T2DM), were included in the study. Thirty-nine patients were T1DM (18.3%), and 174 (81.7%) were T2DM. The average age of the patients was 50.48±13.73 (29.24±10.05 in T1DM patients, 55.24±9.18 in T2DM patients). According to ASRS, 23 (10.8%) of the participants had highly probable ADHD symptoms, 53 (24.9%) had probable ADHD symptoms, and 137 (64.3%) had no ADHD symptoms. One hundred fifty-five of the patients were diagnosed with metabolic syndrome. Four patients with MetS diagnosis were in the T1DM group, while 151 were in the T2DM group.

Sociodemographic variables, presence of MetS, and ADHD symptoms were compared between T1DM and T2DM groups. There was no difference in terms of gender between diabetic groups. MetS was diagnosed in 72.7% (n=155) of all patients. Of the 155 patients with MetS, 151 (97.4%) were in the T2DM group, and 4 (2.6%) were in T1DM group. The prevalence of ADHD was detected as 15.4% in patients with T1DM and 9.8% in those with T2DM. Of all diabetic patients (n=76) who showed symptoms of ADHD, 38.1% had symptoms of inattentive appearance, 28.9% had symptoms of hyperactive-impulsive appearance, and 33% had symptoms of combined appearance. 36.4% of T1DM patients who showed ADHD symptoms had hyperactive-impulsive appearance, 31.8% had inattentive appearance and 31.8% had combined appearance symptoms. In the T2DM group, inattentive appearance symptoms were 40.7%, combined appearance symptoms were 25.9%, and hyperactive-impulsive appearance symptoms were 25.9%.

**Table 1.** Comparison of sociodemographic variables in type 1 and type 2 diabetes mellitus

	T1DM n=39 (%)	T2DM n=174 (%)	Total n=213 (%)	P
Gender				
Female	18 (46.2)	102 (58.6)	120 (56.3)	0.215
Male	21 (53.8)	72 (41.4)	93 (43.7)	
MetS				
Yes	4 (10.3)	151 (86.8)	155 (72.7)	0.001*
No	35 (89.7)	23 (13.2)	58 (27.3)	
ADHD symptoms				
High likely	6 (15.4)	17 (9.8)	23 (10.7)	0.010*
Probable likely	16 (41)	37 (21.3)	53 (24.8)	
Not likely	17 (43.6)	120 (69)	137 (64.3)	
ADHD appearances				
Inattention	6 (15.4)	22 (40.7)	29 (38.1)	0.010*
Hyperactive-impulsive	16 (41)	14 (25.9)	22 (28.9)	
Combined	17 (43.6)	18 (33.3)	25 (32.8)	

Abbreviations: T1DM: Tip 1 Diabetes Mellitus, T2DM: Tip 2 Diabetes Mellitus, ADHD: Adult Attention Deficit Hyperactivity Disorder, MetS: Metabolic syndrome

**Table 2.** Comparison of ASRS scale scores, clinical and biochemical parameters in type 1 and type 2 diabetic groups

Parameters	T1DM (n=39)	T2DM (n=174)	p
Age (year)	29.24±10.05	55.24±9.18	<.001
BMI (kg/m2)	23.43±4.72	33.75±7.35	<.001
WC (cm)	78.10±10.72	105.04±14.06	<.001
HbA1c	9.50±2.7	7.94±1.63	<.001
Glucose	251.76±118.24	157.94±71.74	<.001
Triglyceride	108±55.92	197.18±115.01	<.001
Cholesterol	171.56±40.66	185.06±42.34	.083
HDL	44.55±9.64	37.24±9.59	<.001
LDL	123.99±34.46	138.51±35	.020
AIP	0.35±0.23	0.67±0.28	<.001
Uric Acid	3.32±1.04	5.11±1.39	<.001
Severity of MetS	1.67±.74	3.65±.99	<.001
ASRS/I	14.69±7.80	11.96±7.20	.036
ASRS/HI	13.74±5.60	10.45±6.55	.004
ASRS/T	28.44±11.80	22.43±12.30	.006

Data presented as mean±standard deviation, Abbreviations: T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus, BMI: Body mass index; WC: Waist Circumference, ASRS: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale, ASRS/I: Inattention score, ASRS/HI: Hyperactivity impulsivity score; ASRS/T: Total score; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AIP: Atherogenic index of Plasma; MetS: Metabolic Syndrome.

The comparison of ASRS scale scores clinical and biochemical parameters in T1DM and T2DM patients is demonstrated in Table 2. ASRS total and subscale scores of T1DM patients were significantly higher than those of T2DM patients' (ASRS-IA p=.036; ASRS H/I p=.004; ASRS total p=.006). Age, BMI, WC, TG, LDL, AIP, uric acid, and MetS severity were higher in the T2DM group compared to the T1DM group (p<.001). HbA1c, Glucose, HDL-C, ASRS/HI, ASRS/I, and ASRS/T scores were statistically higher in the T1DM group.

**Table 3.** Independent samples T-test results of ASRS total scale scores in type 2 DM patients according to demographic variables

Demographic variables	ASRS/T x̄±SD	P
Stress related eating		
Yes (n=124)	23.9±12.12	0.011*
No (n=50)	18.72±12.07	
Organ involvement		
Yes (n=23)	29.3±10.7	0.004*
No (n=151)	21.38±12.2	
Additional diseases		
Yes (n=97)	24.2±13.11	0.031*
No (n=77)	20.1±10.85	
MetS		
Yes (n=151)	23.1±12.5	0.043*
No (n=23)	17.6±9.05	

ASRS/T: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale Total score; SD: standard deviation; x̄: mean; t: Independent Samples t-test; MetS: Metabolic Syndrome

It was investigated whether the ASRS/T scale scores of T2DM patients varied according to demographic variables. It was demonstrated that those with MetS, concomitant disease, organ involvement, eating disorders, and stress-related eating had statistically higher ASRS/T scores than those without these symptoms.

**Table 4.** Spearman correlation analysis between ASRS scale scores, metabolic syndrome severity, clinical and biochemical parameters of type 1 and type 2 DM patients

	ASRS/I		ASRS/HI		ASRS/T	
	T1DM	T2DM	T1DM	T2DM	T1DM	T2DM
Age						
r	-0.078	-0.038	-0.069	-0.283	-0.084	-0.120
p	0.636	0.621	0.677	0.016*	0.610	0.115
BMI						
r	-0.066	-0.039	-0.039	0.009	-0.062	0.026
p	0.690	0.614	0.814	0.909	-0.708	0.736
WC						
r	-0.110	-0.059	-0.211	-0.040	-0.173	-0.058
p	0.503	0.440	0.196	0.602	0.291	0.445
HbA1C						
r	0.131	-0.012	0.230	0.075	0.195	0.032
p	0.427	0.874	0.160	0.323	0.233	0.678
Triglyceride						
r	-0.289	0.129	-0.383	0.163	-0.373	0.165
p	0.74	0.091	0.016*	0.032*	0.019*	0.029*
Total cholesterol						
r	-0.166	0.018	-0.372	0.122	-0.286	0.078
p	0.311	0.816	0.020*	0.109	0.077	0.308
HDL						
r	0.157	-0.094	0.061	-0.110	0.133	-0.155
p	0.339	0.218	0.714	0.148	0.421	0.130
LDL						
r	-0.101	-0.013	-0.025	0.062	-0.079	0.024
p	0.539	0.863	0.879	0.420	0.633	0.750
AIP						
r	-0.301	0.095	-0.291	0.167	-0.337	0.148
p	0.063	0.212	0.072	0.028*	0.036*	0.051
MetS severity						
r	-0.183	0.271	-0.168	0.306	-0.201	0.311
p	0.265	0.024*	0.307	0.006*	0.221	0.005*

T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus, ASRS: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale, ASRS/I: Inattention score, ASRS/HI: Hyperactivity impulsivity score; ASRS/T: Total score, BMI: Body mass index; WC: Waist Circumference HbA1c: Glycosylated haemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AIP: Atherogenic index of Plasma; MetS: Metabolic Syndrome.

Correlation analyses were conducted between ASRS scale scores (attention, hyperactivity, and total scores) and clinical and biochemical parameters such as age, BMI, WC, HbA1c, TGS, Total cholesterol, LDL, PAI, and MetS severity in T1DM and T2DM patients. A moderate negative correlation was detected between ASRS/HI score and TG and total cholesterol (r=-0.383, p=0.016; r=-0.372, p=0.020 respectively), and a moderate negative correlation was detected between ASRS/T score and TG and AIP (r=-0.373, p=0.019; r=-0.337, p=0.036) in T1DM. In T2DM, a moderate negative correlation was detected between age and ASRS/HI (r=-0.283, p=0.016), and a weak positive correlation was detected between ASRS/HI and AIP (r=0.167, p= 0.028). A weak positive correlation was detected between the ASRS/T score and TG in T2DM (r=0.165, p=0.029). In the same table, while no relationship was found between MetS severity and ASRS/D, ASRS/HI, and ASRS/T scores in T1DM, a moderate positive correlation was detected in all ASRS scores in T2DM (r=0.271, p=0.024; r=0.306, p=0.006; r=0.311, p=0.005).

**Table 5.** Linear regression analysis model for the effect of ASRS-HI and ASRS-total scale score on MetS severity in type 2 DM patients

	B	SE	β	R	p
ASRS-HI	3.32	0.14	0.206	0.206	0.000*
ASRS-T	3.23	0.15	0.211	0.211	0.000*

SE: Standart error, ASRS: Adult Attention Deficit Hyperactivity Disorder Self-Report Scale, ASRS/HI: Hyperactivity impulsivity score; ASRS/T: Total score

In the linear regression analysis model results regarding the effect of ASRS-HI and ASRS-T Scale Score on MetS Severity in T2DM patients, ADHD-HI and T score were statistically effective on the severity of MetS.

**Table 6.** Comparison of ASRS scores according to DM duration

DM Duration	ASRS/T	ASRS/I	ASRS/HI
1-5 years (n=72)	20.6±12.7	10.5±7.3	10.1±6.6
5-10 years (n=66)	23.9±12.5	12.5±7.3	11.4±6.7
≥10 years (n=75)	25.89±11.5	14.2±6.9	11.6±6.1
p	0.035	0.007*	0.345

\*Bonferroni posthoc difference: 1-5 years and ≥10 years (p=0.005); P<0.016 is significant. ASRS: Adult DM: Diabetes Mellitus, Attention Deficit Hyperactivity Disorder Self-Report Scale, ASRS/I: Inattention score, ASRS/HI: Hyperactivity impulsivity score; ASRS/T: Total score

The ASRS/HI score of 213 patients did not vary according to the duration of diabetes, but as the duration of diabetes increased, the ASRS/T and ASRS/I scores gradually increased. ASRS/T score did not show a statistical difference, but there was a statistically significant difference in ASRI/I score in patients with DM for 1-5 years and over ten years (p=0.008).

## DISCUSSION

DM is a chronic metabolic disease that negatively impacts carbohydrate, protein, and fat metabolism and might follow a severe course. With its rapidly increasing global prevalence, it has become one of the primary public health issues. Hence, it is imperative to emphasize the need for early detection and intervention in managing this disease while acknowledging the societal obligation to enhance the general knowledge of associated consequences. Recent research has indicated a notable association between ADHD and endocrine and metabolic disorders. Among these disorders, DM has emerged as the most often reported condition in adults with ADHD. In a comprehensive cohort research, it was observed that the prevalence of T2DM was 70% higher among those diagnosed with ADHD than those who did not have ADHD.<sup>26</sup> ADHD has been associated with many adverse health outcomes, including reduced physical activity, binge eating, increased body weight, and insulin resistance. These factors may potentially contribute to the development of MetS and T2DM in affected individuals.

The objective of this study is to explore the frequency of ADHD in type 1 and 2 diabetic patients. Additionally, the study aims to investigate the potential association between ADHD and MetS, AIP, and other lipid parameters. Our research indicated that 10.7% of diabetic patients presented with ADHD symptoms.

In our study, a difference was detected between the T1DM and T2DM groups regarding the ADHD symptoms. It was found that ADHD symptoms were significantly higher in patients with T1DM compared to patients with T2DM. However, the higher ASRS scores in T1DM compared to T2DM might be attributed to different mechanisms. For instance, fluctuations in blood sugar, especially hypoglycemia, can adversely affect brain functions, including attention, concentration, and memory. Chronic hyperglycemia, on the other hand, may damage neuronal functions, intensifying the severity of ADHD symptoms. DM management is more difficult in younger individuals, which might trigger ADHD symptoms and signs.

In a recent study predominantly composed of patients with T2DM, the prevalence of ADHD was found to be 2.4%.<sup>27</sup> In another study, 7.2% of patients with T2DM were diagnosed with ADHD based on the ASRS. In our research, ADHD prevalence in T2DM was found to be 9.8%. In a large meta-analysis, ADHD prevalence in children and adolescents with T1DM was found to be 5.3%.<sup>28</sup> In another study comprising adults with T1DM, ADHD prevalence was 9.5%.<sup>29</sup> In our study, similar to the latter research, adults with T1DM were included,

and the ADHD prevalence was a surprisingly elevated 15.4%. Different outcomes in such studies might be possible among different countries, ethnicities, or socioeconomic groups. As can be understood from the tables in our research, all ASRS scale scores were higher in T1DM compared to T2DM, and the likelihood of ADHD diagnosis was also higher in T1DM. In addition, another finding from our study is that the ADHD manifestations in T2DM are mostly inattentive; hyperactivity and impulsivity are more common in T1DM. Due to ADHD presenting differently in young and middle-aged individuals, the lower average age of patients with T1DM compared to those with T2DM in our study might have contributed to the different clinical presentations observed in the two diabetic groups. AIP levels and other metabolic laboratory parameters were lower in T1DM. The younger average age in this group, and consequently the reduced likelihood of accompanying disease that could pose an additional cardiovascular risk, might explain this result. Age, TG, AIP, LDL, Uric Acid, and MetS severity were higher in T2DM, and as MetS severity, PAI, and TGS levels increased, ASRS/HI and total scores also increased. In patients with T2DM, just as with ADHD, there are problems with night eating habits, sleep disturbances, emotional stress, and appetite control. It has been reported that individuals with ADHD have cardiovascular risk twice as high as those without ADHD,<sup>30</sup> just like in DM.<sup>31</sup>

In T2DM, due to higher levels of TG and lower levels of HDL, the AIP level was found to be higher than in T1DM. Additionally, the AIP levels in both groups were found to be above the normal range. In the T2DM group, ASRS-HI and T scores also exhibited a significant effect on the severity of MetS. The increase in TG levels, a primary component of lipotoxicity, which acts as a significant systemic inflammatory stimulator, might cross the blood-brain barrier, potentially causing cerebrovascular inflammation. The positive correlation between ASRS scores and TG and AIP levels in T2DM might be attributable to cerebrovascular inflammation intensifying the ADHD symptoms. The absence of this positive correlation between AIP and ADHD scores in the T1DM group might be due to TG levels being relatively closer to the fact that this positive correlation was not observed in the T1DM group and may be attributed to TG levels being at a normal level.

The prevalence of MetS in the adult population is between 20-25%, whereas it is around 80% in patients with T2DM.<sup>32,33</sup> It was found to be 86.8% in the T2DM group, consistent with these studies in our study. Traditionally, patients with T1DM are believed to have lower BMI and, consequently, a lower risk of MetS.

However, in recent years, the profile of patients with T1DM has been changing rapidly because of increased sedentary lifestyles and intake of energy-dense foods. In a prospective study conducted in patients with T1DM, the prevalence of MetS was 12%.<sup>34</sup> In our study, the prevalence of MetS in the T1DM group was 10.3%. However, in patients with T2DM who have an additional disease, diabetic-related organ involvement, and MetS, the ASRS/T score was significantly higher than those without. Thus, increased oxidative stress and inflammation-induced neuronal degeneration, leading to neurotransmitter metabolism disruptions, may contribute to the development of ADHD, particularly in the presence of genetic factors. In our study, it was also found that as the duration of diabetes increased, the ASRS-Total and Inattention scores increased. This difference was most evident in groups between 1-5 years and above 10 years. There was no relationship between ASRS-HI score and the duration of DM.

### Limitations

This study has some limitations. Firstly, one of these limitations is using self-report scales in our research. Secondly, the cross-sectional nature of our research does not provide sufficient answers regarding causality. However, even if the results do not establish causality, they indicate a strong relationship between DM and ADHD symptoms. However, patients with major psychiatric illnesses and those using psychotropic medications were excluded; the absence of a psychiatric examination can be considered one of the limitations of this study. Although diabetes is inherently a comorbid disease, the exclusion of patients with major comorbidities represents both a strength and a limitation of our study. Despite the limitations, this study also has notable strengths. The enrollment of both type 1 and type 2 diabetic patients, considering BMI, lipid profiles, and the presence and severity of MetS, constitutes the strengths of this study. Additionally, our study results have the potential to contribute to increased self-awareness regarding ADHD symptoms in the diabetic population.

In patients with T1DM, managing glycemic control and adjusting insulin doses by monitoring blood sugar levels may become much more challenging due to ADHD symptoms such as inattention, impulsivity, impairments in planning, and time management skills. Investigating the presence of neuropsychiatric and neurodevelopmental disorders like ADHD provides many benefits in the management. In order to ensure patients' quality of life and metabolic control and even to prevent acute and chronic complications of diabetes, recognizing and treating ADHD symptoms in addition to diabetes management should be considered a medical necessity.

## CONCLUSION

The coexistence of DM and ADHD should be recognized as a high-risk population requiring a comprehensive multidisciplinary approach. In addition to the diabetes and ADHD specialists, this team should include a dietitian, social worker, and psychologist. In clinical practice, this holistic approach potentially reduces the risks of acute and chronic complications, including cardiovascular risk, through the enhanced management of DM. The relationship between ADHD, DM, and MetS is an essential issue that deserves further investigation. Therefore, to manage all these diseases, there is a need for more comprehensive and long-term follow-up studies that will guide clinical practices in these fields.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study protocol was approved by the Erzurum Training and Research Hospital Ethics Committee (Date: 14.06.2023, Decision No: 02/16).

### Informed Consent

All participants provided written and verbal informed consent.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Evaluation of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio in primary hyperparathyroidism before and after parathyroidectomy

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**Cite this article as:** Çetinkaya Z, Keleşoğlu Ş, Gökay F, Yılmaz Y. Evaluation of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio in primary hyperparathyroidism before and after parathyroidectomy. *Anatolian Curr Med J.* 2024;6(1):73-79.

