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Page : 513-7

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Research Article

Did the COVID-19 Pandemic Period Increased Suicide Attempts in Society?

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Abstract

Aim: To analyze the influence of the COVID-19 pandemic and quarantine on suicidality.

Material and Methods: This study was conducted on patients over the age of 15 who were suicidal and admitted to the emergency department of our hospital. The patients were disunited into two groups: pandemic group covering the period from March 11, 2020 to March 11, 2021, the former being the date when the first patient of COVID-19 was identified in Turkey, and pre-pandemic group covering the period from March 11, 2019 to March 10, 2020.

Results: The study was conducted with a total of 271 patients. The number of suicide attempts in the first time period (March-April-May-June) was 42 (28.4%) in the pandemic group and 16 (13.0%) in the pre-pandemic group, with significantly higher numbers in the pandemic group for the first time period (p=0.008). The distribution in the remaining second and third time periods was similar to those in the previous year.

Conclusion: Compared to the pre-pandemic period, suicide attempts significantly increased in the early stages of the pandemic as the first case was identified in Turkey and the lockdown was imposed because of the increasing cases. In the later stages of the pandemic, there was no obvious change in the amount of suicide compared to previous periods.

Keywords: COVID-19, suicide, pandemic

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious disease that can cause significant acute respiratory failure. It had a devastating impact around the world, killing more than 6 million people worldwide. It has emerged as the most important global health problem since the 1918 flu pandemic (1). Infectious diseases can cause organic pathological consequences and symptoms in the human body. Even in the case of an individual illness, it is possible for the person to be affected psychologically. In a worldwide pandemic that affects the whole country and even all humanity, people are affected spiritually and some psychological symptoms may occur. In previous outbreaks, stress was the most common mental health symptom. This was a symptom of acute stress, distress or post-traumatic stress. Less frequently, it was seen as anxiety, fear, depression and sleep disorders (2). As a result of the research, symptoms such as anxiety, depression and stress are more common in the community regarding mental health related to COVID-19, unlike previous pandemics (3).

Due to the impact on social structure, few changes were observed in the suicide rates following the natural disasters worldwide (4). It is known that infections such as MERS and SARS-CoV-2, which have lately affected the world, leads to negative psychosocial impacts on communities, and the suicide rates increased in those parts of the world where these diseases led to an epidemic (5).

Studies have revealed that different types of changes due

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to the COVID-19 pandemic can cause suicidal thoughts and behaviors in individuals and society in general (6). The emotional reaction of people to pandemics may differ according to countries or geography, and even according to the religions believed. Moreover, it was observed that positivity and the desire to live declined in China, whereas negativities, such as anxiety, depression, and anger, continued to increase (7).

Experienced stress or affective disorders both affect the quality of life and cause some psychosocial consequences. If people cannot cope with their negative feelings and thoughts, it is possible for them to initiate the process that leads them to suicide. Suicide attempts result from multiple factors that are related to long-term social isolation, economic and psychosocial status as well as physical health (8). In most societies across the world, the economic, social, and personal burdens due to the pandemic may contribute to the suicidal attempts (9).

With the onset of the pandemic in Turkey, various measures have been introduced including closure of schools, full or part-time lockdowns, closure of certain categories of businesses, and introduction of travel restrictions. These measures led to various social and economic consequences in the society. This article investigates the effect of the COVID-19 pandemic and lockdown on suicidality in Turkey.

MATERIAL AND METHOD

Study Design and Setting

This is a one-center and cross-sectional investigation comprising patients who were presented to the emergency department of a tertiary university hospital, that annually admits 300,000 patients. The data were taken from the hospital's data system.

Patient Selection

The first patient of COVID-19 was identified in Turkey on March 11, 2020 and led to the onset of the pandemic. The pre-pandemic group included patients aged 15 years and older who were presented to the emergency department of our hospital between March 11, 2019 and March 10, 2020 for attempted suicide, whereas the pandemic group comprised patients aged 15 years and older who were presented for attempted suicide between March 11, 2020 and March 11, 2021. Patients were excluded if they were pregnant, under 15 years, or had any missing data.

Data Collection

Patients were disunited into two groups based on the pandemic and pre-pandemic period. Patients' age, gender, history and method of suicide, history of psychiatric illness and suicide attempts, and the need for hospitalization were determined for each group. In addition, the history of COVID infection was determined for the patients included in the pandemic group. The methods of suicide attempt were classified as intoxication with drugs, hanging, self-laceration with a sharp object, and jumping from a height. Demographic characteristics were compared between the two groups. The study aimed to determine whether there was a change amount of suicide attempts in the years of pandemic compared to the pre-pandemic date. Changes in the amount of suicide attempts during the period when lockdowns and restrictions were imposed and when the pandemic peaked were compared to those in the previous year. For both the groups, the incidents of suicide were divided into three time periods consisting of four-month intervals. These four-month periods were associated with specific lockdown periods. The first time period lasted through March-April-May-June, 2020, when the first case was identified, cases rapidly increased, and several lockdowns were imposed; the second time period included July-August-September-October, when the number of cases sharply declined and there was no lockdown; the third time period of November-December-January-February was when the number of cases increased again and the lockdowns were reintroduced.

Statistical Analysis

To summarize data from the investigation, descriptive statistics are given in tables with mean ± standard deviation or median, minimum, and maximum for continuous (numerical) variables. The normality of numeric variables was confirmed with the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson–Darling tests. For comparing two independent groups in cases where numerical variables were not normally distributed, the Mann-Whitney U Test was used. For the comparison of categorical variables by the groups, the Pearson Chi-square test was used in 2×2 tables with expected cells of 5 and over and the Fisher Freeman Halton test was used in RxC tables with expected cells < 5. Statistical analyses were performed with "Jamovi project (2021)," Jamovi (Version 2.2.2.0 [Computer Software]; retrieved from https://www.jamovi.org) and JASP (Version 0.16; retrieved from https://jasp-stats.org) programs, and the level of significance in statistical analysis was set at 0.05 (p-value).

Ethical clearance was obtained from the Ethics Committee of Non-Interventional Clinical Researches of Karabuk University.

RESULTS

The study was conducted with a total of 271 patients. There were 148 patients in the pandemic group, consisting of 79 men (53.4%) and 69 women (46.6%), whereas 123 patients were involved in the pre-pandemic group, occur of 56 men (45.5%) and 67 women (54.5%). Mean age was statistically higher in the pandemic group than the patients in the pre-pandemic group (p=0.013). There was no statistical difference between the two patient groups in terms of gender distribution (p=0.198). Although 45.3% and 42.3% of the patients in the pandemic and pre-pandemic groups had a known history of psychiatric illness, respectively, there was no statistical difference between them (p=0.621). Compared to 22.8% in the pre-pandemic group (p=0.496), 39 patients (26.4%) in the

pandemic group had a previous history of failed suicide attempts. Only five patients (3.4%) had a history of COVID infection in the pandemic group. The groups showed no difference in terms of the need for hospitalization for attempted suicide (Table 1). There were no deaths reported in the emergency department or during hospitalizations in patients admitted to the hospital for attempted suicide.

Table 1. Demographic and clinical characteristics of the groups

	groups		
	pandemic group (n=148)	pre-pandemic group (n=123)	p-value
Age (year)†	30.3±11.4	27.7±13.3	0.013*
ª	28.0 [15.0–74.0]	23.0 [14.0–59.0]	
Gender‡			
Man	79 (53.4)	56 (45.5)	0.198**
Women	69 (46.6)	67 (54.5)	
History of psychiatric illness ‡	67 (45.3)	52 (42.3)	0.621**
History of suicide attempts‡	39 (26.4)	28 (22.8)	0.496**
History of COVID infection‡	5 (3.4)	0 (0)	--
Need for hospitalization‡	72 (48.6)	72 (58.5)	0.104**

†: mean±standard deviation
, ‡: n (%), ª: median [min.-max.]
*. Mann-Whitney U test
**. Pearson Ki-square test

In the pandemic group, the highest number of suicide attempts was reported to be 18 cases in July (12.2%), whereas the highest number reported in the pre-pandemic group was 17 cases in January (13.8%). There was no statistical difference between the two patient groups in the distribution of suicide attempts by months (p=0.188) (Table 2) (Figure 1).

Attempting suicide using drugs was the most common method of suicide in both the groups (69.6% and 77.2%). No statistical difference was observed between the groups in terms of suicide attempt method (p=0.485).

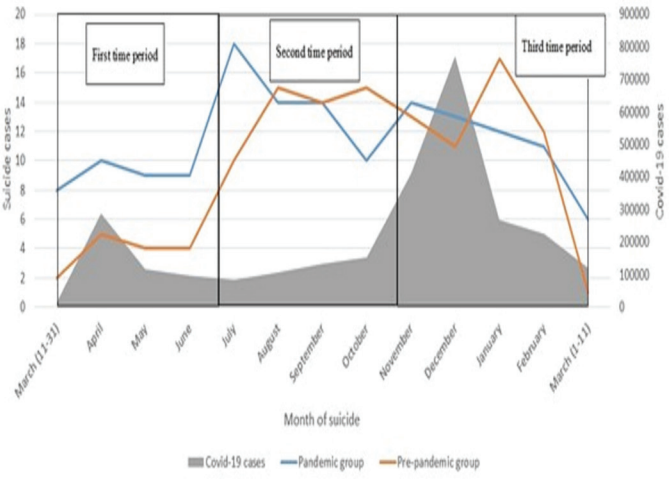

Figure 1. Distribution of suicide attempts by month

Table 2. Temporal distribution of suicide attempts and cross-group comparison by method

	groups		
	pandemic group (n=148)	pre-pandemic group (n=123)	p-value
Month of suicide attempt‡			
January	12 (8.1)	17 (13.8)	
February	11 (7.4)	12 (9.8)	
March	14 (9.5)	3 (2.4)	
April	10 (6.8)	5 (4.1)	
May	9 (6.1)	4 (3.3)	
June	9 (6.1)	4 (3.3)	0.188
July	18 (12.2)	10 (8.1)	
August	14 (9.5)	15 (12.2)	
September	14 (9.5)	14 (11.4)	
October	10 (6.8)	15 (12.2)	
November	14 (9.5)	13 (10.6)	
December	13 (8.8)	11 (8.9)	
Method of suicide‡			
Drugs	103 (69.6)	95 (77.2)	
Hanging	5 (3.4)	2 (1.6)	0.485
Self-laceration with a sharp object	33 (22.3)	23 (18.7)	
Jumping from a height	7 (4.7)	3 (2.4)	

‡: n (%)
Used Fisher-Freeman-Halton test

There were 42 (28.4%) cases of suicide attempts in the first time period (March-April-May-June) in the pandemic group compared with 16 (13.0%) in the pre-pandemic group, with significantly higher numbers present in the first time period in the pandemic group (p = 0.008). The distribution was similar in the remaining second and third time periods for the groups compared to those in the previous year (Table 3).

Table 3. Cross-group comparison of suicide attempts by temporal distribution and method

	groups		
	pandemic group (n=148)	pre-pandemic group (n=123)	p-value
Period of suicide attempt ‡			
1. time period (March-April-May-June)	42 (28.4) a	16 (13.0) b	
2. time period (July-August-September-October)	56 (37.8)	54 (43.9)	0.008
3. time period (November-December-January-February)	50 (33.8)	53 (43.1)	

‡: n (%)
Used Pearson Ki-square test

DISCUSSION

The results of this investigation showed an important increase in the suicide cases between March and June, which is the same period when the first patient of COVID-19 was identified in Turkey, lockdowns and restrictions were imposed, the number of cases increased,

and the pandemic reached its first peak, compared to the same time period of the last year. There was no important change in the number of suicide cases between November and February of the pandemic period, which marked the second peak with lockdowns and restrictions, compared to the same time period of the last year. Likewise, there was no important change in the number of suicide cases in July–October, the period without any increase in cases and lockdowns. In the United States, similar to Turkey, ın the early of the pandemic, the number of suicide attempts increased, with a gradual decrease in suicide attempts seen in the later course of the pandemic (10). The lack of knowledge of COVID-19 infection and social isolation may have caused extreme anxiety among people in the first period of the pandemic. Several factors may have helped people to cope with the pandemic in the later stages, including getting used to the new situation, the emergence of alternative communication methods, and increased socialization.

Although similar results were obtained in our study in the United States, Rachel S Bergmans found a decrease in suicide cases in the first 7 months of the COVID 19 pandemic in her research in Washtenaw County, Michigan. He suggested that the reason for this may be the decrease in socialization in the early period of the pandemic, the closure of schools due to remote working from home, the decrease in the stress factor due to the absence of academics from school, and the difficulty in accessing suicide tools. In the same study, it was stated that the decrease in suicide attempts in men, caucasians and unmarried people was not very clear. In the light of this information, it can be concluded that there may be different rates of suicide attempts in different regions within the borders of the same country (11).

In the pandemic and pre-pandemic groups, the patients who attempted suicide were similar in terms of previous history of psychiatric illness. There was no statistical difference between the two patient groups in terms of previous failed suicide attempts. Likewise, there was no meaningful difference between the two groups in terms of their need for hospitalization due to attempted suicide. There were no patients who attempted suicide during the course of COVID-19 infection.

In various parts of the world as well as in Turkey, suicidal thoughts and suicide attempts have increased during the pandemic period (11,12). A UK-based study found increased suicidal thoughts and suicide attempts, especially in young adults, during the COVID-19 pandemic when the lockdowns were imposed (13).

In the study of William D S Killgore et al., it was determined that there was an increase in suicide attempts in people who were isolated and under restraint in the early period of the pandemic, and there was no change in suicide attempts and thoughts in individuals without restriction and isolation compared to the previous period. Considering that there are strict restrictions in the early period of the pandemic in Turkey and that individual isolation is applied in large quantities, the results of changes in suicide attempts are similar (14).

In Turkey, the mean age of individuals who attempted suicide in the pre-pandemic group was similar to that of those who attempted suicide in routine life (15). However, the mean age of those who attempted suicide in the pandemic group was significantly higher than that of those who attempted suicide in routine life. This can be attributed to the economic issues experienced throughout the quarantine.

It is difficult to attribute the increase in suicide cases to a single cause. Multiple factors may have contributed to suicidal thoughts among people during the pandemic period, such as restrictions, social isolation, economic distress, physical and mental health concerns, excessive stress, and anxiety.

CONCLUSION

In this study, the changes in cases of suicide in the pandemic period and pre-pandemic period of the covid-19 infection, which affects the whole world, were evaluated. In the early period of the pandemic, when the first case was seen in Turkey, the number of cases increased and quarantines were applied, suicide attempts increased significantly compared to the pre-pandemic period. In the later time periods of the pandemic, no significant change was observed in the suicide attempt compared to the pre-pandemic period. The COVID-19 pandemic has not only affected people physically, but also mentally, as in other pandemics in the past.

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Research Article

Evaluation of the Correlations of SYNTAX scores, Anthropometric Measurements and Epicardial Fat Tissue in Predicting the Risk of Coronary Artery Disease

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Abstract

Aim: To investigate the strength of correlations between some anthropometric parameters, SYNTAX scores and epicardial adipose tissue (EFT) in coronary artery disease (CAD). Also to determine for the first time that the upper half of the chest circumference (CCuH) and neck circumference (NC)/neck length (NL) ratio may be an indicator for predicting cardiovascular risk

Material and Methods: This study included 370 individuals (198 males and 172 females), who were either diagnosed with CAD (n=300) or who were the control group participants (n=70). The EFT was measured and calculated SYNTAX score. Anthropometric measurements included height, weight, NL, NC, Waist circumference (WC), CCuH, Hip circumference (HC), and sagittal abdominal diameter (SAD), Body Mass Index (BMI), Waist circumference/Hip circumference ratio (WHR), and NC/NL ratio. The study was approved by the Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee (Protocol number: 2019/29).

Results: The statistical differences in the NL, CCuH, HC, and SAD were observed to be non-significant between the CAD patients and the control group. The NC (367.06±1.99, 37.49±2.64, p=0.04), NC/NL ratio (2.44±0.16, 2.50±0.21, p=0.02), WC (104.69±8.27, 107.55±10.77, p=0.04), Left Ventricular Ejection Fraction (LVEF) (62)-(51) (p<0.001), and EFT (3.06±0.33)-(3.41±0.80) were statistically significantly different between the control group and the CAD group (p<0.001). Elevated SYNTAX scores (r=0.15, p=0.01) and increased EFT (r=0.21, p<0.001) were more common in male patients.

Conclusion: The SYNTAX score was determined to be correlated with the NC, NC/NL ratio, CCuH, WC, HC, WHR, SAD, and EFT and it was found that these parameters increased significantly with increasing SYNTAX scores. These results show that, in addition to the SYNTAX score, anthropometric measurements and EFT quantity can be used for determining the severity of CAD.

Keywords: Anthropometric measurement, coronary artery disease, epicardial fat tissue, syntax score

INTRODUCTION

Changes in eating habits (obesity), smoking, and increased urbanization and the resulting sedentary lifestyle in today's modern societies have caused an increase in cardiovascular system diseases (1-3). Cardiovascular diseases (CVDs) are the leading disorders with the highest mortality and morbidity globally (4). CVDs constitute the main cause of mortality in more than four million deaths every year in Europe. CVDs account for about half (47%) of all these deaths (52% of deaths in women and 42% of deaths in men). The globally high prevalence and the high number of cardiovascular diseases have led to the search for new methods to be used in the diagnosis of the disease (5).

Coronary angiography is an important imaging technique for visualizing coronary vessels and determining the severity of coronary artery diseases. Several scoring methods have been developed by utilizing angiographic images. SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) is a scoring method that can measure the degree of atherosclerosis in the entire coronary artery tree and is calculated separately for each lesion (5,6). This scoring method is used for determining the anatomical features of the coronary vessels, the severity

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of the disease, and the complexity of the event by using angiography images. The SYNTAX score is calculated by answering 12 basic questions of a computer program and allows for the prediction of potential untoward conditions (cardiac and cerebrovascular), which may develop in patients undergoing coronary balloon angiography and stent placement (7-9). This scoring system is globally recommended to determine the revascularization strategy and predict complications in individuals with the disease in the left main coronary artery and/or 3 coronary arteries (5,10).

Obesity is a high risk factor for cardiovascular diseases. Anthropometric measurements are used to predict this risk, individuals and diseases below the risk limits (11). Anthropometric measurements are a set of quantitative measurements to understand the muscle, bone, and adipose tissue composition of the body. To identify the risk of diseases such as diabetes mellitus, cardiovascular diseases, and hypertension; several parameters are measured usually including the weight, height, the circumference of some body parts (waist, hip and limbs), BMI and the waist/hip ratio (12,13). Compared to biochemical tests and imaging techniques; anthropometric measurements are more advantageous owing to the ease of measurement and application, low costs, and easy use in population studies (14).

Accumulating between the visceral pericardium and the myocardium, the epicardial adipose tissue (EFT) is a component of adipose tissue found around the muscles or internal organs (15,16). Studies have found a relationship between the quantity of EFT with the presence and severity of coronary heart diseases (16).

The aim of this study is to investigate the strength of the relationship between some anthropometric parameters, SYNTAX score and EFT in individuals with coronary artery disease. In addition, we sought for the first time to determine whether upper half of the chest circumference (CCuH) and neck circumference/neck length (NC/NL ratio) could be indicators of cardiovascular risk.

MATERIAL AND METHOD

Study Design and Participants

The study included 370 individuals (198 males, 172 females) in the age range from 36 to 86 years, consisting of control participants (n=70) and patients (n=300) diagnosed with coronary artery disease, who applied to the cardiology department of Niğde Ömer Halisdemir University Training and Research Hospital in the period between November 2019 and May 2020. The case group (n=300, Males 55%) in the study was composed of patients; who had at least 50% occlusion of the coronary artery lumen and who underwent angiography, while the control group (n=70, Males 47%) was composed of individuals with normal coronary arteries detected by angiography. The demographic information of the patients was examined. The study was approved by the Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee (Protocol number: 2019/29).

Echocardiographic Evaluation

Echocardiography (echo) was performed only by a cardiologist using a 3.5 MHz transducer while the patients were lying in the left lateral decubitus position. EFT was measured by echo before or after angiography (Figure 1).

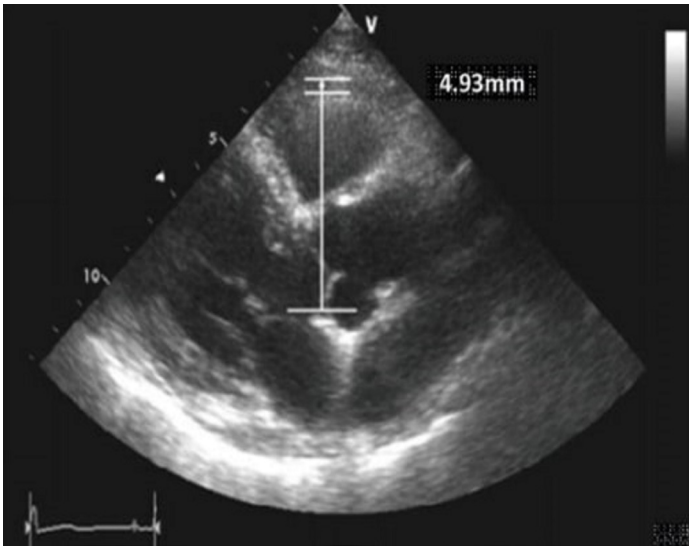

Figure 1. Epicardial fat tissue

EFT was measured in the right ventricular free wall using the long and short axis of the parasternal view. The mean of three beats was calculated and the obtained values were recorded. Measurements were repeated three times and mean values were calculated. Echocardiographic measurements were made in accordance with the standards set by the American Society of Echocardiography (17). Simpson's method was used to calculate the LVEF (18).

Evaluation of the SYNTAX Score

The angiographic images of the patients were evaluated by at least two experienced cardiologists and cardiovascular surgeons. When the same patient was assigned different SYNTAX scores by the experts, these scores were re-evaluated and the SYNTAX score was calculated in a common session by the participation of both parties. The SYNTAX score was calculated on the computer by answering 12 basic questions from the website (www.syntaxscore.com) taking into account the vessels with a diameter of at least 1.5 mm having more than 50% occlusion of the vessel lumen. The 300 CAD patients, whose SYNTAX scores (SS) were calculated, were divided into three groups as the low (A) (SS≤17), intermediate (B) (SS=18-28), and high (C) (SS≥29) score groups.

Anthropometric Evaluation

The anthropometric parameters including the height, weight, BMI, NL, NC, WC, CCuH, HC, and the SAD were measured before or after coronary angiography. By proportioning some of these measurements, the WHR, the NC/NL ratio, and BMI were calculated. A scale for body weight, a measuring tape, and a stadiometer were used for the anthropometric measurements. The points and the

parameters used for the anthropometric measurements are presented in Table 1.

Table 1. Anthropometric parameters and descriptions

Waist Circumference (WC)	Measured on the imaginary horizontal line extending circumferentially around the waist on the middle of the distance between the edge of the lowest rib and the iliac crest;
Hip Circumference (HC)	Measured on the arbitrary horizontal line extending over the two major trochanters of the femur circumferentially, while the patient is standing up with legs held together;
Neck Circumference (NC)	Measured on the arbitrary horizontal line passing just below the laryngeal prominence (Prominentia laryngea) circumferentially around the neck;
Neck Length (NL)	Measured alongside the sternocleidomastoid muscle between the sternoclavicular artery and the mastoid process;
Upper Half-Chest Circumference (CCuH)	Measured along an arbitrary horizontal line around the chest at the level of the uppermost parts of the axilla;
Sagittal abdominal diameter (SAD)	Measured on the midline between the iliac crest and the lowest rib at the level of the umbilicus.
BMI	Kg/m^2

Statistical Analysis

Study data were analyzed using the SPSS package program version 23.0. One-way ANOVA, Chi-square and correlation analysis methods were used in the data analysis of this study. ANOVA was used when the dependent variable was continuous and the independent variable was the group. When both variables were dichotomous, Chi-square was used to evaluate the difference. Correlation analysis was used to evaluate the relationships between variables. Statistical significance was accepted as $p<0.05$.

RESULTS

It was found that 47% of the control group and 55% of the case group were males (Table 2). The age range of the participants in the study was 57.22±11.31 in the case group and 55.74±10.11 in the control group (Table 2). Considering the demographic information of the patients, peripheral artery disease (PAD) was detected in 40 (13%) patients in the case group and in 3 (4%) patients in the control group. The difference between the two groups was statistically significant (p=0.03) (Table 2). The examination of the medical histories of the patients revealed 1 (1%) hyperlipidemia (HL) patient in the control group and 45 (15%) HL patients in the group of CAD patients, whose SYNTAX scores were calculated. There was a statistically significant difference between the two groups (p<0.001) (Table 2). The number of COPD, DM, and HT patients were 10 (14%)-54 (18%), 15 (21%)-87 (29%), and 17 (24%)-102 (24%) for the case and control groups, respectively. As for the smoking status, no statistical differences were observed between the case group and the control group.

It was observed that the statistical differences in the NL, CCuH, HC, and the SAD were non-significant between the CAD patients and the participants in the control group (Table 2). The statistical differences in BMI (p=0.3), WHR (p=0.2), NC/NL ratio (p=0.02), WC (p=0.04), NC, LVEF (p<0.001), and EFT (p<0.001) were significant (Table 2). Table 2 shows that the statistical differences between the CAD patients and the control group were non-significant for the NL and NC but significant for the NC/NL ratio (p=0.02).