Received: 28.10.2023

Accepted: 25.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** This study aimed to evaluate Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios, which are new ventricular repolarization (VR) parameters in primary hyperparathyroidism (PHPT) patients, and also investigate the potential effect of parathyroidectomy (PTx) on these parameters.

**Methods:** In total, 27 patients with PHPT who underwent PTx and 25 control subjects were selected for our study. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios of patients planned for PTx were compared to healthy matched controls. Electrocardiographic parameters measured 6 months after the surgery were also compared with preoperative values for each patient.

**Results:** Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in PHPT patients compared to the control group ( $p < 0.001$ , for all). It was observed that the parameters mentioned after surgery decreased significantly, and there was no statistical difference when compared to the control group. The correlation analysis revealed a significant and positive correlation between corrected calcium (CCa) and PTH levels with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio (for Ca;  $r = 0.515$ ,  $p = 0.006$ ;  $r = 0.398$ ,  $p = 0.040$ ;  $r = 0.797$ ,  $p < 0.001$  respectively vs. for PTH;  $r = 0.538$ ,  $p = 0.04$ ;  $r = 0.422$ ,  $p = 0.028$ ;  $r = 0.812$ ,  $p < 0.001$  respectively).

**Conclusions:** This study showed that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were prolonged in PHPT. These values, which are accepted as an indicator of sudden cardiac death after PTx, decreased significantly. In addition, both high PTH and high calcium (Ca) levels appear to have the potential to cause arrhythmogenic effects separately.

**Keywords:** Primary hyperparathyroidism, ventricular repolarization, parathyroidectomy, ventricular arrhythmia.

## INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disease characterised by excessive release of parathyroid hormone (PTH), resulting in dysregulation of calcium (Ca) metabolism.<sup>1</sup> Although clinical practice focuses more on adverse effects such as renal complications and osteoporosis in PHPT, PHPT has been shown to be associated with increased cardiovascular morbidity and mortality.<sup>2</sup> Accordingly, there has recently been increased interest in cardiac evaluation in patients with PHPT. Parathyroidectomy (PTX) surgery is the first choice and most effective treatment method in symptomatic patients with PHPT and asymptomatic patients with significant hypercalcemia ( $>1.0$  mg/dL/ $0.25$  mmol/L).<sup>3</sup>

Electrocardiographic data has shown that shortening the QT interval, a well-known risk factor for arrhythmias, is common in PHPT patients; however, the exact prevalence of short QT interval, and more importantly, arrhythmias in PHPT patients is unknown.

In ECG, research on ventricular recovery and augmented dispersion of repolarization are useful markers for ventricular arrhythmias. Some ventricular repolarization markers are useful to predict arrhythmias, including the QT interval, QT dispersion, and T-wave alternans.<sup>4,5</sup>

Recent studies have suggested that new indexes such as Tpeak-Tend (Tp-e) interval and Tp-e interval/QT interval (Tp-e/QT) ratio may be associated with ventricular arrhythmias in various clinical scenarios.<sup>6-8</sup>

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The aim of this study was to evaluate Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios, which are new arrhythmia markers in PHPT patients by electrocardiographic and compare these parameters with those of control subjects. We also aimed to investigate the potential effect of PTx on these parameters.

## METHODS

The study was carried out with the permission of Kayseri City Hospital, Clinical Researches Ethics Committee (Date:03.09.2020, Decision No: 146). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Study Population and Study Protocol

38 PHPT patients who underwent PTx between January 2019 and November 2020 were included in the study. At the beginning of the study, physical examination findings, a detailed medical histories and laboratory characteristics of the study patients and control groups were recorded. The control group consisted of 25 people with normal blood PTH levels and comparable with the patient group in terms of age, gender, and cardiovascular risk factors. The electrocardiographic examination was performed in all patients at baseline and six months after surgery. Five patients did not come for control six months later, so they were excluded from the study.

Other exclusion criteria were: uninterpretable ECG (left bundle branch block, the presence of a pacemaker, those with U waves and negative T waves in the ECG), those with severe valvular disease, known coronary artery disease and heart failure, hypothyroidism and hyperthyroidism, creatinine clearance (CrCl)  $\leq$  60 ml/min. None of the registered patients were using any medication that affected the QT interval.

After 11 patients were excluded from the study, the data of the remaining 27 patients were used in the analysis. Cardiovascular risk factors such as hypertension (HT) and diabetes mellitus (DM) were defined as previously described (9). Smokers were current smokers and had been using for at least 10 years.

Corrected calcium (CCa) levels were used for calcium levels in the study group (Corrected calcium = serum calcium + 0.8 X (4 - serum albumin))

### Electrocardiogram (ECG) Analysis

All standard 12-lead ECGs were acquired at rest in the supine position simultaneously using a recorder (Philips brand machine) set at 25 mm/s paper speed and 1 mV/cm standardization. All ECGs were scanned and transferred to personal computers an electronic caliper (Cardio Calipers, version 3.3 software; Iconico.com, Philadelphia, PA, USA) was used under magnification to record the

measurements. Assessments of the ECG were done by two cardiologists blinded to the clinical data and to diminish the error measurements. Patients whose ECGs showed U waves and negative T waves were excluded from the study.

The Tp-e interval was defined as the distance between the peak of the T-wave and the end of the T-wave. All Tp-e intervals were measured using the best available T-wave in lead V5 (10). When the lead V5 result was not suitable for analysis, the V4 and V6 were used.

The QT interval was measured from the beginning of the QRS complex to the end of the T wave in precordial lead V6, which best reflects the transmural axis of the left ventricle (11), and corrected for heart rate using the Bazett formula:  $cQT = QT \sqrt{(R-R \text{ interval})}$ . The Tp-e/QT ratio and Tp-e/QTc (Tp-e divided by QT and Tp-e divided by QTc) were calculated from these measurements. Interobserver and interobserver coefficients of variation were less than 5%, respectively.

### Echocardiography

Conventional echocardiography was performed with 2-dimensional, M-mode, pulsed wave, continuous, colour Doppler and tissue Doppler imaging (TDI) using the Vivid 7 Pro ultrasound system (Vivid 7 pro, GE, Horten, Norway, 2-4 MHz phased array transducer ultrasound system). Conventional echocardiographic images were obtained from the parasternal and apical views according to the guidelines of the American Society of Echocardiography (12). Left ventricular (LV) diameters and wall thickness were measured from the parasternal views by M-mode echocardiography. The Simpson's method was used for the calculation of the LV ejection fraction. The left atrial area and diameter were measured from the parasternal long axis view. Mitral inflow velocities were measured from apical views. Conventional echocardiography evaluations were performed by a cardiologist blinded to the clinical data.

### Statistical Analysis

Statistical analyzes were performed using SPSS Statistics Package version 21.0 (SPSS Inc, Chicago, IL, USA) for Windows. The normal distribution of variables was analyzed using the Kolmogorov-Smirnov method. Continuous data means and standard deviations were evaluated and recorded. The chi-square test was used for categorical variables and was calculated as a percentage. Descriptive data was given as mean  $\pm$  standard deviation, depending on normality of distribution. Median and interquartile range were given when the variable did not follow a normal distribution. The independent sample t-test was used for the comparison of normally distributed quantitative variables, and the Mann-Whitney U test was used for the comparison of non-normally distributed quantitative variables.

ANOVA test was performed to analyse the variables between control group, PHPT patient data, and patient data after PTx. Variability between groups was performed by the LSD test. Correlation analyses were performed using Pearson's and Spearman's coefficient of correlation. A probability value of  $p < 0.05$  was considered significant, and 2-tailed p values were used for all statistics.

### RESULTS

A total of 52 participants were selected in the current study. The PHPT group consisted of 27 subjects (2 men, 25 female), and the control group included 25 individuals (3 men, 22 female). Baseline demographic features and laboratory measurements of the study groups are presented in **Table 1**. The study population was similar regarding sex distribution, age, smoking status, frequencies of HT and DM were not significantly different between patients and the control group ( $p > 0.05$ ). As expected, patients with PHPT had higher serum PTH levels and CcCa levels compared to the control group, while serum phosphorus levels were significantly lower ( $p < 0.001$ , for all). Other blood parameters were similar between groups. Serum PTH and CcCa levels significantly decreased, whereas serum phosphorus levels significantly increased after PTx surgery. After surgery, 16 of the patients were receiving vitamin D supplements and 5 patients were receiving bisphosphonate treatment because osteoporosis developed.

The electrocardiographic and echocardiographic parameters of the groups are shown in **Table 2**. There was no statistically significant difference between the echocardiographic parameters of PHPT and the control group.

Heart rate and QRS duration among the electrocardiographic parameters were similar between the groups ( $p = 0.409$ ,  $p = 0.562$  respectively). Although the QT interval and QTc interval were shorter in PHPT patients, it was not statistically significant ( $p > 0.05$ , for both). Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in PHPT patients compared to the control group ( $p < 0.001$ , for all).

The correlation analysis revealed a significant and positive correlation between Ca levels with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio ( $r = 0.515$ ,  $p = 0.006$ ;  $r = 0.398$ ,  $p = 0.040$ ;  $r = 0.797$ ,  $p < 0.001$  respectively) (**Figure 1**). There was the same correlation relationship between PTH levels and Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. ( $r = 0.538$ ,  $p = 0.04$ ;  $r = 0.422$ ,  $p = 0.028$ ;  $r = 0.812$ ,  $p < 0.001$  respectively) (**Figure 2**). The change in electrocardiographic parameters of PHPT patients 6 months after PTx compared to baseline is shown in **Table 3**. It was observed that the parameters mentioned after surgery decreased significantly, and there was no statistical difference when compared to the control group (**Table 4**).

**Table 1.** Baseline demographic features and laboratory measurements of the study groups

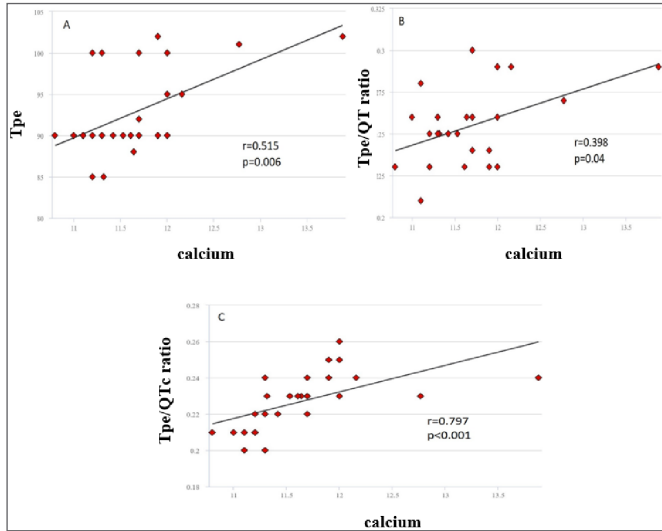
Variables	Control group (n=25)	PHPT (n=27)	P Value
Age (years)	51.2 (41-62.5)	54.7 (44-63)	0.279
Male/female	3/22	2/25	0.575
Hypertension (HT)	5 (20%)	8 (29%)	0.423
Diabetes Mellitus (DM)	3 (12%)	5 (18%)	0.515
Smoke	0	1 (3%)	0.331
Body Mass Index (BMI)	26.41±1.83	27.12±2.26	0.480
Systolic Blood Pressure (CBP) (mm/hg)	125.5±8.2	127.2±10.5	0.521
Diastolic Blood Pressure (DBP) (mm/hg)	78.2±7.2	80.7±6.3	0.612
Glucose (mg/dL)	91.3±5.9	96.8±13.2	0.064
Kreatinin (mg/dL)	0.83±0.15	0.81±0.14	0.732
AST (U/L)	22.6±5.1	20.9±7.4	0.333
ALT (U/L)	20.4±6.3	22.7±11.7	0.382
Albumin (mg/dl)	4.3±0.50	4.5±0.3	0.056
Corrected calcium (mg/dl)	9.1 (8.8-9.5)	11.6 (11.2-11.9)	<0.001
Phosphorus (mg/dl)	3.5 (3.3-3.9)	2.4 (2.1-2.9)	<0.001
Parathyroid Hormone (PTH)	37.6 (32.5-42)	265.5 (123-395)	<0.001
Thyroid Stimulating Hormone (TSH)	1.8 (0.9-2.4)	1.9 (0.8-2.4)	0.762
D Vitamin	21.4±6.4	18.0±6.5	0.066
White Blood Cell (WBC) (10 <sup>3</sup> /uL)	8.4±2.5	7.9±1.8	0.425
Hemoglobin (g/l)	13.7±1.1	14.2±1.2	0.127
Platelet (/mm <sup>3</sup> )	241.5±78.0	265.2±66.6	0.292
Previous medications, n			
Angiotensin converting enzyme inhibitor	2	3	
Angiotensin-aldosterone antagonists	2	4	
Calcium channel antagonists (dihydropyridine)	1	1	

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables.

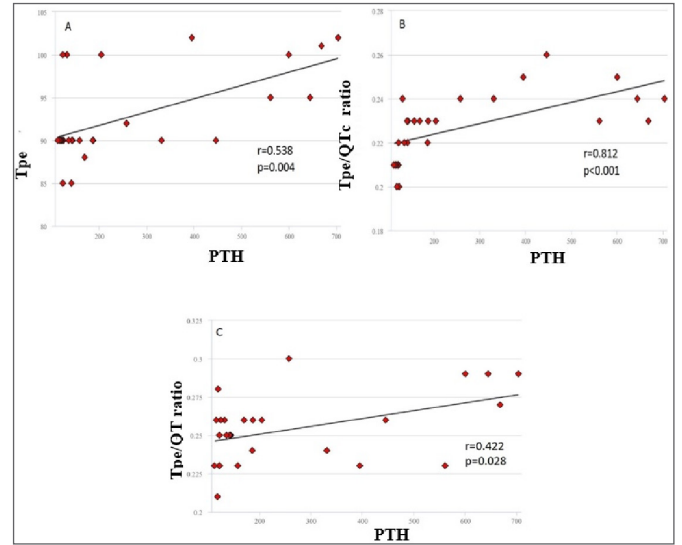
**Table 2.** Electrocardiographic and Echocardiography Characteristics of the study population

Variables	Control group (n=25)	PHPT (N=27)	P value
<b>Electrocardiographic Finding</b>			
Heart rate (beat/min)	76.2±9.3	78.8±12.5	0.409
QRS duration (ms)	84.1±7.8	82.7±9.4	0.562
QT interval (ms)	378.2±20.9	367.6±28.7	0.147
QTc interval (ms)	417.3±16.5	408.7±23.9	0.071
Tp-e interval (ms)	81.9±10.4	92.7±5.2	<0.001
TPe/QTc ratio (ms)	0.19±0.02	0.22±0.01	<0.001
TPe/QT ratio (ms)	0.21±0.03	0.25±0.02	<0.001
<b>Echocardiography Characteristics</b>			
LVEDD (cm)	4.72±0.42	4.70±0.45	0.870
LVESD (cm)	3.13±0.47	2.98±0.30	0.196
IVSD (cm)	1.02±0.19	1.08±0.11	0.146
PWD (cm)	0.97±0.20	1.08±0.10	0.021
LVEF (%)	62.6±2.9	63.1±4.6	0.667

Tp-e= T wave interval from peak to end, c=corrected, LVEDD: Left Ventricular End Diastole Diameter, LVESD: Left Ventricular End Systole Diameter, IVSD: Interventricular Septal Diameter, PWD: Posterior Wall Diameter, LVEF; Left Ventricular Ejection Fraction



**Figure 1.** (A) Correlation between Tpe interval and calcium count (B) Correlation between Tpe/QT ratio and calcium count. (C) Correlation between Tpe/QTc ratio and calcium count.



**Figure 2.** (A) Correlation between Tpe interval and PTH level (B) Correlation between Tpe/QTc ratio and PTH level. (C) Correlation between Tpe-e/QT ratio and PTH level.

Table 3. Laboratory Measurements, Electrocardiographic and Echocardiographic Findings before and after Parathyroidectomy.			
Variables	Parathyroidectomy		P value
	Before	After	
<b>Laboratory Measurements</b>			
Corrected calcium (mg/dl)	11.6 (11.2-11.9)	9.2 (9-9.6)	<0.001
Phosphorus (mg/dl)	2.4±0.5	3.3±0.5	<0.001
Parathyroid hormone (PTH)	265.5 (123-395)	44.8 (35-57)	<0.001
D Vitamin	18.0±6.5	21.2±5.9	0.064
TSH	1.92 (0.8-2.4)	2.01 (1.03-2.7)	0.716
<b>Electrocardiographic Finding</b>			
QT interval, (ms)	367.6±29.1	377.6±16	0.124
QTc interval (ms)	408.7±17.1	416.8±12.8	0.053
Tpe interval (ms)	92.7±5.2	84.1±7.3	<0.001
TPe/QT ratio (ms)	0.25±0.02	0.22±0.02	<0.001
TPe/QTc ratio (ms)	0.22±0.01	0.20±0.01	<0.001
<b>Echocardiographic Finding</b>			
LVEDD (cm)	4.70±0.4	4.72±0.4	0.860
LVESD (cm)	2.98±0.30	3.10±0.4	0.300
IVSD (cm)	1.08±0.1	1.06±0.1	0.535
PWD (cm)	1.08±0.1	1.04±0.1	0.236
LVEF (%)	63.1±4.6	62.4±3.2	0.565

**DISCUSSION**

This study showed that Tpe interval, Tpe-e/QT, and Tpe-e/QTc ratios were prolonged in PHPT patients without known cardiovascular disease, as compared to controls. In addition, in our study, we found a significant correlation between Tpe interval, Tpe-e/QT ratio, Tpe-e/QTc ratio and Ca levels and PTH levels in PHPT patients. One of the most important results of our study is, these values, which are accepted as an indicator of sudden cardiac death (SCD) after PTx, decreased significantly.