Table 2. Evaluation of the case group (A+B+C) and the control group by the study parameters

Parameters	Control group (n=70)	CAD GROUP (n=300)	p
Male, n (%)	33 (%47)	165 (%55)	.24
Age (years)	55.74±10.11	57.22±11.31	.32
Height (cm)	1.67±.08	1.67±.08	.39
Weight (kg)	76.59±13.56	77.17±14.08	.09
BMI (kg/m^2)	26.56±2.53	27.28±3.44	.10
NL(cm)	15.27±1.16	15.08±1.30	.25
NC (cm)	37.06±1.99	37.49±2.64	.20
NC/NL	2.44±.16	2.50±.21	.02
CCuH (cm)	103.03±5.00	104.80±5.80	.07
WC(cm)	104.69±8.27	107.55±10.77	.04
HC (cm)	108.23±5.93	108.88±4.66	.32
WHR	.97±.06	.99±.09	.08
SAD (cm)	25.86±1.80	26.08±1.81	.35
LVEF (%)	62 (60-64)	51(45-58)	.00
EFT (mm)	3.06±.33	3.41±.80	.00
PAD n, (%)	3 (%4)	40 (%13)	.03
COPD n, (%)	10 (%14)	54 (%18)	.46
DM n, (%)	15 (%21)	87 (%29)	.20
HT n, (%)	17 (%24)	102 (%24)	.12
HL n, (%)	1 (%1)	45 (%15)	.00
Smokers, n (%)	28 (%40)	122 (%41)	.91

BMI: Body Mass Index, WC: Waist circumference, HC: Hip circumference, NC: Neck circumference, NL: Neck length, NC/NL: Neck circumference/Neck length ratio, CCuH: Upper half-chest circumference, SAD: Sagittal abdominal diameter, WHR: Waist circumference/Hip circumference ratio, LVEF: Left Ventricular Ejection Fraction, PAD: Peripheral Arterial Disease, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, HT: Hypertension HL: Hyperlipidemia

The coronary artery patients were divided into three groups by the SYNTAX scores as low (A), intermediate (B), and high (C) score groups to demonstrate the relationships across them (Table 3). In A, B, and C groups; 69 (48%), 51 (59%), and 46 (66%) individuals were males,

respectively, this was statistically significant between the patients with low and high SYNTAX scores (p=0.02). The mean age of 62.43±13.02 years in the high SYNTAX score group was found to be significantly different compared to the patients in both the low and the intermediate score groups (p<0.001; p<0.001).

Table 3 shows that the statistical differences in BMI, NL, NC, the NC/NL ratio, WC, HC, SAD, PAD, COPD, DM, HT, and the number of smokers were non-significant between the A and B groups. However, the differences in the CCuH, WHR, LVEF, EFT and HL were found to be significant between the groups A and B (p<0.05). The evaluation of the differences in the study parameters between the groups A (low-score group) and C (high-score group) revealed that the statistical differences in the NL, LVEF, COPD, and the smoking status were non-significant but the statistical differences in BMI, NC, NC/NL ratio, CCuH, WC, HC, WHR, SAD, EFT, PAD, DM, HT and HL were significant (p<0.05).

Between the groups B and C, the statistical differences in the NL, NC/NL ratio, SAD, LVEF, and COPD were non-significant but the statistical differences in BMI, NC, CCuH, WC, HC, WHR, EFT, PAD, DM, HT, HL, and the smoking status were significant (p<0.05).

The correlation of the parameters with SYNTAX scores and EFT are presented in Table 4. High SYNTAX scores (r=0.15, p=0.01) and more EFT (r=0.21, p=0.00) were observed in male patients more commonly. The SYNTAX scores were found to increase significantly with advancing age (r=0.28, p=0.00) but no correlations were found between EFT and age.

BMI (r=0.39, p<0.001; r=0.36, p<0.001), NC (r=0.29, p<0.001; r=0.29, p<0.001), CCuH (r=0.34, p<0.001; r=0.48, p<0.001), WC (r=0.40, p<0.001; r=0.42, p<0.001), HC (r=0.25, p<0.001; r=0.18, p<0.001), WHR (r=0.28, p<0.001; r=0.14, p=0.01), and the SAD (r=0.19, p<0.001; r=0.30, p<0.001) were positively correlated with both the SYNTAX scores and EFT (Table 4). The NC/NL ratio (r=0.14, p=0.02) was positively correlated with the SYNTAX scores but not correlated with EFT. The NL (r=0.24, p<0.001) was positively correlated with EFT but not correlated with the SYNTAX scores. The LVEF value was non-significant by the SYNTAX scores but negatively correlated with EFT (r=-0.16, p<0.001). When the correlation between the SYNTAX score and EFT was examined, it has been observed that these two parameters were statistically significant for each other and showed a positive correlation (r=0.59, p<0.001).

Table 3. Evaluation of the low, intermediate, and high syntax scores by the study parameters

Parameters	Low SYNTAX scores (A) n=143	Intermediate SYNTAX scores (B) n=87	High SYNTAX scores (C) n=70	A-B p-value	A-C p-value	B-C p-value
Male, n (%)	69 (%48)	51 (%59)	46 (%66)	.18	.02	.29
Age (years)	55.02±10.42	56.64±9.94	62.43±13.02	.25	.00	.00
Height (cm)	1.68±.08	1.67±.08	1.70±.08	.63	.00	.03
Weight (kg)	73.31±9.46	75.72±14.98	86.84±16.33	.14	.00	.00
BMI (kg/m2)	26.31±2.51	26.87±3.77	29.75±3.53	.17	.00	.00
NL (cm)	15.04±1.27	15.01±1.37	15.23±1.30	.86	.32	.31
NC (cm)	37.03±1.54	37.28±1.95	38.69±4.31	.29	.00	.01
NC/NL	2.47±.16	2.50±.18	2.55±.30	.31	.02	.18
CCuH (cm)	102.86±4.59	104.36±6.13	107.53±6.40	.04	.00	.00
WC (cm)	104.50±7.15	106.83±10.68	114.69±13.56	.07	.00	.00
HC (cm)	108.22±4.58	108.24±4.03	111.04±4.94	.97	.00	.00
WHR	.97±.07	.99±09	1.03±.11	.02	.00	.02
SAD (cm)	25.81±1.93	26.20±1.47	26.50±1.87	.11	.01	.25
LVEF (%)	52 (46-52)	50 (45-51)	50 (42-58)	.04	.08	.85
EFT (mm)	3.05±.36	3.31±48	4.27±1.09	.00	.00	.00
PAD n, (%)	6 (%4)	9 (%10)	25 (%36)	.07	.00	.00
COPD n, (%)	20 (%14)	18 (%21)	16 (%23)	.18	.11	.74
DM n, (%)	31 (%22)	21 (%24)	35 (%50)	.67	.00	.00
HT n, (%)	33 (%23)	28 (%32)	41 (%59)	.13	.00	.00
HL n, (%)	3 (%2)	8 (%9)	34 (%49)	.01	.00	.00
Smokers, n (%)	58 (%40)	43 (%49)	21 (%30)	.19	.13	.01

BMI: Body Mass Index, WC: Waist circumference, HC: Hip circumference, NC: Neck circumference, NL: Neck length, C/NL: Neck circumference/Neck length ratio, CCuH: Upper half-chest circumference, SAD: Sagittal abdominal diameter, WHR: Waist circumference/Hip circumference ratio, LVEF: Left Ventricular Ejection Fraction, PAD: Peripheral Arterial Disease, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, HT: Hypertension HL: Hyperlipidemia

Table 4. Correlations of the syntax scores and eft with the study parameters

Parameters	SYNTAX score		Epicardial fat tissue	
	r-value	p-value	r-value	p-value
Male, n (%)	.15	.01	.21	.00
Age (years)	.28	.00	.08	.11
Height (cm)	.20	.00	.33	.00
Weight (kg)	.39	.00	.47	.00
BMI (kg/m2)	.39	.00	.36	.00
NL(cm)	.10	.09	.24	.00
NC (cm)	.29	.00	.29	.00
NC/NL	.14	.02	-.02	.72
CCuH (cm)	.34	.00	.48	.00
WC(cm)	.40	.00	.42	.00
HC (cm)	.25	.00	.18	.00
WHR	.28	.00	.14	.01
SAD (cm)	.19	.00	.30	.00
LVEF (%)	-.05	.36	.-16	.00
EFT (mm)	.59	.00	1	1
SYNTAX score	1	1	.59	.00

BMI: Body Mass Index, WC: Waist circumference, HC: Hip circumference, NC: Neck circumference, NL: Neck length, NC/NL: Neck circumference/Neck length ratio, CCuH: Upper half-chest circumference, WC: waist circumference, HC: hip circumference, WHR: Waist circumference/Hip circumference ratio, SAD: Sagittal abdominal diameter, NC/NL: Neck circumference/Neck length ratio, LVEF: Left Ventricular Ejection Fraction, EFT: Epicardial fat tissue

DISCUSSION

SYNTAX scores are used for selecting the treatment method for revascularization in CAD. The review of the literature has shown that the relationships across the SYNTAX scores, EFT, and anthropometric measurements were determined for the first time in this present study. Our study results have shown that; compared to the patients with low SYNTAX scores, the patients with high SYNTAX scores had significantly higher values of age, weight, height, BMI, NC, NC/NL ratio, CCuH, WC, HC, WHR, SAD, EFT, PAD, DM, HT, and HL. Furthermore, high SYNTAX scores were observed significantly more in males. The intermediate and high SYNTAX score groups were similar according to the study parameters excluding gender, the NL, NC/NL, and SAD. The number of smokers was significantly higher in the intermediate SYNTAX score group. The medical histories of the patients with high SYNTAX scores revealed that these patients had smoked but stopped smoking in the past. Between the intermediate and low SYNTAX score groups, there were no significant differences by the study parameters excluding the CCuH, LVEF, EFT, and HL.

The correlation analysis has shown that SYNTAX scores significantly increase with the increases in EFT, age, height, weight, BMI, NC, NC/NL, CCuH, WC, HC, WHR, and the SAD. EFT significantly increased with low LVEF values and high values of SYNTAX scores, height, weight, BMI, NL, NC, CCuH, WC, HC, WHR, and the SAD.

The number of coronary vessels with lesions is not adequate alone to determine the severity of coronary artery disease. The location of the lesions, the effects of lesions on the blood flow, the degree of vascular stenosis, classification of lesions, the vessel diameter and calcification, technical feasibility of percutaneous coronary intervention (PCI) and the prognosis of PCI are the major factors affecting the severity of the disease (7,19,20). SYNTAX is a scoring method used for determining the anatomical structure of the coronary vessels, the severity of the disease, and the complexity of the event in coronary artery disease (21). The SYNTAX scoring system is also a highly effective method both in predicting prognosis and determining the treatment method (22). The SYNTAX scoring system is recommended in clinical guidelines and is increasingly used in daily clinical practice (21). After calculating SYNTAX scores, the obtained scores can be categorized as low (SS≤17), intermediate (SS=18-28), and high (SS≥29) score groups (23). Currently, the decision to perform whether coronary artery bypass graft (CABG) surgery or PCI is made based on the SYNTAX scores (21). PCI is an alternative to bypass surgery in patients with three-vessel disease and a SYNTAX score of ≤22. Patients with three-vessel disease and SYNTAX score ≥23 should undergo CABG (21). In this present study, the SYNTAX scores were classified under 3 categories as low (SS≤17), intermediate (SS=18-28), and high (SS≥29) score groups similar to the categorization used by Karakurt et al. (23) (Table 3). Our study results demonstrating the association of high SYNTAX scores with advanced age and higher incidences of DM, HT, and HL are compatible with the results reported by Karakurt et al. (2016) (23). However, another finding of the same study showed a significant difference in LVEF across the low, intermediate, and high SYNTAX score groups. In our study, a significant difference in LVEF was found only between the low and intermediate SYNTAX score groups (23). The correlation analysis in our study revealed that no relationships existed between the SYNTAX scores and LVEF (r=-0.05, p=0.36).

One of the strategies to reduce cardiovascular morbidity and mortality is to reveal cardiovascular risk factors (24). Obesity, type II diabetes mellitus, hypertension and dyslipidemia are risk factors for coronary heart disease (25). Anthropometric measurements have been proposed to estimate the amount and location of body fat (26). Advantages of using anthropometric parameters include ease of use, less invasiveness, and minimal costs. These advantages of anthropometric measurements provide a practical option for use in clinical settings and population studies (26,27). The results of longitudinal studies investigating the period from childhood to adulthood showed that anthropometric measurements obtained in childhood are an indicator of cardiovascular risk in adulthood (28,29). Among the suggested anthropometric indexes; BMI, WC and WHR are the most frequently studied parameters (30). Some studies have reported

the robustness of these anthropometric measurements in determining cardiovascular risks (31,32). In our study, the study parameters listed in Table 1 were compared between the control group of 70 individuals and the case group of 300 patients, who underwent angiography due to suspected coronary artery disease. The anthropometric measures, EFT, and some cardiovascular risk factors (9) were compared between the control group of 70 individuals and the case group of 300 individuals, whose SYNTAX scores (7) were calculated. Zen et al. (2012) (33) have reported that a large NC is a risk factor for coronary artery diseases in their study investigating the relationship between the NC and cardiovascular diseases. In our study, it was found that the increase in the NC was positively correlated with high SYNTAX scores and increased EFT.

EFT is associated with several parameters including age, diabetes mellitus, obesity, and hypertension. Therefore, the measurement of EFT is recommended for use in the diagnosis of cardiovascular diseases. EFT is reported to be an important parameter in determining the presence and severity of coronary artery disease (16). Abbara et al. (2006) (34) reported that EFT thickness increased with increasing age, while Lacobellis et al. (2003) (35) found no correlations between age and EFT thickness. The strong correlation of the EFT quantity with the WC was demonstrated in the study by (35). The findings in our study are compatible with the study findings of Lacobellis et al. (2003) (35) about age and the WC.

Our study has some limitations. Firstly, the data of this study represent only the central Anatolian population in Turkey. Secondly, it is a single-centre study and included only a limited number of patients.

CONCLUSION

In conclusion, we have determined that the SYNTAX score and EFT are correlated with the NC, NC/NL ratio, CCuH, WC, HC, WHR, and SAD. We found that as the SYNTAX scores increased, the measured values of these parameters increased significantly. These results show that, in addition to the SYNTAX scores, anthropometric measurements and the quantity of EFT can be used for determining the severity of coronary artery disease.

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Research Article

Investigation of the Sox-9 and Caspase-6 Immune Activity in Placentas of Pregnant Women with GDM

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Abstract

Aim: In this study, we investigated the immunohistochemical staining of Sox-9 and Caspase-6 expression in placentas of pregnant woman with gestational diabetes mellitus (GDM).

Material and Methods: Placentas of 20 healthy and 20 women with GDM were processed for routine histological tissue processing. The biochemical and clinical parameters of patients were recorded. Placentas were stained with hematoxylin-eosin and Sox-9 and Caspase-6 immunostaining.

Results: In control group, Sox-9 expression was negative in decidual and connective cells and endothelial cells. In GDM group, Sox-9 expression was increased especially in the decidual cells. For the Caspase-6 expression, Caspase-6 reaction was mainly in maternal region in control group. In GDM group, Caspase-6 reaction was increased in decidual cells, in endothelial cells and in the syncytial nodes.

Conclusion: Expression of Sox-9 transformed the decidua cells and lead to apoptotic pathway via Caspase-6 expression.

Keywords: Sox-9, caspase-6, GDM, placenta

INTRODUCTION

Many complications can develop during pregnancy and these are called maternal morbidity. The most common diseases among pregnancy complications are gestational hypertension (GHT), preeclampsia, eclampsia, superimposed preeclampsia, gestational diabetes mellitus (GDM), postpartum hemorrhage and infections (1,2). Regular pregnancy follow-ups are important for the early diagnosis of these diseases, but there is no definitive and clear screening and test according to studies. Detailed medical and obstetric history is still the most commonly used method for diagnosis. Most pregnancy complications may be resolved after delivery however their long-term effect may be continued future (3,4).

Gestational diabetes mellitus (GDM) is carbohydrate intolerance that occurs during pregnancy or is first noticed during pregnancy (5). It affects approximately 1 out of every 10 women worldwide. It may have various negative consequences such as macrosomia, fetal hypoglycemia, neonatal intensive care support and fetal mortality. There are also long-term effects. Conditions such as various cardiovascular diseases, insulin resistance, and diabetes may occur (5,6). The placenta is an important organ for fetal growth and development. It provides adaptation to the changes that occur in the uterus during normal and pathological pregnancies. Compared to normal pregnancies, increased vascularization is observed in placentas with GDM. This may seem counterintuitive

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because of increased maternal nutrition, but improved fetal aerobic metabolism stimulated by insulin reflects the increased oxygen demand of the fetus. The mechanisms underlying enhanced angiogenesis have not been fully elucidated (7,8).

The aim of this study is to investigate Sox-9 and Caspase-6 expression of in placentas of women with GDM by histochemical and immunohistochemical methods.

MATERIAL AND METHOD

Ethical approval was taken from Dicle University Medical School, Non-interventional Clinical Trials Ethical Committee (2020/68). In our study, 20 healthy women and 20 women with GDM were included. Placentas were obtained from Gynecology and Obstetrics Clinics. All patients were informed about the data and experimental protocol. For each patient, biochemical and clinical parameters were noted after their approval. for each patient were recorded. Patient informed consent form was read to all patients and they signed the forms.

Histological Tissue Processing

Placental samples were dissected and stored for histological dye experiments. The placental tissues were taken into formalin solution, dehydrated in increasing alcohol series, soaked in xylol solution and incubated in paraffin wax at 58°C. samples were put into paraffin blocks and 4 µm sections were cut and stored for hematoxylin eosin staining (9).

Immunohistochemical Examination

Placental sections were cleared in xylol solution, dehydrated in alcohol and cleared in distilled water. Epitope retrieval was inducted by EDTA (ethyl diamine tetra acetic acid) solution (pH:8.0) for 15 minutes in a microwave oven at 90°C. After sections were cooled down, they were rinsed in phosphate buffered saline (PBS) three times for 5 minutes. 3% hydrogen peroxide (H2O2) was dropped on slides to block endogen peroxidase activity. After washing in PBS, sections were incubated with rabbit polyclonal Sox-9 and Caspase-6 (AFG Scientific, US, 1/100) overnight at + 4°C. Sections were dipped into PBS and biotinylated antibody solution (ThermoFischer, US) was dropped onto slides for 14 minutes. Sections were reacted with streptavidin peroxidase solution was (ThermoFischer, US) for 15 minutes. After PBS washing, diaminobenzidine (DAB) chromogen was used to observe color change for maximum 10 minutes. Reaction were stopped with PBS solution and sections were stained with hematoxylin dye. Slides were analyzed under light microscope (10).

Statistical Analysis

The data were recorded as median (minimum – maximum). Statistical analysis was done using the IBM SPSS 25.0 software (IBM, Armonk, New York, US).

RESULTS

Biochemical Parameters

Age, gravida, parity, systolic BP, diastolic BP, hemoglobin, platelet, glucose, urea, creatinine, ALT, AST-urine protein was recorded in healthy and GDM women. Data were shown in Table I. Glucose level were higher in GDM group than in healthy group. Graphical illustration of Table I was shown in Figure 1.

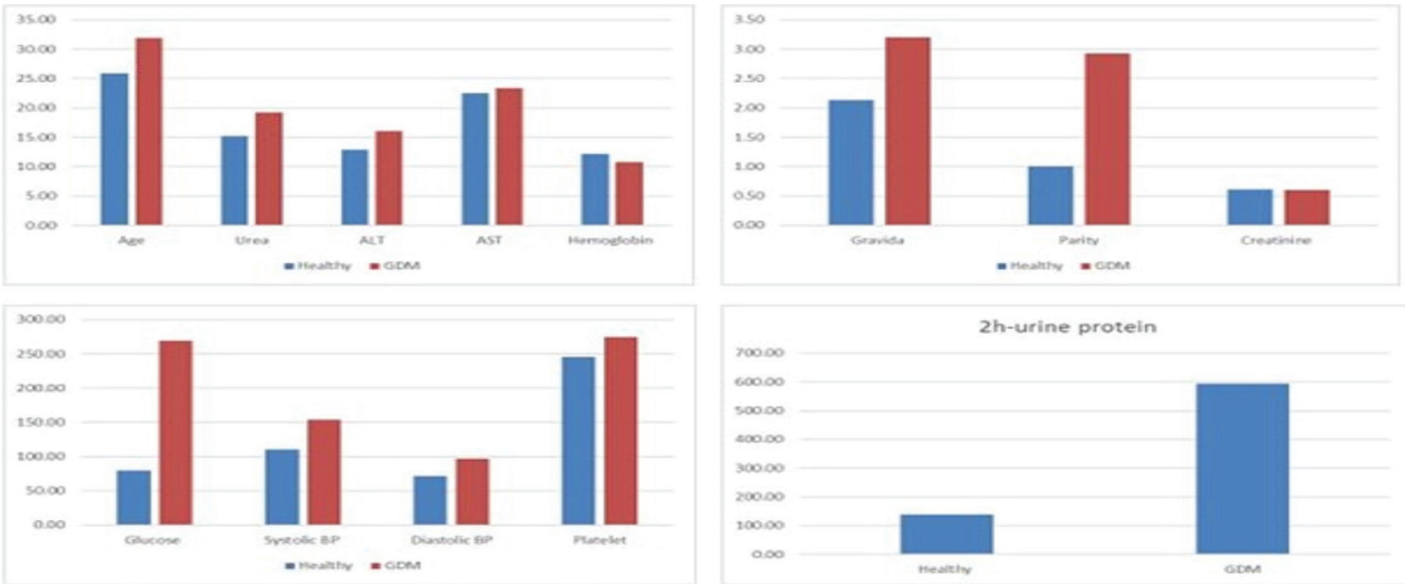

Figure 1. Graphical illustration of biochemical and demographical parameters

Histopathological Staining

Although mild dilatations were observed in some vessels in the GDM control group section, it was observed that the Sox-9 reaction was negative in endothelial cells and negative in connective tissue cells in general, while positive Sox-9 expression was detected in moderate decidual cells. It was also observed that Sox-9 was negative in the syncytial regions. Again, no Sox-9 reaction was observed in intervillous areas (Figure 2a). In the GDM preparation taken from the maternal region, that the reaction increased especially in the decidual cells, the nucleus showed

negativity in some places, but the cytoplasmic activity was positive in the direction of Sox-9 in the aggregated areas. Again, although there was shrinkage in nuclei in some areas, the expression was found to be positive for Sox-9 (Figure 2b).

In the section taken from the maternal region, although Caspase-6 reaction was negative in cells in some areas, positivity was observed in individual decidual cells, it was seen that the reaction was negative in the maternal region in general. Similarly, negativity for Caspase-6 was detected in endothelial cells (Figure 2c). In the GDM group, the caspase reaction showed widespread and intense positivity especially in decidual cells, the Caspase-3 reaction increased in the same way in endothelial cells, apoptotic cells were abundant, and Caspase-6 was positive in some areas due to vessel dilatation, especially in the vascular endothelium. It was determined that the Caspase-6 reaction increased in the syncytial nodes in these regions (Figure 2d).