As is known, PHPT is an endocrinological disease that is typically characterised by high or non-suppressed PTH levels together with high serum Ca levels.<sup>1</sup> Studies have shown that both PTH and Ca levels affect cardiomyocyte, heart conduction system, smooth vascular and endothelial cells. Excessive secretion of PTH can affect the myocardium and alter the repolarization. Although the effects of PTH on the heart were thought to be due to hypercalcemia, it is now known that PTH itself causes hypertrophy in cardiac myocytes and vascular smooth muscles independent of Ca levels. In addition, it has been reported in the literature that there is a direct relationship between endothelial dysfunction and PTH.<sup>13-17</sup>

Table 4. Post Hoc Test									
	Control group	Group 1	P value	Control group	Group 2	P value	Group 1	Group 2	P value
QT (msn)	378.2	367.6	0.097	378.2	377.6	0.923	367.6	377.6	0.110
QTc (msn)	417.3	408.7	0.057	417.3	420.9	0.421	408.7	420.9	0.007
Tpe (msn)	81.9	92.7	<0.001	81.9	84.1	0.321	92.7	84.1	<0.001
TPe/QTc ratio (ms)	0.19	0.22	<0.001	0.19	0.20	0.539	0.22	0.20	<0.001
TPe/QT ratio (ms)	0.21	0.25	<0.001	0.21	0.22	0.394	0.25	0.22	<0.001
Corrected calcium (mg/dl)	9.17	11.6	<0.001	9.17	9.24	0.646	11.6	9.24	<0.001
Phosphorus (mg/dl)	3,5	2,4	<0.001	3,5	3,3	0.116	2,4	3,3	<0.001
PTH	37,6	265,5	<0.001	37,6	44,8	0,823	265,5	44,8	<0.001

Group1. Patients with Primary hyperparatiroidism, Group 2. Patients with Parathyroidectomy. Tpe-e= T wave interval from peak to end.

PHPT-induced hypercalcemia is a risk factor for cardiac arrhythmias.<sup>18,19</sup> Hypercalcemia, which develops in PHPT, is conventionally accepted to cause a shortening of the QT interval.<sup>20,21</sup> The shortening of the refractory period due to QT shortening may lead to complex ventricular arrhythmias or SCD.<sup>20,21</sup>

The QTc interval and QT dispersion which show myocardial repolarization status have been used for risk stratification in different patient groups.<sup>22</sup> In recent years, the use of the Tp-e interval and the Tp-e/QTc ratio in determining ventricular arrhythmias and risk of SCD has become increasingly common. Tp-e interval is the duration of the transmural distribution of myocardial repolarization.<sup>23</sup> There is a relationship between the Tp-e and the life-threatening arrhythmic events, and therefore Tp-e helps to predict the risk of developing arrhythmias.<sup>7,24-28</sup> However, QT and Tp-e intervals vary widely between individuals, and the Tp-e interval is affected by the changes in the heart rate. For this reason, the Tp-e/QT ratio has been more consistent among the individuals and their heart rates, regardless of their Tp-e interval values.

Pepe et al.<sup>29</sup> demonstrated that the mean QTc values of patients with PHPT lie within the normal range, but they were significantly lower than the mean QTc values of the control group. They also found that PHPT patients had a higher prevalence of both supraventricular (SVBP) and ventricular premature beats (VPB) in 24-hour ECG monitoring. In addition, they showed that while both SVBP and VPB rates decreased significantly in PHPT patients who underwent PTx after 6 months, QTc values returned to normal levels. As a result, they showed that short QTc caused by hypercalcemia due to PHPT increased the prevalence of SVPBs and VPBs, and these arrhythmic events decreased significantly with PTx.

Similarly, Curione et al.<sup>30</sup> found that QTc was significantly lower in PHPT patients, while QT dispersion was higher. Accordingly, they showed that the possibility of life-threatening arrhythmias in PHPT patients increased. In their other study, Curione et al.<sup>31</sup> showed that in PHPT patients who underwent PTx, QT duration and QTc dispersion returned to the normal range after the procedure. They claimed that the surgery performed in this patient group eliminated the myocardial electrical instability.

In our study, we also have found that the QT intervals were shorter in the patient group than in the control group. In addition, similar to the findings of the aforementioned studies, we also did not find any statistically significant difference between the QTc intervals of the patient and the control groups, and the QTc intervals we have found were within normal limits, as well. In addition, we have found that Tp-e intervals, Tp-e/QT ratios and Tp-e/QTc ratios were higher in patients with PHPT compared to the

control group. In our previous study, we detected similarly high levels of Tp-e intervals, Tp-e/QT ratios and Tp-e/QTc ratios.<sup>32</sup> Yan et al.<sup>33</sup> showed that a prolonged Tp-e/QT ratio was an independent predictor of nocturnal PVCs in OSA patients. Tashiro et al.<sup>34</sup> claimed that prolonged absolute and corrected Tp-e intervals and an increase in the Tp-e/QT ratio may be useful predictors of life-threatening arrhythmia in children with hypertrophic cardiomyopathy. Yamaguchi et al.<sup>23</sup> suggested that the Tp-e/QT ratio is a better predictor for torsade de pointes compared to the QTc interval. Watanabe et al.<sup>27</sup> have demonstrated that longer Tp-e intervals are associated with spontaneous ventricular tachycardia. On the other hand, Shimizu et al.<sup>35</sup> have demonstrated that the Tp-e/QT ratios were higher in patients who developed SCD than those who did not. Hevia et al.<sup>7</sup> revealed that the incidence of recurrent cardiac events is significantly higher in patients with increased Tp-e ranges. Ventricular arrhythmias in PHPT were generally reported in the form of case reports in the literature, and follow-up studies of the long-term cardiovascular consequences of PHPT are not available in the literature. Nilsson et al.<sup>36</sup> and Pepe et al.<sup>29</sup> have reported an increase in VPB in patients with PHPT. In our study, which was also not a follow-up study, we have found that the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, which are strong predictors of cardiac arrhythmia, have increased. These rates decreased significantly after PTx. Along with the results reported in the literature, our results suggest that patients with PHPT may be at risk for severe ventricular arrhythmia and SCD and that surgery in these patients may reduce the risk of SCD.

In our study, we have found a correlation between Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio and Ca levels and PTH levels in PHPT patients. This result suggests that PTH levels, together with Ca levels, may have an effect on arrhythmogenesis mechanisms. PTH has chronotropic effects in animal models and affects coronary blood flow and contraction.<sup>37</sup> PTH may cause both hypertrophy and necrosis by directly affecting the cardiac myocytes.<sup>38</sup> Hypercalcemia may also affect Tp-e and QT durations by electrically shortening the plateau phase of the cardiac action potential and the effective refractory period.<sup>39,40</sup> Considering that PTH has direct cardiac effects, we can speculate that in addition to the arrhythmia-promoting effects of Ca levels, PTH levels may also increase the risk of arrhythmia development.

This study has the following limitations: it is hard to estimate how long the participants have been exposed to Ca and PTH. Furthermore, as the number of participants is low, it is not possible to determine the cut-off value of PTH with respect to the level and exposure period of its cardiac effects. The orbit of the disease may change in presymptomatic patients and with an intervention

in the level of hypercalcemia. We evaluated at the Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, which are good marker for ventricular arrhythmias and SCD, but the development of ventricular arrhythmias has not been directly investigated. Long-term follow-up is required to identify cases that will cause ventricular arrhythmias.

To date, the risk of cardiac arrhythmia in studies conducted in PHPT patients has been investigated over the QT interval. It is well known that shortening the duration of the QT interval is associated with an increased risk of arrhythmia and SCD. It is a matter of debate whether the risk of arrhythmia increases in PHPT patients with a normal QT interval. In this study, we have demonstrated that ventricular repolarization showed an abnormal distribution with an increase in Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in PHPT patients with normal QT interval regardless of the QT interval, and that this group of patients is more susceptible to future ventricular arrhythmias and SCD. We also found that PTx surgery performed in this patient group decreased the mentioned arrhythmia indicators and decreased the risk of possible SCD in these patients.

## CONCLUSION

The clinical results of this study should be confirmed with a larger sample size and long-term follow-up. If the results of this research are validated, our study will likely change the PTx proposal, which focuses only on traditional aspects of PHPT, such as skeletal and kidney involvement.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 03.09.2020, Decision No: 146).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Using hormone therapy in breast cancer and its relationship with metabolic syndrome

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**Cite this article as:** Sayın M. Using hormone therapy in breast cancer and its relationship with metabolic syndrome. *Anatolian Curr Med J.* 2024;6(1):80-86.

Received: 07.11.2023

Accepted: 27.12.2023

Published: 15.01.2024

## ABSTRACT

**Aims:** This study aims to investigate whether the use of hormone therapy pharmaceuticals causes metabolic syndrome-like symptoms in patients diagnosed with breast cancer and to compare the long-term effects of the drugs.

**Methods:** This retrospective file analysis was conducted on breast cancer patients who presented to the Radiation Oncology clinic between January 2019 and April 2022. Files of 75 patients diagnosed with breast cancer, postmenopausal, and without any previous chronic diseases such as diabetes or hypertension were included in the study. Patients who were started on medications with different active ingredients (tamoxifen citrate, letrozole or anastrozole) in the adjuvant period were examined in 3 groups. Waist circumference thickness, body weight, blood pressure, and blood biochemical tests (blood glucose, lipid levels) were measured before and 6 months after the start of the drugs, and the values were compared retrospectively.

**Results:** Of the 75 patients included in the study, the average age of patients using tamoxifen was 59.6; The average age of patients using letrozole was 59.12 years and the average age of patients using anastrozole was 63.56 years. There was an increase in fasting blood sugar ( $p:0.014$ ) and waist circumference ( $p:0.009$ ) in the tamoxifen group. There was an increase in fasting blood sugar, weight, waist circumference, blood pressure and lipid levels in the letrozole and anastrozole arms ( $p<0.0001$  for all). Furthermore, comorbidities such as diabetes mellitus and hypertension that developed after using drugs were ascertained.

**Conclusion:** We think that there is a significant association between hormone therapy medicines used in breast cancer and metabolic syndrome. While we found increases in blood lipids, FBG, body weight, and waist circumference in most of the patients, we observed that these increases were significantly higher in the groups using aromatase inhibitors. These patients should be examined in detail before starting hormone therapy. Diet, active lifestyle, and sports should be recommended.

**Keywords:** Aromatase inhibitor in breast cancer, metabolic syndrome, hormone receptor-positive breast cancer

## INTRODUCTION

Breast cancer is the most prevalent form of cancer in women and the second leading cause of cancer-related deaths globally.<sup>1</sup>

Breast cancer risk can be associated with many factors including genetics, hormonal parameters, metabolic syndrome (MS), and lifestyle.<sup>2</sup> As is well known, hormone therapy is an important part of the treatment of patients who are diagnosed with breast cancer and have positive hormone receptors (estrogen and progesterone receptors). Hormone therapy drugs are classified as tamoxifen citrate (TMX) and aromatase inhibitors (letrozole, anastrozole).<sup>3</sup>

It has been shown that estrogen hormone has an important role in the development of breast cancer. This carcinogenic effect can be prevented by receptor blockade through antiestrogens or by inhibiting estrogen synthesis with

aromatase inhibitors. While the main site of estrogen production in the premenopausal period is the ovary, in the postmenopausal period it is fat and muscle tissue.<sup>3,4</sup>

TMX is a non-steroidal anti-estrogenic agent with weak estrogen agonist effects and is used in palliative and adjunctive treatment of breast cancer, also reduces the incidence of breast cancer in women at high risk and the risk of invasive breast cancer in women with ductal carcinoma in situ (DCIS). Because of the competition between estrogen and TMX for binding to estrogen receptors (ER) in the breast, TMX abolishes the augmentation effect of estrogen on breast cancer patients.<sup>4-6</sup>

Aromatase inhibitors have been used in hormone receptor-positive postmenopausal breast cancer patients for many years and have been proven to reduce recurrence and increase survival in many studies.<sup>7-9</sup>

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Many hormonal, metabolic, and inflammatory mechanisms are known to play a role in the progression of breast cancer.<sup>10</sup> Increased visceral fat, increased insulin resistance, and insulin biosynthesis lead to increased extra-glandular estrogen production and elevated estradiol levels, which exert mitogenic effects on breast epithelial cells.<sup>11</sup>

Especially menopause is a triggering factor for metabolic syndrome. According to the data of the World Health Organization, metabolic disorders were observed 2 times more in patients with breast cancer in 5000 women aged 50-80 years, and these rates were higher after menopause.<sup>12,13</sup>

Metabolic syndrome (MS), described as a cluster of metabolic abnormalities including abdominal adiposity, insulin resistance, hypertension, and dyslipidemia, has been linked to an increased risk of various cancers.<sup>14,15</sup>

Increased waist circumference, elevated triglycerides (TG), low HDL cholesterol, elevated blood pressure, and fasting blood glucose (FBG) are the main components of MS, the incidence of which has increased in our country and worldwide in recent years. The presence of at least 3 of these parameters is required for diagnosis.<sup>16,17</sup>

It is a known fact that type 2 diabetes, dyslipidemia, and hypertension are more common in women with breast cancer compared to other healthy individuals.<sup>18</sup>

The factors recognized as features of the metabolic syndrome are well known. However, the general consensus is that at least 3 of the following factors are required for diagnosis:

- Central, visceral, abdominal obesity and large waist circumference.
- Elevated fasting blood glucose levels (>100 mg/dl)
- High blood pressure (hypertension) (systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg)
- High TG levels (>150 mg/dl)
- Low HDL (male <40 mg/dl, female <50 mg/dl)

Having three or more of these factors signifies the risk of cardiovascular diseases such as heart attack or stroke and type 2 diabetes, which is regarded as a late-onset disorder but is increasingly seen in young people with these risk factors.<sup>3,19,20</sup>

In our previously published hypothesis, we reported that aromatase inhibitors may have a role in glucose intolerance in obese men.<sup>21</sup>

In our study, we aimed to investigate the relationship between the use of hormonotherapy (TMX and aromatase inhibitors) and the development of metabolic syndrome in postmenopausal breast cancer patients.

## METHODS

Ethics committee approval of Ankara Training and Research Hospital Ethics Committee (Date: 07.09.2022, Decision No: 1067/2022) was taken. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Total 98 patients with positive hormone receptors (estrogen and progesterone receptors) who were diagnosed with breast cancer and started treatment between January 2019 and April 2022 were evaluated. All patients had undergone surgery. All patients received anthracycline and taxane-based chemotherapy in the adjuvant period. The number of chemotherapy sessions and the drugs used were the same.

### Criteria for inclusion in the study:

- Those diagnosed with breast cancer,
- Postmenopausal patients,
- Those in stages I, II, or III Women patients,
- Patients who have undergone surgery and completed chemotherapy.

### Criteria for exclusion from the study:

- Cancers other than breast cancer,
- Pre- or perimenopausal patients,
- Stage IV (metastatic) patients,
- Patients who have not undergone surgery or chemotherapy,
- Patients with previous diabetes, hypertension, heart disease, or hyperlipidemia, and male patients.

As a result of the screening, 23 patients were excluded from the study because their metabolic values were abnormal. As a result of the scanning, 75 postmenopausal patient files were eligible for the study.

Before starting adjuvant hormonal therapy, a routine gynecological examination and bone densitometry were performed. According to the results, TMX was started in 25 postmenopausal patients with severe osteoporosis. Letrozole and anastrozole were started in patients without osteoporosis.

In addition, blood pressure (mmHg), waist circumference (cm) and body weight (kg) were measured in all patients before starting treatment. Hemogram and biochemical blood tests (FBG (mg/dl), TG (mg/dl), LDL (mg/dl), cholesterol (mg/dl), HDL (mg/dl)) were analyzed and noted in their files. During patient follow-up, the same measurements were repeated every 6 months and noted in our routine clinical practice for the monitorization of patients weight management, blood pressure and metabolic status. We compared the data in the files for the study and presented statistical analysis. Bone densitometry is performed every 2 years for patient follow-up, while gynecological examination is repeated every year.



Patients diagnosed with diabetes, hypertension (HT), hyperlipidemia and heart disease were also identified and the necessary medical examinations and treatments were arranged. All patients took their medications.

For hormone therapy, 25 patients were given TMX 20 mg/day PO, 25 patients were given letrozole 2.5 mg/day PO, and 25 patients were given anastrozole 1 mg/day PO. They were planned to be used for 5 years.

### Statistical Analysis

All data were analyzed using SPSS v25. Categorical variables were expressed as counts and percentages. In the comparison of the parameters before and after the use of drugs, the Shapiro-Wilk test was used to determine whether the variables were normally distributed. Wilcoxon signed ranks test was used to compare the parameters before and after the use of drugs if at least one variable was not normally distributed before and after.

Also, a Paired sample t-test was used if both data before and after the use of drugs were normally distributed. Kruskal Wallis test was used for age distribution. The chi-square test was also used. A value of  $P < 0.05$  was considered statistically significant.

### RESULTS

The mean age of the patients using TMX was 59.6 years (min 50, max 81); the mean age of patients using letrozole was 59.12 years (min 50, max 77); and the mean age of patients using anastrozole was 63.56 years (min 49, max 82). There is no statistically significant difference between the ages of the participants according to the drugs they use ( $p=0.08$ ) (Table 1).

For each of the drugs, baseline and follow-up data were compared. Accordingly, TMX, letrozole, and anastrozole are shown in Table 2.

	Tmx (n=25)			Letrazol (n=25)			Anastrazol (n=25)			P Kruskal Wallis Test
	Median	Min.-Maks.	mean.±SD	Median	Min.-Maks.	mean±SD	Median	Min.-Maks.	mean±SD	
Age	56	50-81	59.6± 9.2	56	50-77	59.12± 7.3	63	49-82	63.56± 9.3	0.08

Tmx: Tamoxifen, SD: standart deviation

TMX (n=25)	Before use			After use			P
	Median	Min.-Max.	mean.±SD	Median	Min.-Max.	mean.±SD	
FBG	88	81-96	88.08±4.6	90	82-101	90.8±5.1	0.014* (1)
HDL	40	31-73	42.72±9.1	43	33-84	46.28± 10.5	0.014* (2)
LDL	85	42-154	91.68±27	92	62-150	96.72± 24.7	0.052 (2)
Cholesterol	156	46-234	152.92± 45.9	160	105-240	161.96± 38.4	0.122 (1)
Waist circumference (cm)	92	60-126	90.04± 19.3	101	60-127	93.28± 20.7	0.009** (1)
TG	130	70-250	145.16± 52.4	151	67-360	154.96± 58.6	0.166 (2)
Weight (kg)	74	45-101	69.68± 15	72	44-103	70.64±16	0.058 (1)
Letrozole (n=25)	Before use			After use			P
	Median	Min.-Max.	mean.±SD	Median	Min.-Max.	mean.±SD	
FBG	92	82-109	92.36±6	122	86-226	132.08± 38.3	<0.001** (2)
HDL	46	33-113	52±16.5	48	35-130	52.92±18	0.431 (2)
LDL	121	53-210	122.04± 38.8	156	64-220	155.48± 39.7	<0.001** (2)
Cholesterol	182	45-239	170.72± 41	248	111-360	243.8± 51.8	<0.001** (2)
Waist circumference(cm)	96	60-131	97.4±17.8	105	59-138	106.52± 18	<0.001** (1)
TG	153	75-273	153.64± 57	235	96-378	246.12± 77.2	<0.001** (1)
Weight (kg)	70	45-107	72.92± 14.6	79	45-110	79.84± 14.7	<0.001** (1)
Anastrozole (n=25)	Before use			After use			P
	Median	Min.-Max.	mean.±SD	Median	Min.-Max.	mean.±SD	
FBG	91	84-100	91.88±4.2	128	85-194	129.76± 34	<0.001** (2)
HDL	46	31-68	47.92±9.3	48	36-138	52.4±19.5	0.681 (2)
LDL	114	70-159	109± 27.8	138	86-600	158.56± 98.4	<0.001** (2)
Cholesterol	161	46-240	165.8± 46.4	245	116-329	234.04± 53.1	<0.001** (1)
Waist circumference (cm)	101	60-132	97.8±16.6	108	61-134	106.16± 17.4	<0.001** (1)
TG	160	70-277	158.24± 51.4	260	95-829	264.68± 144.7	<0.001** (2)
Weight (kg)	73	45-98	74.04± 14.7	77	46-109	79.76± 15.1	<0.001** (1)

\*:  $p < 0.05$ ; \*\*:  $p < 0.01$ , HDL: High-density lipid (mg/dl), TG: Triglyceride(mg/dl), LDL: Low-density lipid (mg/dl), FBG: Fasting blood glucose(100 md/dl), (1): Paired samples t test, (2): Wilcoxon signed ranks test

There is a statistically significant increase after TMX therapy regarding FBG (p=0.014), HDL (p=0.014), and waist circumference (p=0.009) values of the patients.

There is no statistically significant difference between LDL (p=0.052), cholesterol (p=0.122), TG (p=0.166), and weight (p=0.058) values before and after the use of TMX. Increased blood pressure was detected in 4 patients (16%).

There is a statistically significant increase regarding FBG (p<0.001), LDL (p<0.001), cholesterol (p<0.001), waist circumference (p=0.001), TG (p<0.001), weight (p<0.001) after the use of letrozole.

There is no statistically significant difference between HDL values before and after the use of letrozole (p=0.431). Increased blood pressure was detected in 11 patients (44%).

There is a statistically significant increase regarding FBG (p<0.001), LDL (p<0.001), cholesterol (p<0.001), waist circumference (p<0.001), TG (p<0.001), body weight (p<0.001) values of patients after anastrozole use.

There is no statistically significant difference between HDL values before and after anastrozole use (p=0.681). Increased blood pressure was detected in 13 patients (52%).

**Table 3** shows the statistical data of changes in FBG, HDL, LDL, cholesterol, waist circumference, TG, and weight for all drugs (**Table 3**).

Table 3. Descriptive statistics of FBG, lipid levels, waist circumference, and weight gain after drugs					
Medicine	N	Min	Max	Avg.	SD
<b>Tmx</b>					
FBG increase	25	-9	16	2.72	5.1
HDL increase	25	-5	33	3.56	7.8
LDL increase	25	-80	72	5.04	25.2
Cholesterol	25	-29	114	9.04	28.2
Waist circumference increase	25	-3	19	3.24	5.7
TG increase	25	-58	133	9.80	37.7
Weight increase	25	-3	5	0.96	2.4
<b>Letrozole</b>					
FBG increase	25	1	132	39.72	38.9
HDL increase	25	-20	17	0.92	8.3
LDL increase	25	-2	94	33.44	29.1
Cholesterol	25	-24	221	73.08	53.3
Waist circumference increase	25	-1	25	9.12	7.6
TG increase	25	3	254	92.48	63.5
Weight increase	25	-1	21	6.92	6.3
<b>Anastrozole</b>					
FBG increase	25	-4	102	37.88	33.4
HDL increase	25	-11	107	4.48	22.1
LDL increase	25	-26	523	49.56	107.5
Cholesterol	25	-21	213	68.24	67.1
Waist circumference increase	25	-5	36	8.36	9.7
TG increase	25	-29	658	106.44	137.2
Weight increase	25	-3	21	5.72	6.5

HDL: High-density lipid TG: Triglyceride, LDL: Low-density lipid, FBG: Fasting blood glucose

In the 6<sup>th</sup> month or later months after the initiation of the medication, some of the patients were disturbed by the increase in blood values such as glucose, lipids, and blood pressure, and these patients were re-examined by internal medicine and cardiology, and medication was started for these additional diseases. Statistical data on the use of antihypertensive drugs are given, and cardiac drugs, antidiabetic drugs, and anti-lipid drugs are shown in **Table 4**.

Table 4. Statistical data on the use of antihypertensive drugs, cardiac drugs, antidiabetic drugs and anti-lipid drugs				
		Anti HT		Total
		Not present	Present	
Tmx	n	21	4	25
	%	84%	16%	100%
Letrozole	n	14	11	25
	%	56%	44%	100%
Anastrozole	n	12	13	25
	%	48%	52%	100%
Total	n	47	28	75
	%	62.7%	37.3%	100.0%
Heart medication				
		Not present	Present	Total
Tmx	n	25	0	25
	%	100.0%	0.0%	100.0%
Letrozole	n	22	3	25
	%	88.0%	12.0%	100.0%
Anastrozol	n	22	3	25
	%	88.0%	12.0%	100.0%
Total	n	69	6	75
	%	92.0%	8.0%	100.0%
Anti DM				
		Not present	Present	Total
Tmx	n	25	0	25
	%	100.0%	0.0%	100.0%
Letrozole	n	10	15	25
	%	40.0%	60.0%	100.0%
Anastrozole	n	10	15	25
	%	40.0%	60.0%	100.0%
Total	n	45	30	75
	%	60.0%	40.0%	100.0%
Anti-lipid				
		Not present	Present	Total
Tmx	n	23	2	25
	%	92.0%	8.0%	100.0%
Letrozole	n	5	20	25
	%	20.0%	80.0%	100.0%
Anastrozole	n	8	17	25
	%	32.0%	68.0%	100.0%
Total	n	36	39	75
	%	48.0%	52.0%	100.0%

Tmx: Tamoxifen, AntiHT: Antihypertensive AntiDM: Antidiabetic

There is a statistically significant difference between drugs in terms of the formation of HT after starting the use of drugs (p=0.022). The highest presence of HT was observed in anastrozole (52%) and the least presence of HT was observed in TMX drugs (16%).

There is no statistically significant difference between drugs in terms of the use of cardiac medication after the initiation of medications ( $p=0.196$ ). The highest use of cardiac medication was seen in letrozole and anastrozole (12%), while no patient was found to use the cardiac medication after TMX use.

There is a statistically significant difference between drugs in terms of the occurrence of DM after the initiation of the drugs ( $p=0.0001$ ) ( $p=0.0001$ ). The presence of DM was highest in letrozole and anastrozole (60%), while the presence of DM was not detected after the use of TMX.

There is a statistically significant difference between drugs in terms of lipid formation results after the initiation of drugs ( $p=0.0001$ ). The highest anti-lipid drug use was detected in those using letrozole (80%) and the lowest in those using TMX (8%).

## DISCUSSION

As seen in our study, we observed that aromatase inhibitors in particular, which we used in the treatment of patients who had no chronic disease prior to the diagnosis of breast cancer, caused the formation of metabolic syndrome or there was an indirect link between them.

In most of the studies, it is stated that breast cancer is already more common in patients with metabolic syndrome, and the frequency increases, especially in menopausal patients.<sup>10,22</sup>

Breast cancer is more associated with type 2 diabetes, hyperlipidemia, and hypertensive heart diseases, while it has also been stated in publications that all these metabolic disorders trigger each other.<sup>23</sup>

Few studies have investigated whether chemotherapy and hormonotherapy used for adjuvant breast cancer treatment are associated with the syndrome.<sup>24,25</sup>

We excluded hormone receptor-negative, premenopausal, and perimenopausal patients from the study. As a result of our personal observations, we decided to investigate more scientifically, especially after we noticed an increase in waist circumference and lipid levels following the initiation of aromatase inhibitors in postmenopausal patients.

In most of the studies, patients already had diabetes, hypertension, and hyperlipidemia before treatment.<sup>25</sup> However, we conducted the study by excluding patients with chronic diseases. And we wanted to investigate whether we really triggered such a risk. We followed up the patients who already had chronic diseases with other standard clinical follow-up methods.

The effects of TMX were also investigated in perimenopausal and premenopausal patients, but no

significant relationship was found between metabolic syndrome and TMX use. Its estrogenic properties have been found to reduce the risk of cardiovascular disease.<sup>26,27</sup>

Considering the cardioprotective effect of TMX, we aimed to have a control group in postmenopausal patients. In our study, we showed that TMX was not significantly associated with metabolic syndrome.

As reported in a review of 6 articles published in Pubmed, some studies were conducted on the effects of chemotherapy and drugs used on insulin and glucose levels in breast cancer patients, and although there was no scientific significance, it was observed that drugs such as Taxanes increased metabolic syndrome-like findings.<sup>24-29</sup> Since all patients received the same chemotherapeutic agents in the same way in our study, the effect of chemotherapy was not analyzed in this study.

When the lipid profiles of the patients were analyzed, TG levels increased by 70.7% in all patients, with the highest increase in those using anastrozole. Statistically, the increase was significant in the letrozole and anastrozole groups ( $p<0.0001$ ). HDL levels decreased by 26.7% in all patients but were statistically significant only in those using TMX ( $p:0.014$ ).

While an overall 50.7% increase in FBG levels was observed in all patients, the highest increase was found in the letrozole group. The increase was statistically significant in all groups.

In our cases, the initial weight and waist circumference of the patients were measured and the increase or decrease was monitored in the following period, so overweight patients were enrolled in the study.

An increase in waist circumference thickness was observed in 58.7% of all patient groups. This increase was highest in the letrozole group. It was statistically significant in all groups. While weight gain was observed in all drugs, it was statistically significant in the letrozole and anastrozole groups.

In our study, anti-lipid drugs were started in 52% of the patients in the early period. Of these patients, 94.8% were in the group receiving aromatase inhibitors (AI) (letrozole+anastrozole).

Again, 37.3% of patients started to use antihypertensive drugs in the early period, and 86% of this group was in the AI group.

While 40% of the patients started to use oral antidiabetics, 20% of them (6 patients) started to use insulin.

Another 34.6% (26 patients) continued their hormone therapy without any medication, only diet arrangements, increased activity, and an active lifestyle.

## Limitations

There were some limitations to this study. Firstly, TMX was preferred over an aromatase inhibitor in patients with severe osteoporosis, since our study was conducted on postmenopausal patients. Second, the number of patients in the study was not large, as patients with any chronic disease were excluded before starting treatment, but still statistically significant results were obtained. Conducting the study on a larger number of patients will help obtain more robust results. Metastatic patients were not included in the study. In this group of patients, the use of chemotherapy and targeted drugs was preferred instead of only hormone therapy. Another limitation is whether metabolic syndrome develops in patients who do not use any hormone medication, but we consider it unethical to follow up without treatment. Therefore, all patients received hormone therapy. 6th month data is presented in the study. However, the data obtained will be more accurate when patient follow-up is completed for at least 5 years.

## CONCLUSION

The study first revealed that the drugs lead to metabolic syndrome-like effects. We notice that metabolic syndrome develops especially in patients diagnosed with breast cancer who are treated with aromatase inhibitors. We think that we can reduce the risk of developing metabolic syndrome with a strict diet, sports, and active social life from the very beginning, regardless of whether it is due to breast cancer or the use of hormone therapy. In the patient group where these do not help, it is our recommendation to start treatment for the metabolic disorder in the early period.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ankara Training and Research Hospital Ethics Committee (Date: 07.09.2022, Decision No: 1067/2022).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Temporal alterations in P-wave electrocardiographic metrics post patent foramen ovale closure: a retrospective study

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**Cite this article as:** Erdoğan A, Genç Ö. Temporal alterations in P-wave electrocardiographic metrics post patent foramen ovale closure: a retrospective study. *Anatolian Curr Med J.* 2024;6(1):87-92.

Received: 16.12.2023

Accepted: 03.01.2024

Published: 15.01.2024

## ABSTRACT

**Aims:** This study aimed to analyze the electrocardiograms (ECG) of 69 patients before and after patent foramen ovale (PFO) closure, specifically investigating novel ECG parameters, over a 6-month post-procedure period.

**Methods:** ECGs from 69 patients undergoing PFO closure were examined at three time points: before the procedure, and at 1<sup>st</sup> and 6<sup>th</sup> months post-procedure. A comprehensive set of ECG parameters, including P-wave (PW) maximum (PWmax), PW minimum (PWmin), PR interval, PW dispersion (PWdis), PW peak time in lead D2 (PWPTD2), PW peak time in lead V1 (PWPTV1), P-axis, PW terminal force in the V1 (PWTF) and heart rate, were analyzed using a generalized linear mixed model (GLMM).

**Results:** The GLMM analysis revealed significant changes in novel ECG parameters at 1-month post-procedure compared to baseline values. Parameters including PWmax (OR=8.898, 95% CI 7.521-10.275,  $p<0.001$ ), PWmin (OR=6.579, 95% CI 5.611-7.548,  $p<0.001$ ), PR (OR=4.159, 95% CI 3.031-5.288,  $p<0.001$ ), PWdis (OR=2.594, 95% CI 1.607-3.581,  $p<0.001$ ), PWPTD2 (OR=4.261, 95% CI 2.928-5.593,  $p<0.001$ ), PWPTV1 (OR=5.261, 95% CI 4.529-5.992,  $p<0.001$ ), and PWTF (OR= 5.781, 95% CI 2.083-16.044,  $p<0.001$ ) exhibited notable alterations, indicating a transient impact on cardiac conduction. However, these changes returned to baseline values by the 6-month follow-up. No statistically significant differences were observed in P-axis and heart rate across all time points.

**Conclusion:** The analysis of ECG in patients undergoing PFO closure highlighted dynamic changes in novel ECG parameters in the early post-procedural period, with subsequent normalization by 6 months. Further research is warranted to elucidate the clinical implications of these dynamic electrocardiographic shifts and their potential association with long-term cardiovascular outcomes.

**Keywords:** Atrial fibrillation, patent foramen ovale, p-wave, stroke

## INTRODUCTION

Stroke continues to pose a substantial global health challenge, with 15% to 30% of cases classified as cryptogenic stroke despite advances in technology.<sup>1</sup> A major contributor to cryptogenic strokes is the presence of patent foramen ovale (PFO), which has been identified in a significant number of cases.<sup>2,3</sup> Recent prospective studies indicate that PFO closure reduces the recurrence of strokes. However, some large-scale studies have observed an increase in atrial tachycardias post-closure when compared to patients undergoing medical monitoring.<sup>4</sup> While this rate was observed to be 4-6% in follow-ups of symptomatic patients and ambulatory Holter analyses, it was reported to be much higher in intracardiac recording studies. Among these atrial tachycardias, atrial fibrillation (AF) is of particular importance.<sup>4,5</sup> While most cases resolve spontaneously without causing ischemic events, some may progress to permanent AF and lead to

recurrent ischemic events.<sup>6,7</sup> Although the underlying pathophysiology has not been fully elucidated, regardless of the cause, identifying the factors predictive of AF is crucial for early diagnosis and meticulous patient management.<sup>8</sup> Silent forms of AF, which traditional methods cannot detect, pose a challenge in the diagnosis and treatment of this condition.<sup>9</sup> Although AF detection proved more accurate in implantable cardiac recording studies with a limited number of patients in previous research, its widespread use was hindered by the high cost and complications associated with invasive interventions. Consequently, there is a demand for robust predictive parameters capable of anticipating the risk of development.

P-wave (PW) changes observed on electrocardiogram (ECG) have begun to be used as the latest strong atrial

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arrhythmia predictors. As it is known, atrial arrhythmias are closely related to the PW on ECG.<sup>10-12</sup> PW terminal strength (PWTF), abnormal PW, PW dispersion (PWdis), and a much more specific parameter, PW peak time (PWPT), provide undeniable information about the risk of developing atrial arrhythmia.<sup>11-13</sup>

In this study, we aimed to examine the effect of PFO closure on atrial arrhythmia predictors by examining PW changes before and after the procedure.

## METHODS

### Study Design and Patient Selection

This study is a retrospective, single-centre investigation involving patients referred to our facility for PFO closure following cryptogenic stroke, between March 2020 and January 2023. The study focused on patients aged over 18 years who underwent closure due to high-risk PFO following a cryptogenic cerebrovascular event (CVE). Exclusion criteria involved patients not meeting cryptogenic stroke criteria<sup>10</sup> and those meeting any of the following criteria: AF, atrial flutter, atrioventricular and interventricular block, pacemaker rhythm, severe valve dysfunction, segmental movement disorder, mechanical prosthetic valve, or use of antiarrhythmic or rate-limiting drugs. Demographic, laboratory, and clinical data were extracted from the hospital automation system. ECGs were recorded before PFO closure and at 1<sup>st</sup> and 6<sup>th</sup> months post-closure. The study adhered to the ethical principles specified in the Declaration of Helsinki and obtained approval from the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 13.12.2023, Decision No: 2023-12-666). Given the retrospective nature of the study, the requirement for written informed consent was waived for each participant.