Table 1. Clinical and biochemical parameters of healthy and GDM patients

Parameter	Healthy (N=20)	GDM (N=20)
Age	26 (20-35)	28 (24-42)
Gravida	2 (0-5)	3 (1-7)
Parity	0 (0-5)	3 (1-8)
Systolic blood pressure	110 (93-135)	148 (125-220)
Diastolic blood pressure	69 (64-82)	96 (87-109)
Hemoglobin	12 (10-14.5)	10.4 (9.5-13)
Platelet	231 (123-447)	269 (148-398)
Glucose	78 (68-105)	269.39 (105-608)
Urea	15 (12-20)	16 (13.5-42.58)
Creatinine	0.61 (0.54-0.71)	0.58 (0.53-0.84)
ALT	12 (8-23)	13 (7-44)
AST	18 (13-48)	22 (14-43)
2h-urine protein	142 (104-178)	534 (300-980)

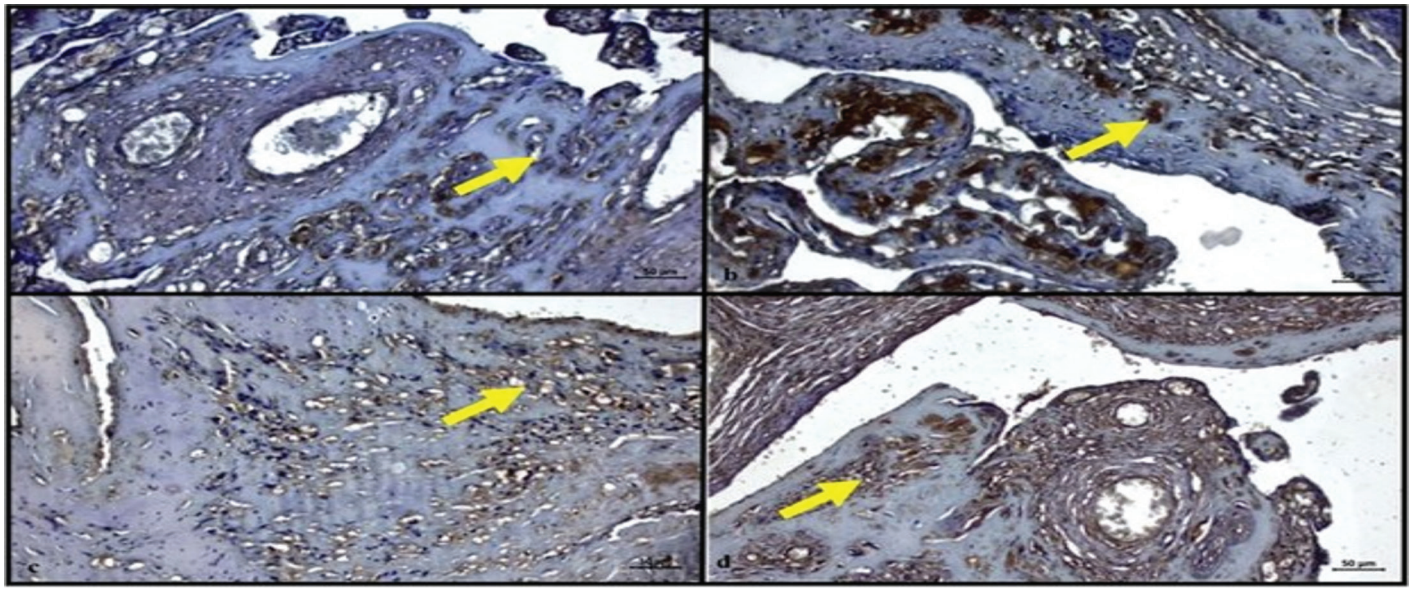

Figure 2. Healthy and GDM placentas with immune staining. Decidual cells (arrows)

DISCUSSION

During pregnancy, complications can lead the placental abnormalities such as preeclampsia, gestational diabetes mellitus (GDM), placenta previa and accrete. GDM can affect placental histology in short or long term. Aldahmash et al studied Saudi women with GDM. 84 placentas were examined and results showed that syncytial knots, calcification, villous agglutination, decidual vasculopathy, and retroplacental hemorrhage were common findings in maternal side. Villous fibrinoid necrosis, chorangiosis, fibromuscular sclerosis, and villous edema were common findings in fetal side (11). Another study by Rudge et al studied mild GMD, GDM and overt GDM patients and analyzed their histopathological lesions. Results showed villous edema and fibrosis, congestion, interstitial hemorrhage, focal hyaline degeneration (12).

SRY-box transcription factor 9 or Sox-9 is a transcription factor that is required for testicular development, organogenesis of liver and pancreas, cytoskeleton and chondrocytes. Mutations in Sox-9 gene can lead to autosomal sex reversal, skeletal formation and testis development (13,14). Sekido et al studied two genes in Sertoli cell by investigating SRY expression. They found that upregulation of Sox-9 gene in supporting cells determine their fate as Sertoli cells, which shows importance of Sox-9 gene in testis (15). Zhao et al studied endothelial to mesenchymal transition in murine endovascular progenitors. They found that endothelial to mesenchymal transition was dependent on relative expression of Sox-9 along with Notch signaling, affecting their plasticity which may be a therapy tool for fibrotic diseases (16). Xian et al studied showed that stimulation of Sox-9 can induce cellular differentiation gene and this can be a mechanism in transformation of extra villous trophoblast to endovascular trophoblasts during placentation (17). In

our study, in control group, Sox-9 reaction was negative in decidual and endothelial cells (Figure 2a). In GDM group, Sox-9 expression was increased in the decidual cells. Shrinkage nuclei showed positive Sox-9 expression (Figure 2b)

Caspases are cysteine proteases that are involved in cell death, immune responses. Caspase-6 is ana executioner caspase. Its role in apoptosis is well known however other roles remain unclear. Development of placenta is dependent on implantation to the uterus and invasion of decidual plate by trophoblast cells (18,19). Cheng et al investigated inflammatory pathway in preeclamptic patients via caspase-1 expression. They found that cell death pathway in increased via elevated active caspase-1 expression (20). Mu et al studied apoptosis in placenta of transgenic mice. They found that apoptosis was observed predominantly in syncytiotrophoblast cells via Tunnel assay. They also performed immunohistochemistry to analyze caspase-3 expression and found that active caspase-3 expression was observed in cells undergoing apoptosis (21). In control group, Caspase-6 reaction was negative in some cells but mainly negative in the maternal decidual cells and endothelial cells (Figure 2c). In the GDM group, Caspase-6 expression was showed widespread and intense positivity especially in decidual cells and endothelial cells (Figure 2d).

CONCLUSION

In conclusion, during GDM development, decidual cells were affected due to trophoblastic invasion and inflammation. Expression of Sox-9 signal in syncytial region and decidua cells could induce transformation and apoptotic process with Caspase-6 expression.

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Conflict of Interest: *The authors declare that they have no competing interest.*

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MEDICAL RECORDS-International Medical Journal

Research Article

Application the Beck Depression Test to Screen for Depressive Findings Before and After Treatment in Patients with Iron Deficiency Anemia and/or Vitamin D Deficiency

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Abstract

Aim: Depression, vitamin D deficiency, and anemia are significant global public health issues. Depression, loss of interest, and a lack of enjoyment are the main warning indicators. In this study, we aimed to compare the results of the Beck depression test before and after replacement therapy in patients with iron deficiency anemia and vitamin D deficiency and to show the relationship between iron deficiency anemia (IDA), vitamin D deficiency anemia and depression in patients.

Material and Methods: 139 patients with vitamin D deficiency and/or IDA who applied to the internal medicine outpatient clinics of Dışkapı Hospital between March 2017 and September 2017 participated in the study. Patients with vitamin D deficiency and/or IDA were included in the study, and the Beck depression test (BDI) questionnaire was applied to these patients before and after their treatment. Then, the scores on these two questionnaires were compared. Statistical analyzes were performed using SPSS version 20.0 (Armonk, NY: IBM Corp.).

Results: All patients had Vitamin D deficiency, 59% (n=82) had both IDA and Vitamin D deficiency, and 41% had only Vitamin D deficiency. The mean follow-up time of the patients after treatment was 64.2±23.4 days. There was a significant decrease in BDI scores in both male patients (p=0.025) and female patients (p<0.001) after treatment compared to before.

Conclusion: In our study, it was shown that the risk of depression is high in patients with vitamin D deficiency and/or IDA, and depressive symptoms decreased after short-term replacement therapy with vitamin D and iron.

Keywords: Iron deficiency anemia, vitamın D deficiency, depression

INTRODUCTION

Erythrocyte count and/or hemoglobin levels falling below normal levels in healthy people is referred to as anemia. Hypochromia and microcytosis in erythrocytes, a decrease in serum iron and serum ferritin levels, a drop in transferrin saturation below 15%, and an increase in total iron binding capacity are all signs of iron deficiency anemia (IDA), which develops when the body is unable to meet its daily iron requirements through food and after its iron reserves have been used up. This particular form of hypochromic microcytic anemia is distinguished by Palpitations, shortness of breath, chest pain, weakness, fatigue, appetite loss, menorrhagia, hair loss, nail breakage, and dysphagia are the most common symptoms (1). Recent years have seen a rise in research on vitamin D insufficiency. Vitamin D status and bone health and development are closely related, and extensive study is being done on vitamin D in different contexts (2). Although the exact role of vitamin D in the brain is not entirely understood, it has been linked to depressive symptoms and other psychiatric illnesses

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because vitamin D receptors are found in parts of the brain that are involved in the onset of depression (3,4).

Depression, reluctance, loss of enjoyment in the affective field, exhaustion in the psychomotor area, slowing of behavior, slower thinking, guilt-related thoughts, and feelings of worthlessness; An major public health issue is depressive disorders, which shows up as difficulties with eating, sleeping, and engaging in sexual activity (5). Depression can be prevented in part by proper nutrition. Nutritional deficits can damage the brain's neural networks and lead to mental health issues like depression (6). Depression has been associated with some vitamin deficiencies (folic acid, vitamin B12, niacin, and vitamin C) (7). Beck Depression Scale (BDI), on the other hand, is a screening test that reduces false positive depression rates for primary care (8). There is a correlation between low vitamin D levels and depression (9) and low ferritin levels and depression, but studies on the effects of short-term vitamin D replacement and iron therapy in iron deficiency anemia have not been conducted (10).

In this study, we aimed to compare the results of the Beck depression test before and after replacement therapy in patients with iron deficiency anemia and vitamin D deficiency and to research whether replacement therapy has an effect on depressive symptoms in patients.

MATERIAL AND METHOD

The study included 139 individuals who applied to the internal medicine outpatient clinics of University Of Health Sciences Dışkapı Yıldırım Beyazıt Education And Research Hospital between March 2017 and September 2017 and had vitamin D deficiency and/or iron deficiency anemia. Each patient participating in the study was informed, their consent was obtained, and they were allowed to participate in the study voluntarily. Patients with vitamin D deficiency and/or iron deficiency anemia were included in the study, and Beck depression test, which is one of the depression screening tests, was solved in these patients before and after their treatment. Then their scores on these two questionnaires were compared. Patients with comorbidity, previously diagnosed with depression, and patients under the age of 18 and over the age of 65 were not included in the study. Patients with high Beck depression test scores were referred to the psychiatry department for further evaluation and treatment. With application number 43/26, the Ministry of Health, Health Sciences University, and Dşkap Yldrm Beyazt Training and Research Hospital got ethics committee permission for our study on November 27, 2017. According to the principles outlined in the Declaration of Helsinki, our study was conducted.

The package program SPSS version 20.0 (Armonk, NY: IBM Corp.) was used to conduct statistical analyses. Numbers, percentages, means and standard deviations, and median were used to summarize descriptive statistics. Using visual (histogram and probability graphs) and analytical techniques, the variables' conformance to the normal distribution was evaluated (Shapiro-Wilk test). In situations where there was a significant difference, post-hoc analyses using the Tukey and Bonferonni tests were carried out. The Mann Whitney U test and the Kruskal Wallis Test were used to compare non-normally distributed numerical data between two groups, respectively. The Chi-square test was used to compare the two groups' nominal data. Comparisons having a p value below 0.05 were deemed statistically significant in the study's statistical analyses.

RESULTS

The mean age of the patients was 34.2±10.7 years (median 33 years, range of 18-64 years). 90.6% (n=126) of the patients were female and 9.4% (n=13) were male. All patients (n=139) had Vitamin D deficiency, 59% (n=82) had both IDA and Vitamin D deficiency, and 41% had only Vitamin D deficiency. The mean follow-up time of the patients after treatment was 64.2±23.4 days (median 63 days, range of 13-132 days).

Table 1 shows the correlation between the markers of anemia in patients with and without iron deficiency and their vitamin D levels before and after vitamin d replacement.

Before treatment, the mean BDI scores of patients with IDA were 18.3±9.1, and patients without IDA were 20.8±9.1. There was no difference in BDI scores between patients with and without IDA (p=0.095). After treatment, the mean BDI scores of patients with IDA were 16.1±7.7, and those without IDA were 18.9±8.4. BDI scores of patients without IDA were higher than patients with IDA (p=0.046). After treatment, there was a significant increase in vitamin D levels of both patients with IDA (p<0.001) and without IDA (p<0.001) compared to pre-treatment. However, the difference in BDI scores before and after treatment was similar between patients with and without IDA (p=0.926).

Figure 1 summarizes the distribution of BDI scores before and after treatment.

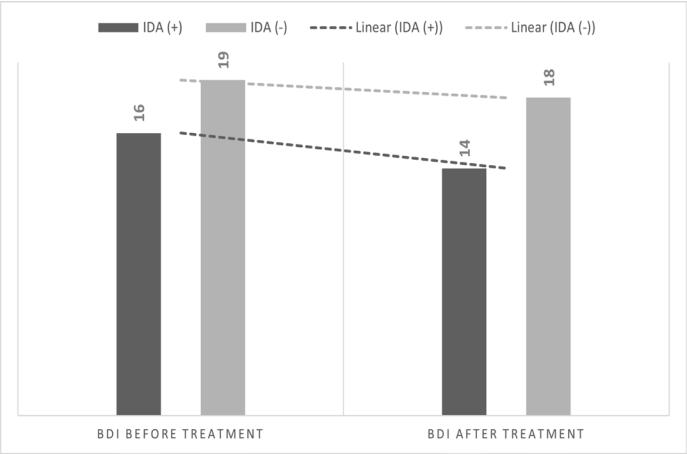

Figure 1. BDI scores before and after treatment

The presence and frequency of depression before treatment is schematized in figure 2.