### Definitions and Risk Factors

The study collected information on several patient factors, including age, smoking status, and comorbidities. To determine the presence of Diabetes mellitus (DM), patients were considered positive if they were using blood glucose-lowering medications, if their fasting plasma blood glucose levels were greater than or equal to 126 mg/dL, or if their postprandial blood glucose levels were greater than or equal to 200 mg/dL.<sup>14</sup> Hypertension (HT) was defined as systolic blood pressure equal to or greater than 140 mmHg and/or diastolic blood pressure equal to or greater than 90 mmHg or if patients were taking antihypertensive medication.<sup>15</sup>

Ischemic stroke was defined as a sudden focal neurological deficit lasting 24 hours or longer or associated with a related infarction on brain magnetic resonance imaging. The definition of cryptogenic stroke included an extensive search to exclude other identifiable stroke mechanisms such as large artery atherosclerotic disease (defined by patients with at least 50% stenosis in one main vessel or one main vessel occlusion), lacunar stroke (defined by small deep infarction)

an established cardioembolic source, small vessel occlusive disease, hypercoagulation disorder requiring anticoagulants, or arterial dissection. All patients underwent computed tomography angiography, magnetic resonance angiography, or ultrasonography to rule out stroke of vascular origin. Holter or long-term cardiac rhythm monitoring was performed to exclude paroxysmal atrial fibrillation.

### PFO Closure Procedure

Percutaneous PFO closure was performed under local or sedation anaesthesia, according to the physician's decision and the patient's convenience. The interatrial defect was assessed before the procedure through transthoracic and transesophageal echocardiography to facilitate the selection of prosthesis size and type. The procedure was performed via the femoral venous route. Prosthesis was positioned under fluoroscopic control and transesophageal echocardiography in case of local anaesthesia. Two types of prosthesis were implanted: the Amplatzer PFO Occluder (Abbott Vascular, United States of America) and the Occlutech PFO Occluder (Occlutech, Sweden). Intravenous injections of unfractionated heparin (5000 international units) and 300 mg of aspirin, associated with antibiotic prophylaxis were, administered before the procedure. In the absence of contraindication, a dual antiplatelet therapy, including aspirin (between 75-100 mg) and clopidogrel 75 mg was initiated for 3 months followed by long-term aspirin. Transthoracic echocardiography was conducted the following day to verify the positioning of the prosthesis and ensure the absence of complications. Hospital discharge was planned for day 1.

### ECG Analysis

**P-wave indices:** The longest (PWmax) and shortest (PWmin) PW were assessed by measuring the PW across all 12 leads from the onset of the deflection on the isoelectric line to the point of deflection returning to the isoelectric line. PWdis denoted the disparity between PWmax and PWmin. The PR interval spanned from the initiation of the PW (atrial depolarization) to the commencement of the QRS complex. PWPT represented the duration between the onset of the PW and its zenith, calculated from leads D2 (PWPTD2) and V1 (PWPTV1). In V1, housing negative and biphasic PW, the duration from the origin of the PW to the peak of the negative PW was measured. Negative waves for assessment were deemed biphasic if they exceeded or were equal to 0.1 mV; those falling below this threshold were excluded. PWTF was computed by multiplying the depth and duration of the terminal negative component of the PW in V1. An abnormal PWTF was defined as  $PWTF \geq 40 \text{ mm} \times \text{ms}$ . An abnormal PW axis was characterized by values less than 0 or exceeding a 75 PW axis. In cases where the PW morphology consisted solely of positive or negative bias, the bias was calculated for the mean value. In instances of biphasic bias, the absolute sum of biases was computed and analyzed. Both intraobserver and interobserver variations were maintained at less than 5%.

**Reproducibility:** Intraclass correlation coefficients were computed to assess both intraindividual and interobserver variation. A subset of ECGs from ten randomly selected patients underwent reanalysis by the same observer. For interobserver variability, the identical patients and images were subjected to analysis by a second observer (Ö.G). The intra-observer correlation coefficients for PR, PWmax, PWmin, PWPTD2, PWPTV1, and PWTF were 0.907, 0.901, 0.890, 0.917, 0.923 and 0.950, respectively. The inter-observer correlation coefficients were 0.880, 0.936, 0.925, 0.922, 0.912, and 0.937 for the same parameters.

**Statistical Analysis**

R statistical software, version 4.1.2, from the Institute for Statistics and Mathematics in Vienna, Austria, was used to perform the statistical analyses. The distribution of the variables was checked using the Kolmogorov-Smirnov test. The continuous variables were expressed as mean (SD) for normal distributions and median (interquartile range (IQR25-75)) for non-normal distributions. The categorical data were displayed using numbers (n) and percentages (%). Generalized linear mixed models (GLMM), using “lmer” for continuous and “glmer” for categorical dependent variables in the lme4 package, were created to detect the significance of the change of ECG parameters on follow-up. Age, device type, device size, DM, HT, smoking, body mass index, left ventricular end-diastolic diameter, left atrial area, gender, and baseline systolic blood pressure were used as covariates in GLMM models. Estimates (OR) and 95% confidence intervals (CI) were reported. Plots were created to demonstrate the changes in the ECG variables during follow-up using ggplot2 in R. Statistical significance was defined at p < 0.05 for the study analyses.

**RESULTS**

This study consisted of 69 consecutive patients who underwent PFO closure. The mean age was 40.3±8.9 years and 47.8 % of the population were male. Of the patients, 31.9% had HT, 24.6% had DM, and 44.9% were smoking. Occlutech PFO Occluder device was used in 56.5 % of patients and the device size was 25.3 ± 2.4 in the overall population (**Table 1**). GLMM model showed that PWmax (OR=8.898, 95% CI 7.521-10.275, p<0.001), PWmin (OR=6.579, 95% CI 5.611-7.548, p<0.001), PR (OR=4.159, 95% CI 3.031-5.288, p<0.001), PWdis (OR=2.594, 95% CI 1.607-3.581, p<0.001), PWPTD2 (OR=4.261, 95% CI 2.928-5.593, p<0.001), PWPTV1 (OR=5.261, 95% CI 4.529-5.992, p<0.001), and PWTF (OR= 5.781, 95% CI 2.083-16.044, p<0.001) significantly got longer in 1-month after the procedure when compared to baseline values. But all the above-mentioned variables decreased around the basal values again in 6 months. There were no statistically significant differences between all time points regarding the P-axis and heart rate (**Figure**)( **Table 2**).

**Table 1.** Baseline characteristics of study population.

Age, years; mean±SD	40.3±8.9
Male gender, n (%)	33 (47.8)
Body mass index, kg/m2; ±SD	26.8±4.5
Hypertension, n (%)	22 (31.9)
Diabetes mellitus, n (%)	17 (24.6)
Cigarette smoking, n (%)	31 (44.9)
SBP, mm Hg; median (IQR)	130 (125-134)
DBP, mm Hg; median (IQR)	73 (70-80)
WBC,103/dL; mean±SD	7.8 (6.4-9.7)
Hemoglobin , mg/dl; mean±SD	13.1±0.9
Platelet, 103/dL; median (IQR)	224 (193-257)
Creatinine, mg/dL; median (IQR)	0.88 (0.75-0.95)
Sodium, mEq/l; mean±SD	137.1 ± 3.6
Potassium, mEq/l; mean±SD	4.2 ± 0.2
LVDD, mm, mean±SD	45.6±2.8
LVSD, mm, mean±SD	25.4±3.9
LAA, mean±SD	34.2±2.4
Occlutech PFO Occluder , n (%)	39 (56.5)
Device size, mm; mean±SD	25.3±2.4

DBP, diastolic blood pressure; IQR, interquartile range, LVDD, left ventricular end diastolic diameter; LVSD, left ventricular end systolic diameter; LAD, left atrial area ; SD , standard deviation ; SBP, systolic blood pressure; WBC, white blood cell

**Table 2.** Generalized linear mixed model regression for detecting the significance of the change of variables on follow-up

	Estimate	95% CI	p-value
<b>PW max</b>			
1 month	8.898	7.521-10.275	<0.001
6 month	0.724	-0.651-2.101	0.304
<b>PW min</b>			
1 month	6.579	5.611-7.548	<0.001
6 month	0.246	-0.722-1.214	0.619
<b>PR</b>			
1 month	4.159	3.031-5.288	<0.001
6 month	-0.001	-1.128-1.129	0.999
<b>PW dis</b>			
1 month	2.594	1.607-3.581	<0.001
6 month	0.261	-0.726-1.247	0.605
<b>PWPTD2</b>			
1 month	4.261	2.928-5.593	<0.001
6 month	-0.711	-2.042,0.622	0.298
<b>PWPTV1</b>			
1 month	5.261	4.529-5.992	<0.001
6 month	0.289	-0.441,1.021	0.439
<b>P axis</b>			
1 month	0.439	-0.601-1.478	<b>0.409</b>
6 month	0.621	-0.417-1.661	0.243
<b>Heart Rate</b>			
1 month	-0.188	-2.103-1.726	0.847
6 month	0.536	-1.378-2.451	0.584
<b>V1TF</b>			
1 month	5.781	2.083-16.044	<b>0.001</b>
6 month	2.446	0.873-6.852	0.089

PWmax, maximum P wave; PW min, minimum P wave, P wave dispersion (PW dis) was determined as the difference between the maximum and minimum P wave; PR, interval spanned from the initiation of the P wave (atrial depolarization) to the commencement of the QRS complex. PWPTD2, from the beginning of P wave to peak in lead D2. PWPTV1 from the beginning of P wave to peak in lead V1; V1TF, P wave terminal force in lead I.

- Reference group was basal time point.
- Age, device type, device size, diabetes mellitus, hypertension, cigarette smoking, body mass index, left ventricular end-diastolic diameter, left atrial area, male gender, and baseline systolic blood pressure were used as covariates in GLMM model.
- Estimate and 95 % CI values for V1TF reflect odds ratio and 95 % CI for odds ratio.



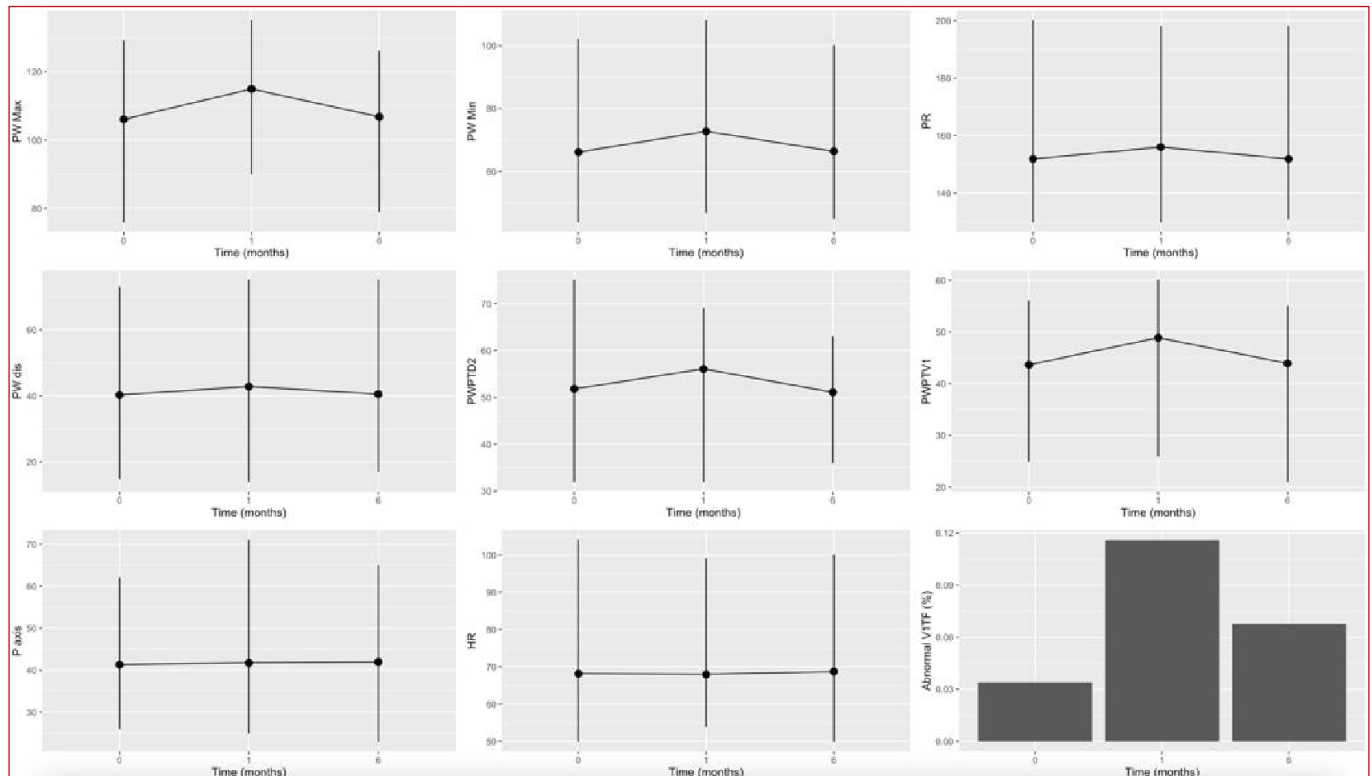


Figure 1.

## DISCUSSION

We observed that changes in PW, which are robust predictors of atrial arrhythmia, shifted in favour of arrhythmia during the early period in patients monitored following PFO closure. These findings underscore the importance of exercising caution regarding the risk of atrial arrhythmia in the initial period after PFO closure.

Prestigious studies and meta-analyses indicate an increase in atrial tachycardias following PFO closure.<sup>4,16</sup> Especially in studies conducted with 72-hour Holter and event recorder, it was observed that the incidence of atrial arrhythmias, especially AF, was much higher than the incidence of AF detected in symptom-based evaluations and analyses performed only with ECG.<sup>16-18</sup> This underscores the need for a comprehensive understanding of the arrhythmic picture after PFO closure and its potential effects on patient care. AF, the major contributing factor to the observed increase in atrial arrhythmias, is a significant clinical problem due to its association with stroke and other adverse cardiovascular outcomes.<sup>19</sup> Serious CVEs can be observed during AF attacks; therefore, it is vital to predict the risk of AF development.<sup>19,20</sup> In our study, we observed a significant increase in PW durations, a strong predictor of AF, during the first month. However, these durations gradually approached the baseline level over time. In the study conducted by Elgendy et al.<sup>21</sup> the rate of forgiveness development was found to be higher in the first

month, which supports our findings. Understanding this early phase after closure is crucial for clinicians to effectively predict and manage potential arrhythmic events.

There are several theories regarding early arrhythmias. Atrial remodelling and heightened sensitivity following PFO closure may be linked to factors such as tissue inflammation, particularly in the vicinity of the PFO closure device. Inflammation within the tissue surrounding the PFO closure device could potentially predispose to atrial arrhythmias.<sup>7,22,23</sup> It may also play a pivotal role in AF by contributing to the barrier macro-reentry cycle induced by the closure device. Additionally, studies have indicated that the utilization of larger-sized devices and the presence of atrial septal aneurysms are correlated with AF.<sup>6,24</sup> Further research is necessary to reveal the specific mechanisms that underlie this phenomenon and explore potential strategies for mitigating the risk of arrhythmias following PFO closure.

The lack of consensus about recurrent CVEs and AF occurring after PFO closure, and the detection of different incidences in follow-ups with ECG, Holter, and event recorder, make it necessary to use simpler and common parameters.<sup>4-6</sup> The electrocardiographic parameters related to PW characteristics—specifically PWmax, PWmin, PWdis, PWPT, and PWPTF—provide valuable insights into their potential associations with AF.<sup>25</sup> These parameters serve as important markers of atrial electrophysiology, offering a window into

the underlying substrate that may contribute to the initiation and maintenance of AF.<sup>11,25</sup> The PW duration, represented by PWmax, and the minimum PW duration are key electrocardiographic parameters that reflect atrial depolarization and are associated with atrial remodelling, and studies suggest that these alterations may be indicative of increased susceptibility to AF. PWdis provides a measure of the heterogeneity of atrial conduction. Increased PWdis may signify irregular conduction patterns, promoting the formation of reentrant circuits and contributing to the substrate for AF.<sup>24</sup> The timing of the peak of the PW, denoted as PWPT, is another parameter that merits attention in the context of AF.<sup>11,26</sup> In addition, The calculation of PWTF involves the multiplication of the depth and duration of the terminal negative component of the PW in lead V1. This index reflects the electromechanical properties of atrial depolarization and provides a quantitative measure that may be indicative of underlying atrial pathology. The identification of PWTF as a potential predictor for AF holds clinical significance.<sup>27</sup> Abnormal values of PWTF may signify alterations in atrial electrophysiology, contributing to an increased susceptibility to AF. Incorporating PWTF into routine electrocardiographic assessments may offer clinicians a non-invasive tool for identifying individuals at risk for AF, prompting further investigation and targeted interventions. Elevated PWTF suggests abnormalities in the terminal phase of atrial depolarization, which may be linked to atrial remodelling. Atrial structural changes and fibrosis, often observed in conditions predisposing to AF, can manifest in the ECG. Monitoring PWTF provides a dynamic assessment of these changes, aiding in the early detection of atrial remodelling and potential AF development.<sup>28,29</sup>

Understanding the relationship between PW parameters and AF has important clinical implications. These electrocardiographic indices, which can be obtained from routine evaluations after PFO closure, provide a non-invasive method for identifying individuals at risk of AF. Integrating these parameters into risk stratification models may improve our ability to predict the development of AF after PFO closure, facilitating targeted interventions and preventive measures.

### Limitation

Our study has several noteworthy limitations that warrant consideration. Firstly, the retrospective nature and the confinement of the study to a single-centre may compromise the generalizability of the findings. Secondly, the study's limitation lies in its relatively small sample size, which may restrict the robustness of statistical analyses; therefore, a larger patient cohort could enhance the validity of the results. Thirdly, the absence of observed AF development after PFO closure within

our study population precludes our ability to provide insights into PW changes before and after the procedure in patients who develop AF. Lastly, the absence of a PFO-related stroke group with medical follow-up in our study prevents a direct comparison of PW parameters. Despite these limitations, our study's findings offer crucial insights into the early-period risk of AF post-PFO closure. However, to establish more definitive conclusions regarding the impact of PFO closure on AF across diverse patient groups, further research with larger sample sizes, prospective designs, extended follow-up periods, and varied patient populations is imperative.

## CONCLUSION

The present study contributes valuable information regarding the ECG changes and arrhythmic effects associated with PFO closure. While transient alterations in ECG parameters were observed, the clinical significance lies in the short-lived nature of these changes. The increased risk of abnormal PW warrants further investigation into the mechanisms and potential long-term implications of arrhythmias following PFO closure. Clinicians should consider these findings in the context of patient care, emphasizing the need for ongoing research to refine our understanding of the complex interplay between PFO closure and cardiac electrophysiology.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was conducted following the ethical principles stated in the Declaration of Helsinki and was approved by the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (December 2023 dated 2023-12-666).