In Table 3, it is shown how iron deficiency and depression's intensity and consequences compare before and after treatment. The presence and frequency of depression

Table 1. Distribution of anemia parameters in patients and vitamin D levels of patients before treatment vs after treatment			
	IDA (+) (n=82)	**IDA (-) (n=57)**	**p**
Hb (g/dl) Median (Med±SD) (Basal)	10.8 (10.5±1.0)	13.6 (13.6±1.0)	**<0.001***
Hb (g/dl) Median (Med±SD) (Control)	12.2 (12.3±0.7)	13.5 (13.5±1.0)	**<0.001***
P **	**<0.001**	0.096	
Ferritin (mg/l) Median (Med±SD) (Basal)	4.8 (7.2±9.0)	15.6 (19.0±14.6)	**<0.001***
Ferritin (mg/l) Median (Med±SD) (Control)	11.0 (13.3±10.4)	15.9 (19.9±13.7)	**<0.001***
P **	**<0.001**	0.098	
Iron (mg/dl) Median (Med±SD) (Basal)	26.0 (31.2±23.4)	56.0 (60.5±20.2)	**<0.001***
Iron (mg/dl) Median (Med±SD) (Control)	47.5 (51.7±20.9)	61.0 (61.9±17.3)	**<0.001***
P **	**<0.001**	0.350	
TIBC (mg/dl) Median (Med±SD) (Basal)	398 (388±59)	295 (274±62)	**<0.001***
TIBC (mg/dl) Median (Med±SD) (Control)	355 (347±55)	275 (269±55)	**<0.001***
P **	**<0.001**	0.177	
Vitamin D levels of patients before treatment vs after treatment			
	IDA (+) (n=82)	**IDA (-) (n=57)**	**p**
Vitamin D (ng/ml) Median (Med±SD) (Basal)	10.8 (11.4±4.1)	11.0 (11.2±3.8)	0.675*
Vitamin D (ng/ml) Median (Med±SD)(Control)	23.3 (24.3±5.6)	28.3 (28.5±5.6)	**<0.001***
P **	**<0.001**	**<0.001**	

TIBC : Total Iron Binding Capacity
* Mann Whitney U test
**Wilcoxon Signed Rank Test

Table 2. BDI scores of the patients before and after treatment			
	IDA (+) (n=82)	**IDA (-) (n=57)**	**p**
BDI Median (Med±SD) (Basal)	16 (18.3±9.1)	19.0 (20.8±9.1)	0.095*
BDI Median (Med±SD)(Control)	14 (16.1±7.7)	18.0 (18.9±8.4)	**0.046***
P **	**<0.001**	**<0.001**	
BDI Difference Median (Med±SD)	2.0 (2.1±3.4)	2.0 (1.9±1.6)	0.926*

* Mann Whitney U test
**Wilcoxon Signed Rank Test

Table 3. Frequency and severity of depression before treatment vs after treatment				
Presence and severity of depression	**Before treatment**		**After treatment**	
	IDA (+) (n=82)	**IDA (-) (n=57)**	**IDA (+) (n=82)**	**IDA (-) (n=57)**
None n (%)	33 (40.2)	13 (22.8)	35 (42.7)	18 (31.6)
Mild depression n (%)	17 (20.7)	16 (28.1)	27 (32.9)	16 (28.1)
Moderate depression n (%)	20 (24.4)	16 (28.1)	12 (14.6)	15 (26.3)
Severe depression n (%)	12 (14.6)	12 (21.1)	8 (9.8)	8 (14.0)
p	**0.032**		0.185	

*Chi-square test

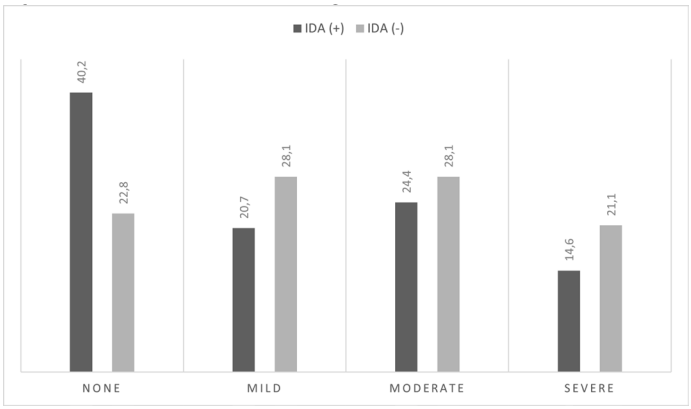

Figure 2. Frequency of depression before treatment

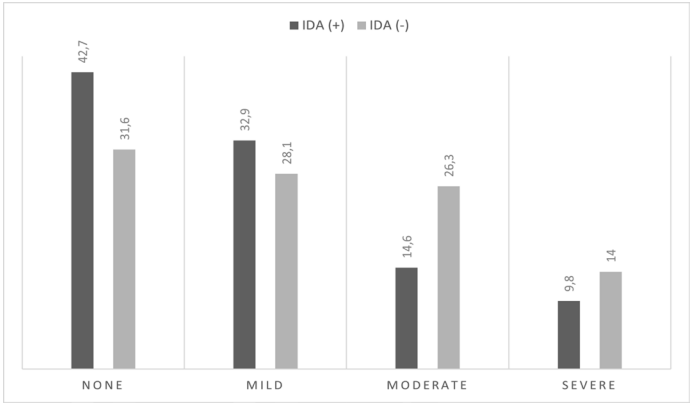

Figure 3. Frequency of depression after treatment

The mean BDI score of male patients before treatment was 21.2±7.9, and 19.1±9.3 for females. Pre-treatment BDI scores did not differ between genders (p=0.279). The mean BDI score of male patients after treatment was 18.7±7.7, and 17.1±8.1 for females. Post-treatment BDI scores were similar (p=0.438). There was a significant decrease in BDI scores in both male patients (p=0.025) and female patients (p<0.001) after treatment compared to before.

DISCUSSION

The World Health Organization identifies IDA as the most prevalent dietary deficit. IDA affects women, adolescents, and children at a rate of 30% in undeveloped cultures (11). The neurological, autoimmune, endocrine, and cardiovascular systems all depend on iron for the composition of hemoglobin, myoglobin, and many enzymes (12). Iron has a role in the myelination of white matter during brain development and modulates the actions of neurotransmitters like dopamine, norepinephrine, and serotonin (13). Because IDA is connected to changes in monoamine neurotransmitters, it has been specifically linked to psychiatric problems (12). A major contributor to disability, depressive disorders afflict 121 million individuals globally. It is listed by WHO as having the fourth-highest global burden of disease (14). There is mounting proof that vitamin D lowers the risk of mental health issues. The link between vitamin D and depression is attributed to the presence of vitamin D receptors in the brain. Vitamin D receptors are found in neurons and glia in the cingulate cortex and hippocampus, among other areas of the brain. Many central functions, including brain growth, neuroplasticity, neuroprotection, control of neurotrophic factors, and neuroimmunomodulation, are influenced by vitamin D. The pathogenesis of depression has been linked to the roles of vitamin D in central processes. It is hypothesized that vitamin D influences mood through inducing the stress response in this manner (16,30). Vitamin D supplementation may be beneficial in the treatment of depression since some theories claim that vitamin D deficiency has a substantial impact on the development of depression and other mental illnesses (16). Data on the early effects of IDA short-term replacement treatment and vitamin D insufficiency on depression, however, are scarce. In this study, we examined the short-term effects of replacement therapy on patients with IDA and/or vitamin D insufficiency for depression and depressive mood.

The initial unexpected result of our investigation was that both patients with vitamin D insufficiency and patients with vitamin D deficiency plus IDA saw a significant drop in BDI scores after taking replacement therapy (p 0.001 for both groups). Our study showed that iron and/or vitamin D replenishment for a short time (median 63 days) had a positive effect on depressive symptoms. On the other hand, around 80% of patients with vitamin D deficiency and about 60% of patients with IDA both had depression. Although there have been many studies on IDA, few have looked at how it affects mood and psychological outcomes. According to recent evidence, IDA patients have an increased risk of developing depression (12,17, 18-19). Also, there are very few studies assessing the depth and severity of depression following IDA treatment.

In the study conducted by Shariatpanaahi et al. (10), ferritin levels and BDI scores of 192 students were evaluated. It was shown that people with depression had lower ferritin levels than individuals without depression. According to the study, in people who have not yet developed anemia, there is a correlation between a drop in ferritin levels and depression.

In a 2012 study by Khalafallah et al., the impact of iron replacement therapy on 183 IDA patients' quality of life and depression was assessed. Health-related quality of life (HRQoL) subscales for general health, depression, and vigor all showed significant improvement after 4 weeks of replacement therapy. The results of our investigation support short-term replacement therapy's beneficial improvement in depression (19). On the other hand, caution should be taken when interpreting our findings because this study included pregnant women.

The students in secondary schools were evaluated in the study by Mansson et al. (21). It was shown that IDA existed in 12% of the students. With iron supplementation, the patients' symptoms of dizziness, restlessness, and depression were shown to diminish. In contrast, this study evaluated the patients' symptoms using the 30-question subjective scale created by the author.

Pamuk et al. (22) 2015 saw the BDI scale used to evaluate 125 IDA and 57 controls. In the study, 71 patients (56.2%) had depression. This rate is really close to what our investigation revealed. Also, this study showed that IDA symptoms can have an impact on depression and quality of life.

Onder et al. (23), 986 patients were evaluated in terms of anemia and depression. Anemia was found in 48 (15%) of 313 patients with depression and 53 (8%) of 673 patients without depression in this study, which used the Epidemiology Studies Central Depression Scale (CES-D) to measure depressive symptoms. Also, it was found that the risk of anemia rose as CES-D scores rose. The study's findings indicated that anemia and depressed symptoms were related.

In a study conducted by Son et al. (24) in 2011, 388 patients' anemia and depression were assessed. The cognitive abilities of anemic patients were lower, and anemic patients with worse cognitive functions were more likely to experience depression, according to this study, which supported the geriatric depression scale.

In a 2012 study by Stewart et al. (25) that analyzed 1875 patients, it was discovered that depressed symptoms were connected to anemia. Lower serum ferritin levels have also been demonstrated to be related to depressive symptoms. However, our study found no statistically

significant relationship between serum ferritin and BDI scores (p=0.062). Yet, studies including a larger patient group can find this connection.

Moy et al. (26) examined the connection between vitamin D insufficiency and depression in a cross-sectional investigation. According to the Depression, Anxiety, and Stress Scale (DASS) 21 scale, two-thirds of people with vitamin D insufficiency are at risk for developing depression. In our investigation, vitamin D supplementation was demonstrated to have beneficial effects on depression in addition to the high prevalence of depression in vitamin D insufficiency. The findings of our investigation were particularly in line with the literature data that had been published in the previous ten years.

In a study conducted by Spedding (27) in 2014, the effect of vitamin D supplementation on depression was evaluated. A meta-analysis of 15 randomized controlled studies found that supplementing with vitamin D reduced depressive symptoms. Also, it has been claimed that vitamin D has a similar impact on depression as antidepressants. The conclusions are however constrained by the heterogeneity of the papers analyzed in the meta-analysis.

According to a 2017 meta-analysis by Parker et al. (28) vitamin D insufficiency is linked to an increase in the occurrence of depression. Studies examining the impact of vitamin D supplementation on depression, however, have shown mixed findings.

The efficiency of treatment was assessed in major depressive patients with vitamin D insufficiency in a randomized controlled research by Sepehrmanesh et al. (29) in 2015. Patients who took weekly vitamin D supplements of 50,000 IU for eight weeks were contrasted with placebo-administered controls. By using the BDI to assess results, it was found that the group getting vitamin D supplements had significantly lower BD ratings than the controls.

In the study carried out by Mozaffari-Khozravi et al. (30) in 2013, 120 patients were placed into three groups, each having a BDI score of 17 or above and low vitamin D levels. The third group received no treatment, while the first group received a single dose of 300,000 IU and the second group received a single dose of 150,000 IU. Three months later, depression and vitamin D levels were assessed again, and only the 300,000 IU therapy group showed a discernible rise in BDI ratings. The study revealed that vitamin D deficiency could be corrected and that a dose of 300,000 IU was more beneficial than a dose of 150,000 IU in treating depression.

In our investigation, it was discovered that individuals with vitamin D insufficiency and/or IDA had a higher chance of developing depression, and that this risk was reduced after receiving short-term replacement therapy with vitamin D and iron. There are a lot of data about how depression is more common in people with IDA and vitamin D insufficiency, but there aren't as many about how short-term replacement therapy affects depression. These data have been expanded by our research. Several specialties are aware of vitamin D insufficiency and the direct impact of IDA on patients.