### Informed Consent

The need for a written informed consent form from each participant was waived due to the study's retrospective nature.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# Exploring the nexus: prevalence, risk factors, and clinical correlations of urinary tract infections in diabetes mellitus patients - a comprehensive retrospective analysis

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**Cite this article as:** Karşlıoğlu M, Olpak Yılmaz M. Exploring the nexus: prevalence, risk factors, and clinical correlations of urinary tract infections in diabetes mellitus patients - a comprehensive retrospective analysis. *Anatolian Curr Med J.* 2024;6(1):93-96.

Received: 08.12.2023

Accepted: 11.01.2024

Published: 15.01.2024

## ABSTRACT

**Aims:** This study investigates the frequency and associated factors of urinary tract infections (UTIs) in patients with diabetes mellitus (DM).

**Methods:** This retrospective chart review focused on patients with diabetes mellitus. Data collection involved demographic details, DM diagnosis, comorbidities such as hypertension, hyperlipidemia, and coronary artery disease, along with medication usage. Laboratory values including blood glucose and HbA1c levels were also analyzed. The primary outcome of interest was the diagnosis of UTI, identified from clinical records.

**Results:** 173 DM patients were included in the study. These patients were divided into two groups according to the presence of UTI: 52 patients in the UTI group and 121 patients in the non-UTI group. The incidence of UTI was significantly higher in women (37.9%) compared to men (10.2%). No significant differences were observed between the groups in terms of age, presence of hypertension, hyperlipidemia, or coronary artery disease. Interestingly, the usage of SGLT-2 inhibitors was significantly higher in the UTI group compared to the non-UTI group (26.8% vs. 14%,  $p=0.043$ ). No significant differences were found in other medication usage or in the levels of glucose and HbA1c between the groups.

**Conclusion:** The study highlights the increased risk of UTIs in DM patients, particularly among women and those using SGLT-2 inhibitors. These findings suggest the need for careful monitoring and tailored approaches in managing UTIs in DM patients, considering gender and specific DM treatments.

**Keywords:** Complication, diabetes mellitus, urinary tract infection

## INTRODUCTION

Diabetes mellitus (DM) occupies a forefront position among global health challenges, contributing to an increase in metabolic irregularities as well as a heightened risk of infections.<sup>1-3</sup> This disease is characterized by a combination of conditions including insulin resistance, reduced insulin secretion, and increased glucose production.<sup>4,5</sup> The prevalence of DM has escalated rapidly in recent years, particularly in developing countries. This surge is linked to various factors associated with lifestyle changes. As of 2015, approximately 415 million adults worldwide were reported to be living with DM, with projections suggesting an increase to 642 million by 2040.<sup>6</sup>

DM markedly elevates the risk of critical health concerns, including cardiovascular diseases, visual impairments, extremity losses, renal disorders, and a range of infections.<sup>7,8</sup> Notably, urinary tract infections (UTIs) are the most frequent among these in diabetic individuals. Around 150

million people globally are estimated to be impacted by UTIs each year.<sup>9</sup> UTIs, infections affecting the urinary system, may involve the urethra, kidneys, or bladder. Beyond their discomfort and pain, UTIs pose a significant risk of severe complications if they advance to the kidneys.<sup>10</sup>

This study aims to assess the prevalence and risk factors of UTIs in patients with DM specifically focusing on those in routine outpatient care.

## METHODS

This study was conducted with the approval of the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 05.05.2023, Decision No: 383). All procedures adhered to ethical standards and aligned with the principles of the Declaration of Helsinki. Ensuring patient confidentiality and data privacy, no data were shared outside the scope of this study.

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This retrospective study included patients diagnosed with DM, presenting to the Internal Medicine Outpatient Clinic of Samsun Gazi State Hospital between September 1, 2022, and February 1, 2023. We included all patients who met the inclusion criteria during the study period, patients under 16 are typically treated in pediatric clinics and thus were not part of this study.

**Data Collection**

Patient data were collected electronically through the Hospital Information Management System. This approach enabled comprehensive access to various data categories relevant to the study.

**Definition and Diagnosis of UTIs**

UTI was defined as any infection involving any part of the urinary tract, namely the kidneys, ureters, bladder and urethra. UTI diagnosis was based on urine analysis.

**Assessment of Risk Factors and Parameters**

The assessed parameters included age, gender, comorbidities (hypertension, hyperlipidemia, coronary artery disease), urine test results (glucosuria), blood test results (fasting glucose and HbA1c), and medication usage (SGLT2 inhibitors, metformin, DPP4 inhibitors, gliclazides, glitazones, and insulin). Risk factors were assessed based on prior studies.

**Statistical Analysis**

Statistical analysis was performed using the Statistical Package for Social Sciences (version 29; IBM Corp. Armonk, NY, USA). Normality of data distribution was evaluated using the Shapiro-Wilk test and visual inspection of histograms. Descriptive statistics included the use of frequency and percentage for categorical variables, and mean±standard deviation or median (interquartile range, 25<sup>th</sup>-75<sup>th</sup> percentile) for continuous variables. To compare categorical variables across independent groups, the chi-square test and Fisher’s exact test were applied. For continuous variables, differences between groups were assessed using either the Student’s t-test or the Mann-Whitney U test. All statistical tests were two-sided, and a p-value less than 0.05 was considered indicative of statistical significance.

**RESULTS**

The study included 173 patients. The mean age of the patients was determined to be 60.8±10.8 years. 71.7% of the patients in the study were female. For detailed demographic and clinical characteristics of the study participants, please refer to **Table 1**.

**Table 1.** Demographic, clinical, and medication characteristics of study cohort

Parameters	Subgroups	Total (n=173)
Age (years)		60.8±10.8
Sex		
	Female	124 (71.7%)
	Male	49 (28.3%)
Co-morbidities		
	Hypertension	98 (56.6%)
	Hyperlipidemia	40 (23.1%)
	Coronary artery disease	19 (11%)
Urine test		
	Glucosuria (mg/dl)	56 (32.4%)
Biochemistry test		
	Glucose (mg/dl)	160 (125-227)
	HbA1c (%)	7.4 (6.7-8.75)
Medication		
	SGLT2 inhibitors	31 (17.9%)
	Metformin	123 (71.1%)
	DPP4 inhibitors	65 (37.6%)
	Gliclazides	26 (15%)
	Glitazones	10 (5.8%)
	Insulin	51 (29.5%)

DM: Diabetes mellitus; UTI:Urinary tract infection; HbA1c:Glycated haemoglobin; SGLT2:Sodium-glucose cotransporter-2; DPP4:Dipeptidyl peptidase 4

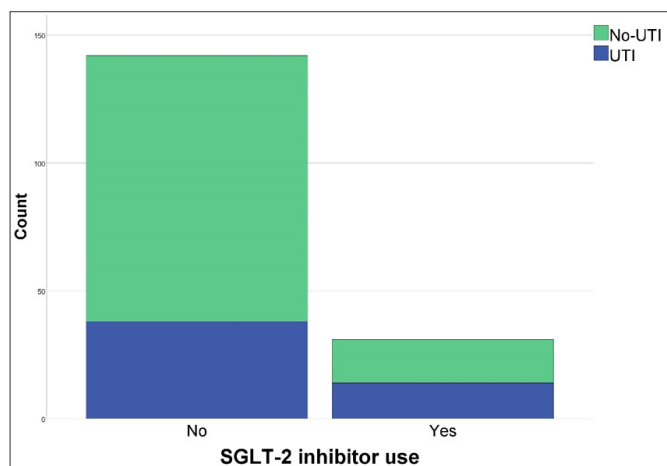
They were divided into two groups based on UTI diagnosis: 30.1% (n=52) diagnosed with UTI (UTI group) and 69.9% (n=121) not diagnosed with UTI (non-UTI group) as seen in **Table 2**. The average age in the UTI group was 61.8±10.7 years, and in the non-UTI group, it was 59.4±10.8 years; no statistically significant difference was observed between the groups (p=0.089). The rate of UTI in women (37.9%, n=47) was significantly higher compared to men (10.2%, n=5) (p<0.001).

**Table 2.** Comparative analysis of demographic, clinical, and medication characteristics between UTI and non-UTI groups in patients with diabetes mellitus

Parameters/ Subgroups	UTI (n=52)	Non-UTI (n=121)	P
Age (years)	61.8±10.7	59.4±10.8	0.089
Sex			
	Female	77 (62.1%)	<0.001
	Male	44 (89.8%)	
Co-morbidities			
	Hypertension	66 (54.5%)	0.395
	Hyperlipidemia	27 (22.3%)	0.701
	Coronary artery disease	13 (10.7%)	0.878
Urine test			
	Glucosuria (mg/dl)	40 (33.1%)	0.768
Biochemistry test			
	Glucose (mg/dl)	160.5 (124 - 238.75)	0.837
	HbA1c (%)	7.35 (6.63-8.88)	0.743
Medication			
	SGLT2 inhibitors	17 (14%)	0.043
	Metformin	83 (68.6%)	0.268
	DPP4 inhibitors	45 (37.2%)	0.874
	Gliclazides	19 (15.7%)	0.705
	Glitazones	8 (6.6%)	0.376
	Insulin	38 (31.4%)	0.397

DM: Diabetes mellitus; UTI: Urinary tract infection; HbA1c: Glycated haemoglobin; SGLT2: Sodium-glucose cotransporter-2; DPP4: Dipeptidyl peptidase 4

No statistically significant difference was observed between the groups in terms of hypertension, hyperlipidemia, and coronary artery disease prevalence (respectively;  $p=0.395$ ,  $p=0.701$ ,  $p=0.878$ ). In the UTI group, the rate of UTI symptoms (69.2%,  $n=36$ ) was significantly higher compared to the non-UTI group (0.8%,  $n=1$ ) ( $p<0.001$ ). Glucosuria was detected in 30.8% of patients ( $n=16$ ) in the UTI group; this rate was 33.1% ( $n=40$ ) in the non-UTI group, with no statistically significant difference observed ( $p=0.768$ ). No significant difference was found between the groups in median glucose and HbA1c values (respectively;  $p=0.837$ ,  $p=0.743$ ). There was no statistically significant difference in the usage rates of metformin, DPP4 inhibitors, gliclazides, glitazones, and insulin between the groups (respectively;  $p=0.268$ ,  $p=0.874$ ,  $p=0.705$ ,  $p=0.376$ ,  $p=0.397$ ). The prevalence of SGLT-2 inhibitor usage among patients in the UTI group was observed to be significantly higher at 26.8% ( $n=14$ ), as opposed to 14% ( $n=17$ ) in the non-UTI group, a difference which was statistically significant ( $p=0.043$ ) (Figure 1).



**Figure 1.** Distribution of SGLT-2 Inhibitor Usage Among Patients With and Without UTI Diagnosis

## DISCUSSION

This research focused on examining the prevalence of UTIs and related risk factors in individuals with DM. The study's outcomes revealed a heightened risk of UTIs, notably among women and those on SGLT-2 inhibitor therapy.

The interplay between DM and UTIs is intricate and multidimensional. DM, marked by disrupted glucose metabolism, potentially enhances infection risks through several pathophysiological pathways. High blood sugar levels, a common phenomenon in DM, create an environment favorable for bacterial growth and adherence, thereby facilitating bacterial colonization in the urinary tract, a prime risk factor for UTIs.<sup>11,12</sup> Furthermore, DM's impairment of the immune system renders patients more susceptible to

bacterial and other microbial infections. This increased vulnerability stems from a weakened immune response, disruptions in white blood cell functionality, and bladder dysfunction due to diabetic complications, all contributing to DM patients' heightened risk for UTIs.<sup>13</sup> These pathophysiological considerations play a crucial role in the complex management and prevention of UTIs in the context of DM.

A salient observation from our research is the prominence of female gender as a key risk factor for UTIs in DM patients. This finding is consistent with current literature and can be explained by women's unique anatomical and physiological traits. The proximity of the female urethra to the anus and its shorter length make it easier for bacteria to enter the urinary system, increasing susceptibility to UTIs. Factors such as hormonal variations and conditions like pregnancy further amplify this risk in women.<sup>14,15</sup> The shift in vaginal flora due to estrogen deficiency post-menopause can also heighten UTI risk. Consequently, these factors contribute to a higher prevalence of UTIs in females with DM, underscoring the need for specialized management and preventive strategies in this demographic.

An additional key finding of our research is the increased occurrence of UTIs in DM patients treated with SGLT-2 inhibitors, corroborating with current research on this medication class's impact on UTI risk. Several studies have shown a correlation between specific diabetes management therapies and the incidence of urinary tract infections, highlighting the need for personalized treatment strategies in diabetic patients. Recent research indicates a notable association between the use of SGLT-2 inhibitors in diabetic patients and an increased risk of urinary tract infections, suggesting a need for vigilant monitoring in these patients.<sup>16,17</sup> SGLT-2 inhibitors work by lowering blood glucose levels via inhibition of glucose reabsorption in the kidneys, leading to heightened glucose levels in urine. This elevated urinary glucose can act as a nutrient for bacteria, thereby raising the risk of UTIs.<sup>16</sup> The glucosuria associated with these drugs provides an optimal environment for the growth of bacterial pathogens. High urinary glucose levels create favorable conditions for the multiplication of UTI-causing bacteria, such as *E. coli*. This increased risk is compounded by the pre-existing immune dysfunction in DM patients. The use of SGLT-2 inhibitors necessitates careful consideration in clinical management, emphasizing the importance of vigilant monitoring for UTI symptoms and prompt intervention to prevent complications in these patients.<sup>17,18</sup> In addition to gender and SGLT-2 inhibitor use, factors like the patient's age, the duration and control of diabetes also play a crucial role in the susceptibility to urinary infections.<sup>18</sup>

Recent studies have indicated that hypertension and other comorbid conditions may exacerbate the risk of urinary infections in diabetic patients, suggesting a multifactorial interplay in these individuals.<sup>19,20</sup>

### Limitations

In evaluating the findings of this study, acknowledging its inherent limitations is essential. The retrospective nature of the study introduces potential issues, including selection bias and data incompleteness. Compared to studies with a prospective design, retrospective analyses often provide less comprehensive information and may overlook key variables.

### CONCLUSION

The study focused on evaluating the prevalence of UTIs and their related risk factors in individuals with DM. The outcomes underscored an elevated risk of UTIs in DM patients, especially in women and those on SGLT-2 inhibitor therapy. These insights are critical for guiding clinical management and developing strategies to mitigate UTI risk in the DM patient population.

### ETHICAL DECLARATIONS

#### Ethics Committee Approval

The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 05.05.2023, Decision No: 383).

#### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

#### Financial Disclosure

The authors declared that this study has received no financial support.

#### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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# ChatGPT in medical writing: enhancing healthcare communication through artificial intelligence and human expertise

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**Cite this article as:** Meşe İ, Kuzan B, Kuzan TY. ChatGPT in medical writing: enhancing healthcare communication through artificial intelligence and human expertise. *Anatolian Curr Med J.* 2024;6(1):97-104.

Received: 27.09.2023

Accepted: 02.01.2024

Published: 15.01.2024

## ABSTRACT

This study explores the capabilities and limitations of ChatGPT, an advanced language model, in medical writing. Leveraging the GPT-4 architecture, ChatGPT has shown potential in aiding various stages of medical article creation, including planning, drafting, revising, and even submission processes. It can summarize extensive literature, suggest research questions, and assist in multi-language research, making it a versatile tool for initial research and planning. During revisions, ChatGPT's strengths lie in improving language, ensuring consistency, and enhancing readability. Despite its abilities, ChatGPT has several limitations. ChatGPT's training data only updates with each new version release, which could result in outdated or incomplete research. It also lacks the critical thinking, domain expertise, and ethical considerations that human researchers bring to medical writing. While ChatGPT can be a useful tool for routine tasks and initial drafts, human expertise remains critical for generating high-quality, ethical, and insightful medical research articles. Therefore, a hybrid approach that combines the computational power of ChatGPT with the intellectual and ethical rigor of human experts is recommended for optimizing medical writing processes.

**Keywords:** Artificial intelligence, language models, medical writing, research methodology

## INTRODUCTION

In recent years, artificial intelligence (AI) has made significant advancements, offering innovative solutions across various industries, including the medical field.<sup>1,2</sup> Among these AI applications, ChatGPT, an advanced language model developed by OpenAI, has emerged as a revolutionary tool with remarkable capabilities in generating human-like text.<sup>3</sup> As ChatGPT has evolved from version 1.0 to 4.0, it has significantly advanced in capabilities. ChatGPT 1.0 offered basic text-based communication and small talk. Version 2.0 showed improvement in contextual understanding, provided more relevant responses, and recognized basic emotions. ChatGPT 3.0 introduced advanced algorithms for personalized responses and multilingual support. 3.5 version further enhanced natural language generation, story creation, and emotion recognition. The latest version, ChatGPT 4.0, added voice-based communication through integration with voice assistants and improved reasoning and decision-making. It also enhanced its ability to handle complex conversations by integrating with external data sources,

including real-time data.<sup>4</sup> Leveraging the GPT-4 architecture, ChatGPT has demonstrated its potential in assisting with medical writing. This is a niche area that requires extensive knowledge, accuracy, and precision in language.<sup>5,6</sup>

Medical writing is a multifaceted process involving several phases, including initial data collection, drafting, editing, and peer review.<sup>7</sup> As medical writing serves as the foundation for disseminating crucial health-related information to both professionals and the general public, ensuring the accuracy and integrity of content is paramount. ChatGPT's proficiency in processing and analyzing vast amounts of information allows it to contribute effectively to each phase of medical writing, streamlining the process while maintaining high-quality standards.<sup>5,6</sup> In this article, we will explore the various roles that ChatGPT can play in the medical writing phases, emphasizing its significance and potential benefits for healthcare communication.

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## PLANNING AND RESEARCH

ChatGPT, an AI language model, offers a range of advantages and disadvantages when used in planning and research for medical article writing.<sup>5,6</sup> ChatGPT can significantly reduce the time spent on initial research by quickly generating summaries, background information, and potential research questions, thereby helping researchers streamline their work.<sup>7,8</sup> ChatGPT can rapidly generate a summary of recent studies on a specific disease, like Type 2 diabetes, summarizing key findings from various medical journals, thus speeding up the initial research phase (Figure 1). This efficiency allows medical professionals to focus on more complex tasks or explore additional research

avenues. The AI tool has been trained on a large volume of text, including medical literature, which allows it to provide relevant information, facts, and suggestions for researchers.<sup>9</sup> Additionally, ChatGPT can work with multiple languages, helping researchers access and understand content in different languages and facilitate international collaboration.<sup>10</sup> This multilingual support can aid in the dissemination of medical knowledge and foster global research networks.

Despite these benefits, ChatGPT's training data only updates with each new version release.<sup>4</sup> It may not have information on more recent advancements, publications, or guidelines in the medical field.<sup>3</sup> This limitation could result in gaps in knowledge and

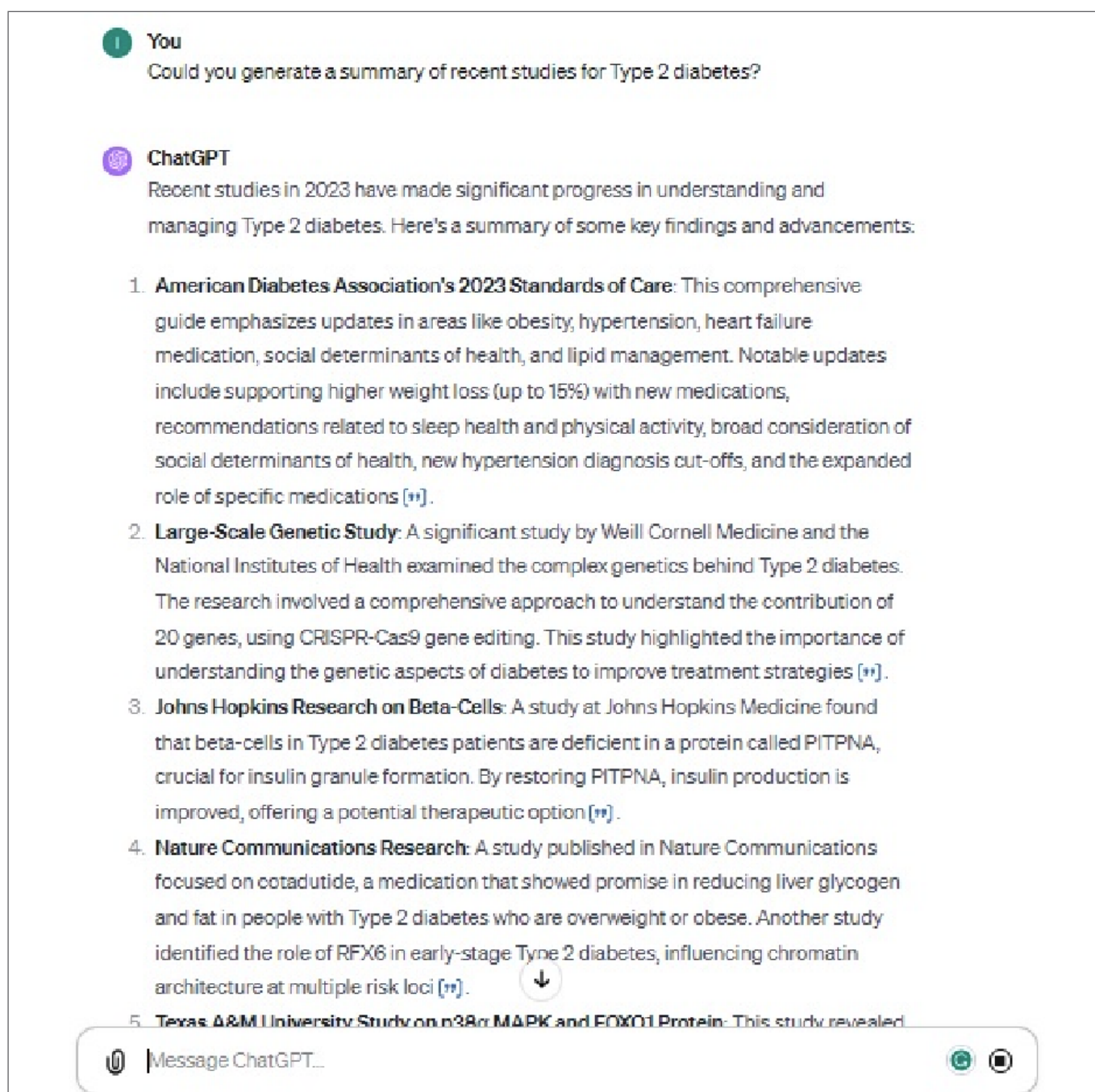


Figure 1. ChatGPT's utility in medical research summarization

necessitate additional research to ensure accuracy and relevance. While generally reliable in the context of medical research, ChatGPT can occasionally produce incorrect or misleading information.<sup>5</sup> This is particularly concerning in the medical field, where accuracy is critical. Researchers using ChatGPT must be vigilant and thoroughly verify any information provided by the AI tool to avoid perpetuating misinformation.<sup>5,6</sup>

The use of AI-generated content in medical research raises ethical questions, such as the potential for plagiarism, the validity of AI-generated data, and the responsibility for any errors.<sup>6,11</sup> Researchers must navigate these ethical considerations carefully when using ChatGPT to ensure the integrity of their work. Lastly, ChatGPT may not always be able to provide context-specific information or critically evaluate conflicting evidence, a crucial skill in medical research.<sup>7</sup> Human researchers must continue to use their expertise and critical thinking skills to make informed decisions and assessments. We have given some prompts for planning and research prior to composing a medical article (Figure 2).

## HUMAN RESEARCHERS' EXPERTISE CRUCIAL IN CREATING HIGH-QUALITY RESEARCH ARTICLES

Creating a research article involves several steps, including identifying the main topic, establishing a structure with main and subordinate headings, choosing and presenting evidence, and continuously reviewing and improving the outline (Figure 3).<sup>12</sup> Human researchers have the advantage of subject matter expertise, the ability to identify research gaps and prioritize information, and critical evaluation skills to select reliable and relevant evidence.<sup>13</sup> Additionally, they can adapt and refine the article structure based on feedback from peers or experts in the field to ensure clarity, coherence, and readability.<sup>14</sup>

In contrast, ChatGPT's capabilities, such as identifying the main topic, generating headings, and selecting supporting evidence, are limited by its training data and lack of domain expertise. While it can make basic text revisions, it may struggle with addressing inconsistencies, redundancies, or structural gaps in an article.<sup>15</sup>

"Summarize a recent research article on [specific topic or medical condition]."
"Provide an overview of the current understanding of [specific disease or disorder]."
"Discuss the pros and cons of [specific treatment method] for [specific condition]."
"Explain the role of [specific factor, e.g., lifestyle, genetics] in the development or management of [specific medical condition]."
"Review the latest advancements in the treatment of [specific medical condition]."
"Analyze the implications of a recent medical breakthrough for [specific patient population]."
"Describe the challenges and potential solutions for improving healthcare access in [specific region or population]."
"Explain the significance of [specific medical study or clinical trial] and its impact on future research or clinical practice."
"Evaluate the effectiveness of [specific public health intervention] in addressing [specific health issue]."

Figure 2. Some prompts for planning and research prior to composing a medical article

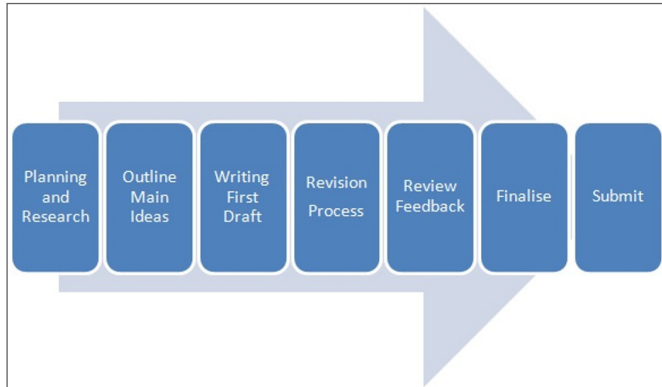


Figure 3. The process of creating a research article

While ChatGPT is an advanced language model capable of generating human-like text, unlike human researchers, it lacks the critical thinking skills necessary to identify gaps in research, question assumptions, and provide a balanced perspective on complex medical issues.<sup>16</sup> This may lead to inaccuracies or oversimplifications in generated content.

Although ChatGPT can generate text that appears to convey intricate concepts, novel techniques, and specialized terminology, its understanding of complex

medical ideas is limited.<sup>16</sup> Consequently, its inability to fully grasp these concepts may lead to misunderstandings or misrepresentations in the articles it generates.

ChatGPT’s limited understanding of ethical guidelines in medical research could lead to unintentional ethical breaches, such as in patient privacy or conflict of interest disclosure, underscoring the need for human oversight.<sup>17-19</sup> It is required for all authors to submit an international committee of medical journal editors (ICMJE) disclosure form when publishing their work (Figure 4). Without the human capacity to navigate ethical challenges, the generated content may not meet the high standards of integrity and professionalism expected in the medical field.

The contextual awareness and historical understanding that human researchers bring to medical topics may not be fully captured by ChatGPT.<sup>20</sup> As a result, it may struggle to draft articles that are insightful, relevant, and contribute meaningfully to the ongoing discourse in the field. This limitation could lead to superficial or outdated content that does not accurately reflect current debates and future directions.

**ICMJE DISCLOSURE FORM**

**Date:**

**Your Name:**

**Manuscript Title:**

**Manuscript Number (if known):**

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author’s relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

	Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<b>Time frame: Since the initial planning of the work</b>		
<b>1</b>	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) <b>No time limit for this item.</b>	<input type="text" value="None"/> <input type="text"/> <input type="text"/> <input type="text" value="Click the tab key to add additional rows."/>

Figure 4. ICMJE disclosure form

Lastly, ChatGPT lacks emotional intelligence, which is essential when addressing sensitive topics or discussing significant implications for patient care and well-being.<sup>21</sup> Without the human capacity for empathy, compassion, and ethical responsibility, it may generate content that is insensitive, disrespectful, or fails to consider the potential impact of the information presented.<sup>22-24</sup> This limitation hinders its ability to communicate complex medical information with the appropriate level of sensitivity and understanding.

### **CHATGPT'S VALUE IN THE REVISION PROCESS OF MEDICAL ARTICLES**

ChatGPT's benefits can be utilized during the revision process, where its ability to maintain a consistent writing style, work with multiple languages, refine language and grammar, and identify inconsistencies can improve the overall presentation and readability of the article.<sup>25</sup> ChatGPT can also generate alternative phrasings, restructure sentences, and suggest improvements in clarity and conciseness, enhancing the final draft while adhering to the stylistic requirements of various medical journals and conferences.<sup>26</sup>

Another advantage of ChatGPT in the revision process is its ability to quickly process large volumes of text, which can be particularly beneficial when working on lengthy or complex medical articles.<sup>5,6</sup> This time-saving aspect allows researchers to focus on other essential aspects of their work, such as data analysis or experimental design, without sacrificing the quality of their written output. Additionally, ChatGPT can detect repetitive phrases or overused terms and suggest more varied language to diversify the content and maintain reader engagement.

ChatGPT can assist authors in revising medical articles by identifying and suggesting the removal of unnecessary information, ensuring coherence throughout the text, and addressing potential biases.<sup>26-28</sup> Its ability to detect redundant statements or irrelevant content helps to create a more focused and concise article. Additionally, ChatGPT can help maintain a logical flow, checking for coherence between the introduction, main points, and conclusion, as well as within each section. Moreover, it can highlight areas where potential biases might be present, promoting a more objective presentation of evidence and claims.

### **THE IMPORTANCE OF HUMAN EXPERTISE IN REVIEWING MEDICAL ARTICLES**

During the revision process, ChatGPT's benefits become evident, particularly in maintaining a consistent writing

style, working with multiple languages, refining language and grammar, and identifying inconsistencies, all of which improve the overall presentation and readability of the article.<sup>29</sup> Colleagues and mentors can provide insights that stem from their own research experiences and familiarity with the field, which can help the author refine their argument, clarify their presentation, and address any gaps or inconsistencies.<sup>29</sup>

On the other hand, ChatGPT may fall short in the review process of medical articles for several reasons. Firstly, it lacks the deep understanding of specific research areas and the contextual knowledge that human reviewers possess.<sup>6</sup> This limits its ability to evaluate the relevance and importance of the article's findings within the broader context of the field or suggest additional sources or ideas that could strengthen the article.

Furthermore, human reviewers can assess the article's tone, readability, and potential impact on the target audience, offering suggestions for how to better engage readers and convey the significance of the research.<sup>29</sup> Their ability to empathize with the audience allows them to provide invaluable guidance on how to communicate complex information in a clear and accessible manner. ChatGPT, however, does not possess emotional intelligence or the capacity to empathize with the audience, which can hinder its ability to accurately gauge the tone or potential impact of the article.<sup>21</sup>

### **CHATGPT'S ADVANTAGES AND LIMITATIONS IN FINAL EDITING OF MEDICAL ARTICLES**

While ChatGPT can be highly effective in final editing tasks, it's important to note that it is still an AI language model and not a human editor.<sup>28</sup> While it may be faster and more efficient than a human editor in certain aspects of final editing, it may lack the contextual understanding, creativity, and subjectivity that a human editor possesses, making it difficult to say definitively that ChatGPT is better than a human editor at final editing. A combination of both may be the most effective approach for achieving the highest quality of written work.<sup>28</sup>

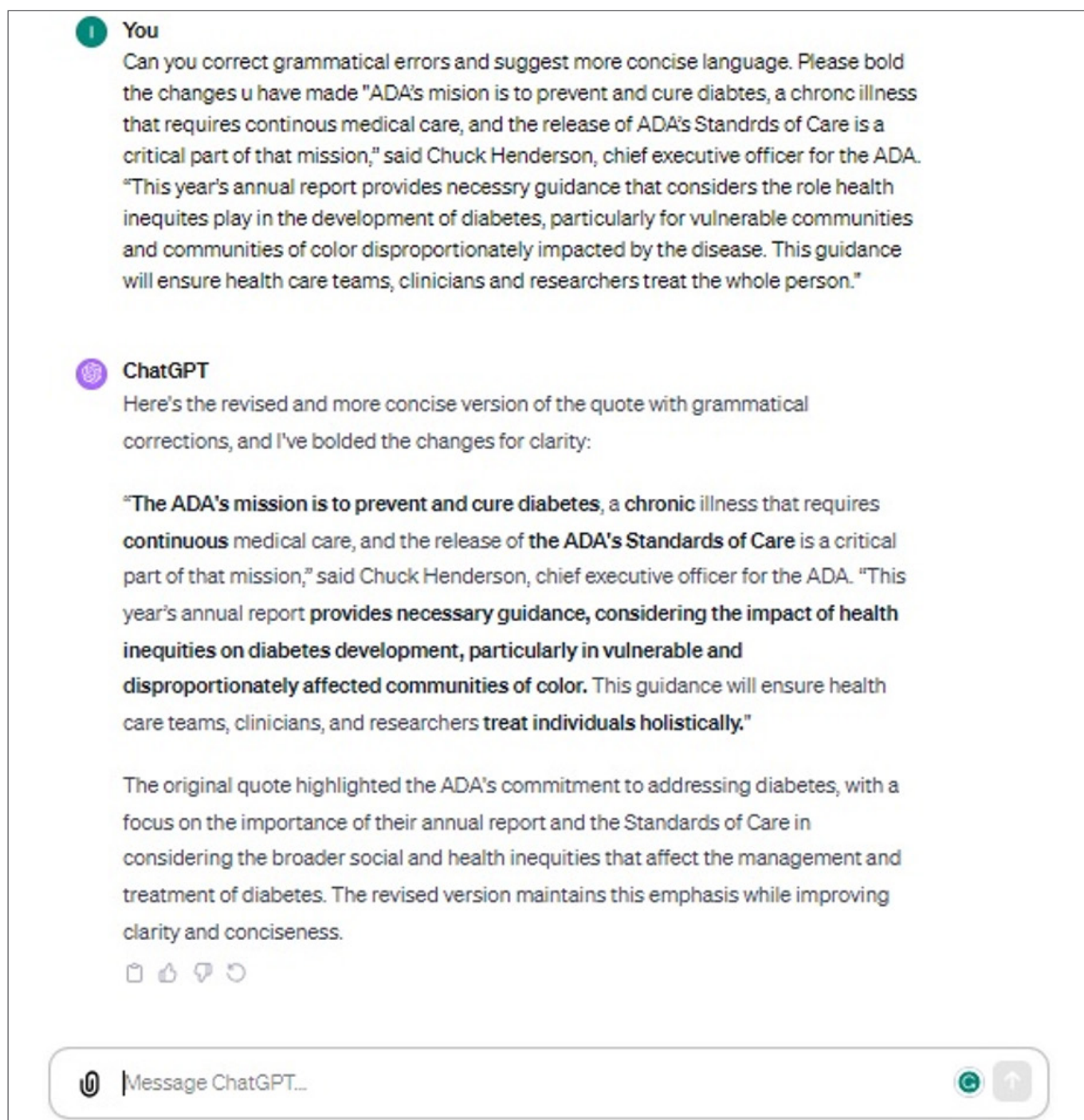
ChatGPT's capabilities in final editing stem from its advanced natural language processing (NLP) algorithms, which allow it to analyze text at a deep semantic level.<sup>6,30</sup> This means that it can not only identify errors in grammar, syntax, and spelling, but also understand the meaning behind sentences and paragraphs.<sup>30</sup> This enables ChatGPT to provide more nuanced and accurate editing suggestions than a traditional spell-check or grammar-check tool. Moreover, ChatGPT can learn from examples of well-written text, and use this

knowledge to suggest improvements to other pieces of writing. This means that the more it is used, the better it becomes at identifying and correcting errors, and providing helpful feedback to users.

In addition to its technical capabilities, ChatGPT's responsiveness and efficiency make it an ideal tool for final editing. It can efficiently correct grammatical errors and suggest more concise language (Figure 5). It can quickly process large volumes of text, enabling authors to make last-minute adjustments or revisions before submitting their work. This can help to ensure that the final product is polished, professional, and free of errors.