Vitamin D deficiency and IDA are both common. Nevertheless, not enough is known about how patients' emotional state and quality of life affect them. In light of our findings, it can be concluded that prompt planning of their treatments, particularly for IDA and vitamin D insufficiency, especially in depressed individuals, will ensure that beneficial results even early in the early phase.

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Ethical approval: *With application number 43/26, the Ministry of Health, Health Sciences University, and Diskapi Yildirim Beyazit Training and Research Hospital got ethics committee permission for our study on November 27, 2017.*

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MEDICAL RECORDS-International Medical Journal

Research Article

Second Allogeneic Stem Cell Transplantation in Acute Leukemia with Post-Transplantation Relapse

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Abstract

Aim: It is known that the prognosis of acute leukemia patients who relapse after the first allogeneic stem cell transplantation (ASCT) is dismal. Our goal was to assess the value of a second allogeneic stem cell transplant in acute leukemia patients who experienced post-transplant recurrence.

Material and Methods: We retrospectively reviewed data from 29 patients with relapsing acute leukemia who underwent a second ASCT. Nineteen patients with acute myeloid leukemia and ten patients with acute lymphoblastic leukemia were included in the study.

Results: Ten AML patients and 10 ALL patients were included in the study. Most patients (62%) were in remission before the second transplantation. The median time between the first and second ASCT was 11.9 months (3.1-42 months). Complete remission (CR) was achieved after the second ASCT in 21 (72%) patients, and 11 (52%) patients relapsed after the second ASCT. During this analysis, six patients (21%) were alive and in remission. Relapse of the disease was the leading cause of mortality. After the second ASCT, overall survival (OS) was 6.34 months, and leukemia-free survival (LFS) was 13.8 months.

Conclusion: For patients with acute leukemia who relapsed after the first ASCT, a second ASCT is a good option and can keep patients alive.

Keywords: Post transplantation relapse, second transplantation, acute leukemia

INTRODUCTION

In order to effectively treat acute leukemias, allogeneic stem cell transplantation (ASCT) is an indispensable step. Unfortunately, the results are poor, and clinicians may occasionally encounter post-transplant relapse and graft failure (1-3). Leukemia patients who develop relapse after ASCT have a brief life span (4). There is no standardized method in their management. One of the treatment approaches is second allogeneic stem cell transplantation (5). But the second ASCT may be more complex than the first due to increased drug side effects and comorbidities (6). Nevertheless, studies have shown that second allogeneic stem cell transplantation is more beneficial than post-relapse chemotherapy (7).

We want to share our single-center experience with acute leukemia patients who underwent a second ASCT following a first allogeneic stem cell transplant due to relapse in this study.

MATERIAL AND METHOD

In this article, we discuss our single-center experience with second ASCT to treat patients with acute leukemia relapse after a first ASCT. Written and signed consents were obtained from the patients included in the study,

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which was approved by the Ethics Committee of Erciyes University (2020/148-26.02.2020).

Patients

The data of patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) who underwent second allogeneic transplantation due to relapse after the first allogeneic transplantation at Erciyes University Bone Marrow Transplantation and Stem Cell Center were retrospectively analyzed. Patients who had a second transplantation due to engraftment failure after the first transplantation were excluded from this study. The study involved 29 patients who were followed between 2010 and 2019. The patients' performance status before the second transplantation was determined according to the Eastern Cooperative Oncology Group (ECOG) performance score (8). Patients were classified according to the HCT-comorbidity index (HCT-CI) in terms of comorbidities before the second transplantation (9). Before starting the second transplant's conditioning regimen, the patients' serum ferritin, albumin, and total blood count values were recorded.

HLA-Typing and Donors

Granulocyte-colony stimulating factor (G-CSF) was applied for graft mobilization in both transplantations, and peripheral stem cells were used as the graft source. The high-resolution molecular typing method was used in HLA typing (HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1) of both patients and donors. As donors, 10/10 HLA matched relative, 9/10 HLA matched relative, full match unrelated, and haploidentical relative donors were used.

Definitions

After HSCT, a blast count >5% in bone marrow was determined as a relapse. In evaluating remission status before transplantation, complete remission (CR) was described as <5% blast in bone marrow, absence of blast in peripheral blood, absence of extramedullary disease, and absolute neutrophil count ≥1.0 × 109 / L, platelet count 100×109/L. Active disease was defined as 5% blasts in the bone marrow, the presence of blasts in peripheral blood, or the development of extramedullary disease. (10) Peripheral complete blood count was used to evaluate engraftment. Neutrophil engraftment was defined as the first day when the absolute neutrophil count (ANC) was ≥ 0.5×109/L. Platelet engraftment was defined as the first day of more than 20 × 109/L for two consecutive days without platelet transfusion. Overall survival (OS) was calculated from the second ASCT to death or last follow-up. The leukemia-free survival (LFS) time was calculated from the second ASCT to the disease relapse date.

Conditioning Regimens and GVHD Prophylaxis

The classification defined by Bacigalupo et al. served for assessing the intensity of the conditioning regimens (11). In all patients, cyclosporine was preferred for graft-versus-host disease (GVHD) prophylaxis. Patients were evaluated and graded for acute and chronic GVHD (12,13).

Statistic

Continuous data matching normal distribution were expressed as mean ± standard deviation, continuous data not matching normal distribution as median and min-max, and categorical data as percentages (%). Categorical data were compared using the Chi-square test. The end points of our study were OS and LFS after the second ASCT. Survival curves were created by the Kaplan-Meier method. The data were analyzed with the SPSS for Windows package software program (v. 22.0, SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered significant.

RESULTS

Table 1 provides an overview of the characteristics of 29 patients.

Table 1. Clinical characteristics of patients

Characteristics	Total n=29 n (%)
Age, year, median (range)	37 (17-67)
Sex	
Male	18 (62)
Female	11 (38)
Disease	
AML	19 (66)
ALL	10 (34)
Disease status at second HSCT	
Remission	18 (62)
Active	11(38)
HCT comorbidity index	
0-1	18 (62)
>2	11 (38)
Donor type	
Same	14
Different	15
Remission duration of first HSCT, months, median (range)	8.2 (1-24.6)
Median time from first to second HSCT, months (range)	11.9 (3.-42)
HLA Type	
Full matched	18 (62)
Haploidentical	11 (38)
Conditioning intensity	
MAC	17 (59)
RIC	12 (41)
Acute GVHD (grade 2-4)	
Yes	7 (24)
No	22 (76)
Chronic GVHD	
Yes	2 (7)
No	27 (93)

AML: Acute myeloid leukemia, ALL:Acute lymphoblastic leukemia, HSCT: Hematopoietic stem cell transplantation, GVHD:Graft versus host disease, MAC: myeloablative regimen
RIC: reduced intensity regimen

Flow diagram of 29 patients who underwent second ASCT is shown in Figure 1. The median age at the second transplantation was 37 (17-67). Eighteen (62%) patients were male, and eleven (38%) were female. Nineteen (66%) and ten (34%) of the study patient population were AML and ALL, respectively. Most patients (62%) were in remission before the second transplantation. The median time between the first and second ASCT was 11.9 months (3.1-42 months). Fifteen patients underwent the second ASCT with a different donor. As conditioning regimens, myeloablative conditioning (MAC) regimens were preferred in 17 (59%) patients, and reduced intensity conditioning (RIC) regimens were preferred in 12 (41%) patients. Engraftment was performed in 22 (76%) patients. In these patients, median neutrophil engraftment occurred in 18th days and platelet engraftment in 17th days. Seven patients died before engraftment. One patient engrafted with active disease.

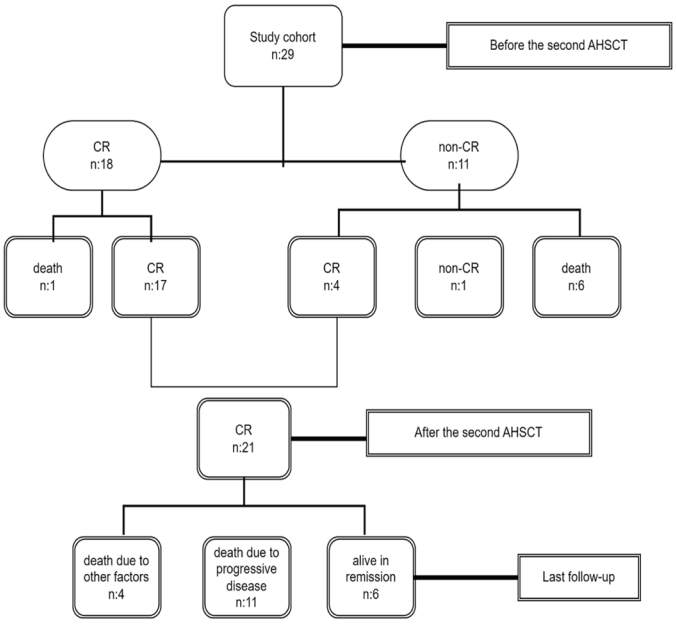

Figure 1. Flow diagram of 29 patients who underwent a second AHSCT

Engraftment did not occur in 6 of 11 patients with the active disease before the second ASCT. Control bone marrow evaluation of 4 out of 5 patients with engraftment resulted in remission. Considering all patients, complete remission (CR) was achieved after the second ASCT in 21 (72%) patients. Eleven (52%) patients relapsed after the second ASCT. The median time from the second ASCT to relapse was 7.5 months (1.4-16.2 months).

A total of six patients (21%) were alive and in remission at the time of this analysis. The median overall survival was 6.34 months (0.2-99.9 months). Overall survival was calculated as 62%, 41%, and 22% at day 100, month 12, and month 18 by the Kaplan-Meier survival analysis, respectively (Figure-3). Median leukemia-free survival was 13.8 months (range, 0-99.9 months). The probabilities of LFS at 100 days, 12 months, and 18 months were 80.7%, 55.2%, and 27.6%, respectively (Figure-2). Of the 29 patients included in the study, 23 died. Considering the causes of death, the most common reason was disease relapse. The median follow-up duration was 29 months (8-100.5 months).

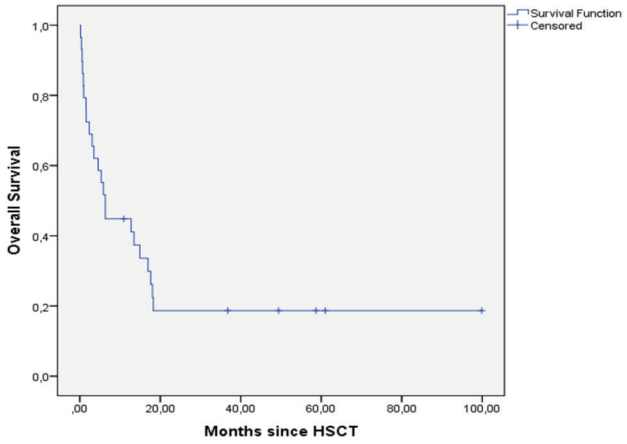

Figure 2. Overall survival of study cohort

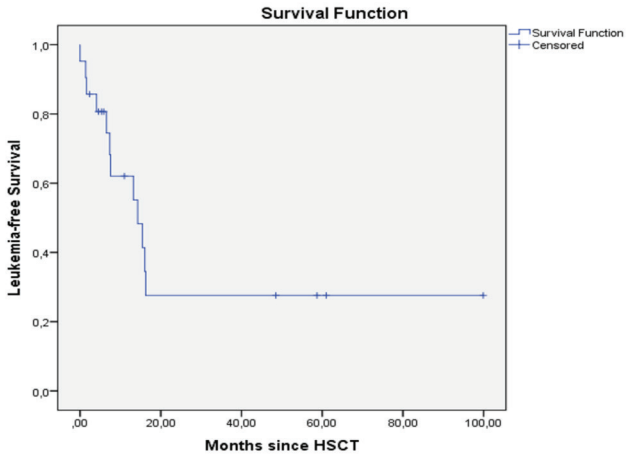

Figure 3. Leukemia-free survival of study cohort

DISCUSSION

The primary cause of treatment failure following allogeneic transplantation is acute leukemia relapse, a considerable problem. Patients with high-risk diseases have several critical treatment options, including second allogeneic transplantation. It is known that active disease during transplantation negatively affects the results of transplantation (14,15). Eleven patients with active disease were transplanted in our study, and four of these patients achieved complete remission. Engraftment did not occur in six patients. On the other hand, 17 of 18 patients with disease in remission were engrafted and followed up with complete remission. Therefore, the pre-transplant disease burden seems to be an essential factor affecting the success of the transplant. However, we think there is a great chance to achieve complete remission after transplantation in patients with active disease.