## CHATGPT'S POTENTIAL ASSISTANCE ON SUBMISSION PROCESSES FOR MEDICAL ARTICLES

ChatGPT can assist in the submission process by helping authors create templates for documents required by a journal's author instructions (Figure 6). By analyzing the specific requirements for the document, including formatting, content, and layout, ChatGPT can create a template that includes all of the necessary elements and formatting, making it easier for authors to create the required document and ensuring that it meets the journal's guidelines.<sup>31</sup>



**You**  
Can you correct grammatical errors and suggest more concise language. Please bold the changes you have made "ADA's mision is to prevent and cure diabtes, a chronc illness that requires continous medical care, and the release of ADA's Standrds of Care is a critical part of that mission," said Chuck Henderson, chief executive officer for the ADA. "This year's annual report provides necessary guidance that considers the role health inequites play in the development of diabetes, particularly for vulnerable communities and communities of color disproportionately impacted by the disease. This guidance will ensure health care teams, clinicians and researchers treat the whole person."

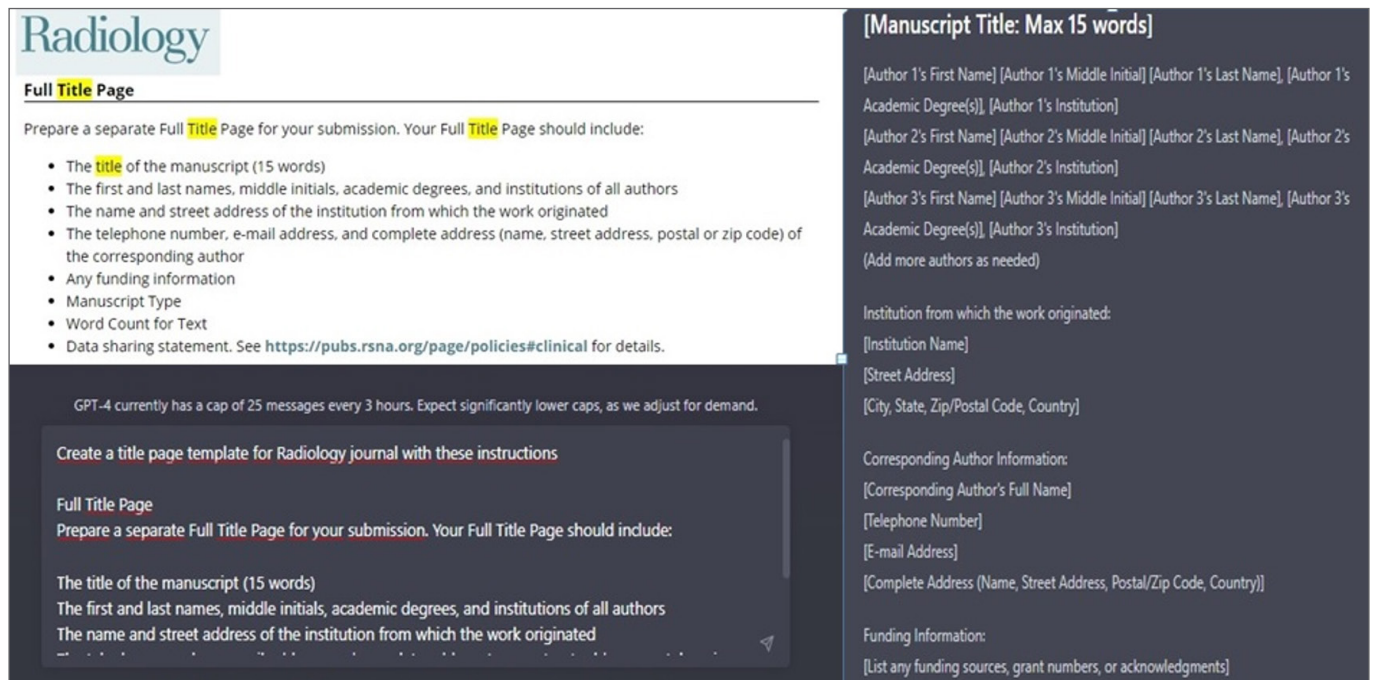
**ChatGPT**  
Here's the revised and more concise version of the quote with grammatical corrections, and I've bolded the changes for clarity:

**"The ADA's mission is to prevent and cure diabetes, a chronic illness that requires continuous medical care, and the release of the ADA's Standards of Care is a critical part of that mission,"** said Chuck Henderson, chief executive officer for the ADA. **"This year's annual report provides necessary guidance, considering the impact of health inequities on diabetes development, particularly in vulnerable and disproportionately affected communities of color.** This guidance will ensure health care teams, clinicians, and researchers **treat individuals holistically.**"

The original quote highlighted the ADA's commitment to addressing diabetes, with a focus on the importance of their annual report and the Standards of Care in considering the broader social and health inequities that affect the management and treatment of diabetes. The revised version maintains this emphasis while improving clarity and conciseness.

Message ChatGPT...

Figure 5. ChatGPT's language refinement capabilities



**Figure 6.** Creating a title page template in accordance with the journal's guidelines for authors

ChatGPT can also be used to create abstracts for journal articles and research papers by analyzing the content, summarizing key themes and topics, providing context, and refining the abstract to match the requirements of the publication.<sup>31</sup> By analyzing the text and identifying the main findings or research, ChatGPT can create a concise and clear summary that meets the guidelines for abstract length and format.

Additionally, ChatGPT can assist with keyword optimization, helping writers to identify relevant keywords and ensure that they are used appropriately throughout the article. This can improve the article's search engine optimization and increase its chances of being discovered by potential readers.

## ETHICAL IMPLICATIONS

The ethical implications of using ChatGPT include concerns about biased and inaccurate outputs, as the tool is trained on a mix of sources, some of which may contain biases. This can result in outputs that reflect these biases or are factually incorrect.<sup>32</sup> The lack of clarity about the tool's training sources and decision-making process also poses a challenge. Privacy is another significant concern. Since ChatGPT stores user interactions for training purposes, there's a risk of personal or sensitive information being inadvertently used in future model training. Users should be cautious about the information they input. In academic settings, there's a risk of using ChatGPT for plagiarism or cheating.<sup>32</sup> This could involve using AI-generated content as one's own work or paraphrasing existing

content without proper attribution. Such actions are against academic integrity principles. ChatGPT might also produce outputs that inadvertently infringe on copyright, as it is trained on various sources, including copyrighted material. Users are responsible for any copyright issues that arise from their use of the outputs. Ethically using ChatGPT involves adhering to institutional guidelines, being transparent about the use of the tool, critically evaluating its outputs, and using it as a guide rather than as a complete substitute for original work.<sup>32</sup>

## CONCLUSION

While ChatGPT offers numerous benefits and can assist in various stages of the medical article writing process, it is important to recognize its limitations and the continued importance of human expertise. A combination of both human researchers and AI tools like ChatGPT can lead to the creation of high-quality medical articles that are well-researched, engaging, and adhere to ethical guidelines.

## ETHICAL DECLARATIONS

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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# Enchondroma of acromion: case report of an unusual tumor location

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**Cite this article as:** Aydın Şimşek Ş, Cengiz T, Yurtbay A, Coskun HS, Dabak N. Enchondroma of acromion: case report of an unusual tumor location. *Anatolian Curr Med J.* 2024;6(1):105-107.

Received: 06.07.2023

Accepted: 23.09.2023

Published: 15.01.2024

## ABSTRACT

Enchondroma is a benign cartilaginous tumor and is rarely located on the shoulder girdle. The lesion that affects the subacromial area can cause rotator cuff impingement's clinical signs. Our aim is to present this patient who has shoulder pain and was finally diagnosed with an acromial enchondroma. A 62-year-old female patient had an insidious left shoulder pain in the last 2 years. At the physical examination of the left shoulder, subacromial impingement syndrome's sign was noticed. Plain radiographs didn't have any typical features and magnetic resonance imaging (MRI) images were used for diagnosis. Well-circumscribed hypointense content on T1-weighted images was observed, and the lesion was seen as hyperintense on T2-weighted images. At the same time, subacromial effusion was noticed. Because of enchondroma's small size, the patient was followed up with medical treatment and radiographical features. At one year follow-up, there was no change in the size of the lesion and no increased complaint about her left shoulder. Physicians should keep in mind that enchondroma may occur rarely in acromion and this condition may cause subacromial impingement. Therewithal, this diagnosis which is a rare reason for subacromial impingement syndrome should be considered in the differential diagnosis of shoulder pain.

**Keywords:** Enchondroma, neoplasm, acromion, shoulder, impingement

## INTRODUCTION

Enchondroma is a common benign cartilaginous tumor, defined more exactly as a benign mature hyaline cartilaginous tumor located in the medullar space of the tubular bones. One type of musculoskeletal tumor of the hand is enchondroma, usually found in the tubular bones. After osteochondroma, enchondroma follows in frequency among benign bone tumors.<sup>1</sup> The tumor arises in the medullary cavity and grows into the cortex, forming a prominent endogenous mass in the bone. This tumor type has no unique clinical symptoms but an enchondroma is always difficult to diagnose.<sup>2</sup> Enchondroma is rarely found in the shoulder girdle. Although most enchondromas are asymptomatic, depending on the lesion's size and localization, radiologic presentation enchondromas can be presented in different clinical features. Enchondromas do not routinely require surgical treatment, unless they are symptomatic, increasing in size, or there is a risk of pathological fracture.<sup>3</sup> The gold standard treatment of enchondromas has been considered curettage and autograft if surgery is required.<sup>4</sup>

In this case, we report a 62-year-old woman with a subacromial impingement syndrome caused by an enchondroma in the center acromion. We describe the clinical features and radiological imaging features. Our aim is to contribute to the unusual localization of enchondroma and also represent a rare reason for subacromial impingement syndrome.

## CASE

A 62-year-old woman who has a mechanical pain in her left shoulder in the last 2 years without previous trauma. The patient was referred to the orthopedic surgery outpatient clinic for insidious left shoulder pain that started 2 years ago. The patient was treated conservatively for one year and her complaints did not regress and she was referred to our clinic.

On physical examination, palpation of the posteromedial edge of acromion was painful. There was full range of motion and the muscle strength was normal comparing to the opposite shoulder. When we

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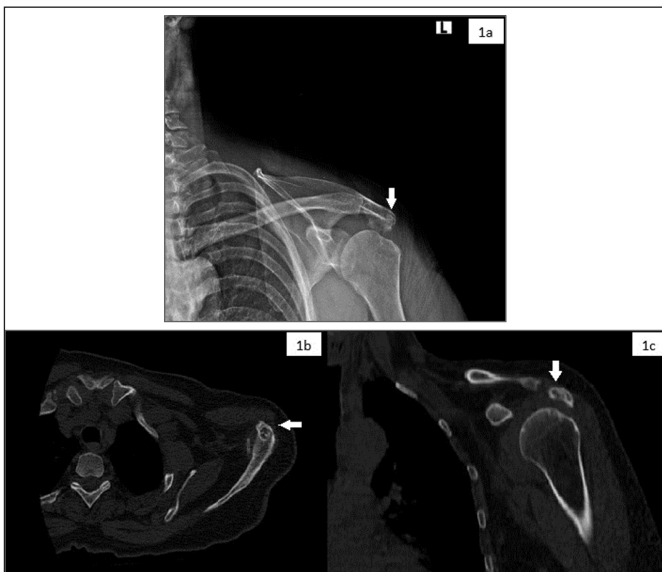
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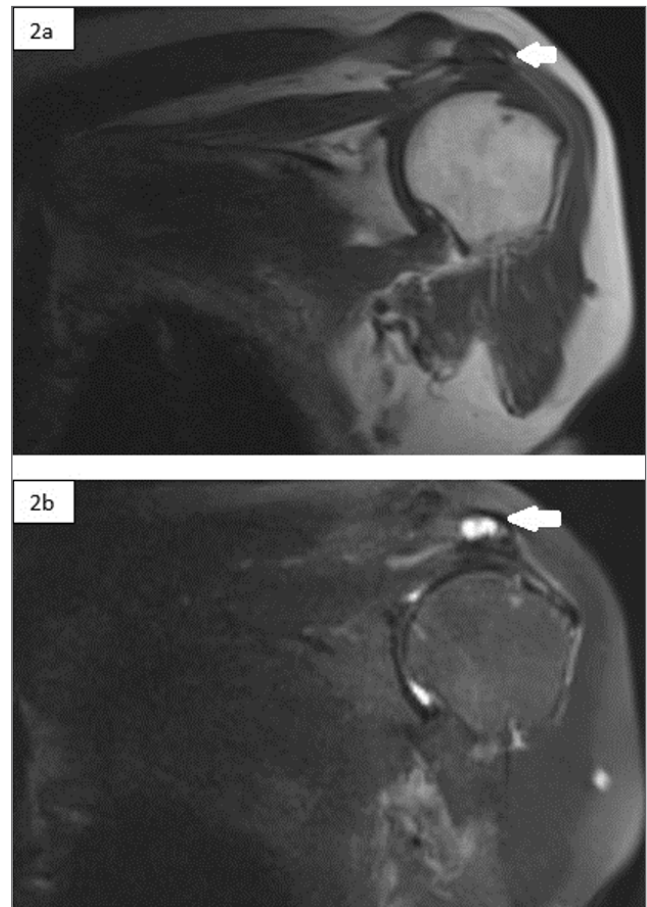
passively raised the patient's right arm to 90 degrees of abduction and forced full extension to the right shoulder, pain increased. Hawkins signs were clearly positive. Afterwards when we stabilized the right scapula and passively raised the arm to flexion, pain increased. Neer impingement sign was also positive.

Plain radiographs showed a degeneration of acromioclavicular joint and irregular appearance at the posteromedial edge of acromion (**Figure 1a**). **Figure 1a** is a specialized projection of acromioclavicular joint, called as Zanca view. According to the computerized tomography images, there is a central localized and benign characterized cystic formation which has sclerotic edges and calcifications on left acromion. This lesion is approximately 1.5 cm in diameters (**Figure 1b-1c**). Magnetic resonance imaging (MRI) without contrast was performed due to the patient's history of contrast material allergy. MRI revealed a well-circumscribed hypointense content on T1-weighted images (**Figure 2a**), which was hyperintense and had some focal regions of signal drop out where calcification was present on T2-weighted images. In addition to this, there was a subacromial effusion on fat suppressed T2-weighted images (**Figure 2b**). So the patient has shoulder impingement secondary to acromial enchondroma.

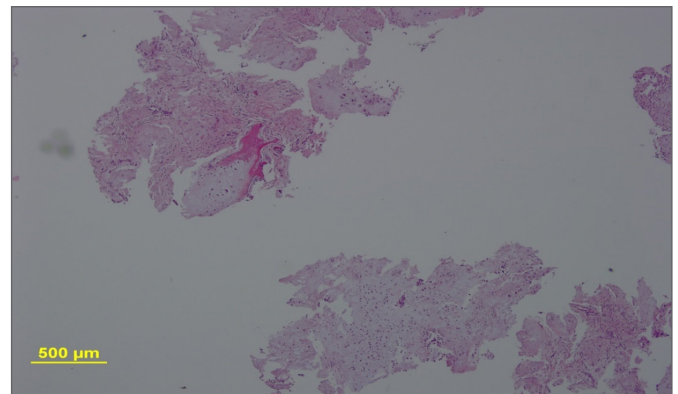
We decided to take a biopsy for tissue diagnosis. Tru-cut biopsy as the initial method of tissue diagnosis in bone tumors, in this way, Tru-cut-type needle was used for obtaining tissue samples. Clinical and radiological findings matched with pathology report as a result, the patient was diagnosed with enchondroma (**Figure 3**).



**Figure 1.** There is a degeneration on acromioclavicular joint and irregular appearance at the posteromedial edge of acromion on Zanca radiograph of the left shoulder (1a). Axial (1b), coronal (1c) CT images showed a central localized cystic formation which has sclerotic edges and calcifications on left acromion.



**Figure 2.** 2a-Coronal T1 MRI images showed that well-circumscribed hypointense content in acromion, 2b-The lesion well-circumscribed hyperintense content which has some focal regions of signal drop out where calcification was present and subacromial effusion on fat suppressed T2-weighted images



**Figure 3.** Histopathology of enchondroma with H&E stain (magnification  $\times 40$ )

Because of the small sizes of the lesion, we decided to follow up the patient with conservative therapy. Medical drugs were used for anti-inflammatory and analgesic effects and physical therapy were simultaneously applied to strengthen the shoulder area muscles. We can decide to operate the patient for acromioplasty in the future, if her complaints don't regress. We've followed up the patient for 1 year and the patient's complaints haven't increased and her shoulder pain is under control by suggested medical treatment. At the same time the acromial lesion's size haven't changed at the radiographical plans.

## DISCUSSION

Enchondroma is developed from fragments of cartilage that are originated from the central physis. This tumor occurs most frequently in the proximal phalanges, followed by the metacarpals and middle phalanges.<sup>5</sup> Considering enchondroma could be useful to investigate the reasons for uncertain pain's etiology. Follow up is sufficient for asymptomatic enchondromas. Classical treatment is curettage and bone grafting if the surgery is required.

Primary malignant bone tumors of the scapula are rarely seen even though the shoulder girdle presents the third most common site for tumors of bone and soft tissue tumors.<sup>6</sup> Scapular tumors normally arise in the scapular blade, and very rarely are situated in the acromion-glenoid complex, causing subacromial impingement.<sup>7</sup> Although most enchondromas are asymptomatic, malignant transformation into secondary chondrosarcoma is possible in 1-9% depending on localization, pain, size, and radiologic presentation.<sup>8</sup>

Subacromial impingement syndrome appears to result from a variety of factors which are inflammation of the tendons and bursa, degeneration of the tendons, weak or dysfunctional rotator cuff musculature, posterior glenohumeral capsule tightness, postural dysfunctions of the spinal column and scapula and bony or soft tissue abnormalities of the borders of the subacromial outlet.<sup>9</sup> At the same time enchondroma can be one of the reasons of subacromial impingement. López et al.<sup>7</sup> reported one case which was about rotator cuff impingement due to enchondroma of acromion. This is a simple case about enchondroma of acromion. In addition to this, the lesion affected the subacromial area and caused the rotator cuff impingement syndrome. They used surgical treatment for the pathology.

## CONCLUSION

According to this data, acromial enchondroma is a very rare case in literature. In addition to this, rotator cuff impingement by acromial enchondroma is a rarer situation, as only one case was reported. We must consider this pathology in differential diagnosis about uncertain pain of shoulder.

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## Financial Disclosure

The authors declared that this study has received no financial support.

## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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