The same or different donor can be used in the second transplantation. No survival benefit from using a new

donor has been demonstrated in the literature (16-18). In our study, a different donor was used in half of the patients. The results were similar in terms of overall survival and leukemia-free survival. To benefit from the graft versus leukemia effect, switching to a haploidentical donor may improve the success of the transplantation (19, 20). However, the small number of patients in our study made it impossible to evaluate this.

There are conflicting results in studies showing the effects of GVHD in preventing relapse (21,22). Acute GVHD, LFS, and OS had no statistically significant correlation in our study. Likewise, there was no statistically significant correlation between chronic GVHD and LFS or OS.

In some studies, a longer time interval between the first ASCT and the second ASCT has been shown to affect survival positively. In our study, 15 and 14 patients relapsed before and after one year (15,16,23). Leukemia-free survival and OS were similar in both groups.

In a study conducted by Hazar et al. in a pediatric group of 51 patients, the complete response rate was 80.4% (24). In our study, the CR was found to be 72%. In the same study, 1-year OS was calculated as 42% and 1-year LFS as 36.9% (24). The results were similar to our research. In another study, OS was 35%, and 2-year LFS and OS were 32%, with a mean follow-up of 64 months (3).

Our study has limitations, such as the small patient group and retrospective nature.

CONCLUSION

As a result, a second transplantation still holds its place to achieve remission in these patients, whose treatment options are minimal. Even if the survival rate is not high, it is promising that six of our patients lived longer than two years after transplantation and remained in remission. Patients who were in remission before the second transplantation had a better prognosis than those who were not in remission. Among leukemia-free survivors after the second transplantation, disease relapse was the most common cause of treatment failure. Furthermore, after the second ASCT, the patients suffered from severe toxicities. We think relapse prevention methods are needed first to improve the outcomes of patients who relapse after transplantation.

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Research Article

Can Cranium Size be Predicted from Orbit Dimensions?

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Abstract

Aim: The morphometry of skeletal remains is of importance to anatomists, forensic experts, and anthropologists. One of the most preferred skeletal remains is the cranium. Orbital morphometry in the cranium and cranium allows us to have information about parameters such as age, gender and lineage. This study was carried out to seek an answer to the question of whether cranium sizes can be estimated from orbital sizes.

Material and Methods: In the study, 21 dry skulls belonging to the were used. Length and width measurements of the cranium and orbit were made. A precision digital caliper was used for measurements.

Results: The ratio of the diameters of the cranium and orbit was calculated as 4.56 on the sagittal axis and 3.35 on the transverse left axis and these ratios were accepted as a related ratio (RR). $Orbit_{RR}$ values were calculated by converging the orbit to the cranium in RR ratios. Statistical validity (Bland Altman Plot) and reliability (Intraclass Correlation Coeffidency) analyzes were performed to evaluate the agreement between the measurements. There was no statistically significant difference between $Orbit_{RR}$ and cranium diameters ($p>0.05$). Since there was no statistical difference, validity and reliability analysis was performed. It was observed that there was statistical validity between $Orbit_{RR}$ and cranium diameter in the sagittal and transverse axis. In the reliability analysis results, low agreement ($r=0.405$) was detected in the sagittal ($r=0.391$) and transverse axis ($0.30<r<0.50$).

Conclusion: There is validity in estimating cranium sizes using orbital measurements. In forensic medicine, cranium dimensions may be estimated based on orbital dimensions in cases without skull integrity.

Keywords: Cranium, orbit, morphometry, prediction, forensic anthropology

INTRODUCTION

Various situations, whether natural or accidental, may require the use of anthropometry. Some of these are situations such as war or accident (1). Forensic anthropology determines data such as gender, age and ethnicity over bone remains. This field of study undertakes more and more important tasks in finding answers to the "who" and "how" questions that form the basis of forensic events (2). Cranium morphometry is also frequently used to obtain these data. While the most reliable skeletal remnant is the pelvis for sex estimation, the secondary reliable method is the skull bone (3,4). The reason for the preference of the skull bone; it is resistant to burning, rotting and deterioration (1).

Age, sex, lineage and evolutionary periods are effective in the development of orbital dimensions, which is one of the formations in the cranium.5 Therefore, orbital measurements are important in forensic anthropology (4,5).

It is very important to obtain personally identifiable data from unknown human bone remains. The integrity of the individual's skeleton is essential in order to obtain accurate results from bone remains. However, it is rare to reach all of the bones of the skeletal system in good conditions (6-8).

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Since deformation and deficiency may occur in the skeletal remains to be studied, the measurement of every formation cannot be made directly. In our study, we sought an answer to the question of whether the deformed cranium dimensions can be reached from skeletal remains whose orbit has not been deformed?

MATERIAL AND METHOD

Design

In our study, macroscopic observations and measurements were made on 21 skulls in the form of dry bones of adult individuals. Cranium length with 0.1 mm precision digital caliper: sagittal diameter (accepted as the distance between glabella and opisthocranion) (Figure A1) and cranium width: transverse diameter (The skull width was measured between the two most remote points located on the right and the left side of the skull) were measured. (Figure A2). Also left orbit (O) width: transverse diameter (The laterally sloping distance from dacryon to ectoconchion) (Figure B1) and left O length: sagittal diameter (distance between the upper and lower edges of the orbit; perpendicular to its width and similarly bisects the orbit) (Figure B2) were measured.

Cranium index (9) and orbital index (10) were calculated from the measurements made with formulas suitable for the literature.

Cranium Index: Cranium width/Cranium length×100

Orbital Index: Orbital length/Orbital width×100

Measurements in the transverse and sagittal planes were used for the new indices in the study. The related ratio (RR) between the measurements was determined by the Cranium/Orbit formula. Cranial Width/Orbital Width formula was used in the calculation of the index in the transverse axis, and Cranial Length/Orbital Length formula was used in the calculation of the index in the sagittal axis.

Statistic

The means and standard deviations of the normally distributed data were obtained. The averages were compared with each other. Orbital and cranium measurements were proportional to each other and relative ratios were calculated. Proportional values were subjected to normal distribution analysis using 5 parameters (Skewness-Kurtosis, Mean/Std, Histogram Q-Q Polts, Shapiro Wilk Test). Normally distributed data were subjected to the related samples T-Test. When it was determined that there was no difference between the data ($p>0.05$), validity and reliability analysis was performed. The Bland Altman Test was used in the validity analysis, and the Intraclass Correlation Coefficient (ICC) test was used in the reliability analysis. In the Bland Altman test, the data for the difference between two measurements were calculated and the Simple Scotter Dat graph was drawn. The reliability (r) value in the ICC test was interpreted according to the literature (11).

RESULTS

While the ratio of the length of the cranium to the length of the orbit in the sagittal axis is approximately 4.56 (RR1≅4.56); The ratio of the width of the cranium to the width of the orbit in the transverse axis was calculated as approximately 3.35 (RR2≅3.35). The findings of the measurements are in Table 1.

Table 1. Descriptive data of orbit and cranium

Axis	Orbit (mm)	Cranium (mm)	Ratio
Sagittal	35.39±1.96	161.08±7.80	4.56
Transvers	39.27±1.88	131.44±6.17	3.35

Parametric data were presented as mean±standard deviation (MEAN±STD). Related Ratio=Cranium/Orbit calculated

In order to find an answer to the question of whether cranium sizes can be calculated using orbital ratios, validity and reliability analyzes were performed after T test (Table 2) was applied to the dependent variables.

Table 2. Comparison of proportionalized orbit and cranium diameters

Axis	$Orbit_{RR}$ (mm)	Cranium (mm)	Sig. (p)
Sagittal	161.38±8.95	161.08±7.80	0.908
Transvers	131.57±6.31	131.44±6.17	0.948

Parametric data were shown as MEAN±STD. Statistical analysis of dependent variables was done with Paired Samples T Test

$Orbit_{RR}$ values were calculated by converging the orbit to the cranium at RR ratios. There was no statistically significant difference between $Orbit_{RR}$ and Cranium diameters ($p>0.05$). Since there was no statistical difference; validity (Figure 2 and Figure 3) and reliability (Table 3) analyses were performed.

Table 3. Reliability analysis between orbit and cranium

Axis	ICC	95% Coiffence	Sig. (p)
Sagittal	0.405[a]	(-0.533) (0.762)	0.136
Transvers	0.391[a]	(-0.571) (0.757)	0.147

Intraclass Correlation Coefficient (ICC) test was applied for reliability analysis. a; low agreement for reliability test 0.30<r<0.50

It was observed that there was a validity agreement between $Orbit_{RR}$ and Cranium diameter on the sagittal axis (Figure 2).

It was observed that there was a validity agreement between $Orbit_{RR}$ and Cranium diameter in the transverse axis (Figure 3).

After these data were obtained, the reliability of calculating cranium diameters using orbital ratios was examined (Table 3). Intraclass Correlation Coefficient (ICC) test was applied for reliability. There is a low agreement between $Orbit_{RR}$ and cranium on the sagittal, likely the transverse axis.

According to the data we obtained from our study, Cranium Index is (CRI)=81.71±4.28 (95% CI 79.75-83.66); Orbital Index (OI)=111.15 ±5.91 (95% CI 108.46-113.85).

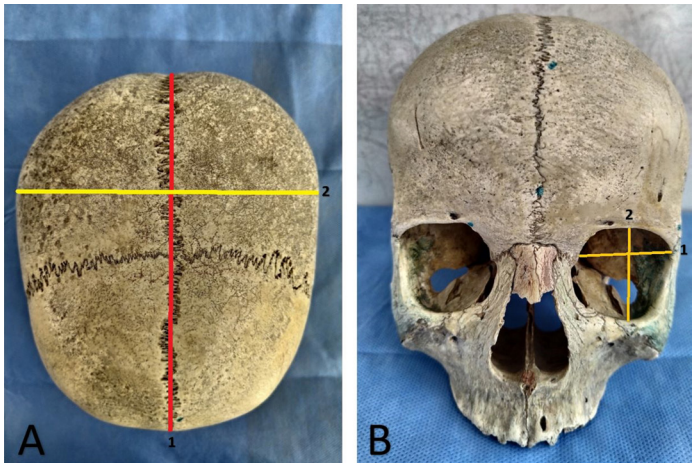

Figure 1. A, B. Measurement of the cranium (A) and orbital (B) dimensions (A1.Sagittal diameter, A2. Transverse diameter) (B1. Transverse diameter, B2. Sagittal diameter)

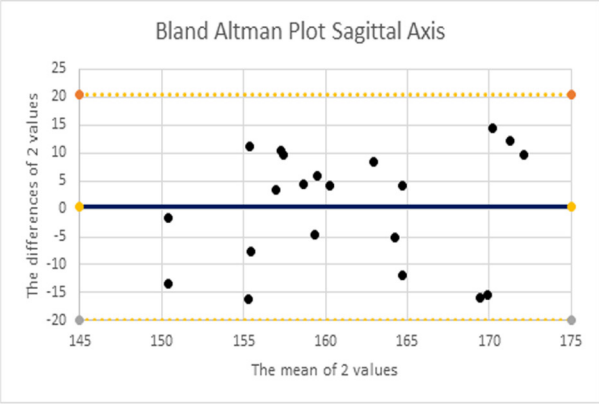

Figure 2. Demonstration of validity agreement between $Orbit_{RR}$ and Cranium diameter on the sagittal axis with Bland Altman Plot (Scotter Dot graphs)

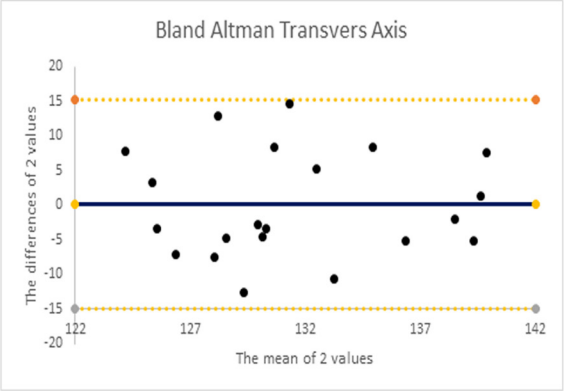

Figure 3. Demonstration of validity agreement between $Orbit_{RR}$ and Cranium diameter on the transverse axis with Bland Altman Plot (Scotter Dot graphs)

DISCUSSION

By using craniofacial dimensions, parameters such as gender and age can be determined from bone remains (12,13). The most important craniofacial dimension is the width and length used to determine the cranial index (14). The cranial index is widely used in forensic anthropology analyzes to predict an individual's ancestry (12,13).

Differences between species provide an important perspective on forensic anthropometry (15). Orbit has been used to predict individuals' race and gender for more than a century (16). The orbital index, which is obtained from the height and width of the orbit, is an extremely important anthropometric tool in forensic research, in the analysis of ethnic and racial relations and in gender estimation (15,10).

According to Mahakkanukrauh et al. (17) in their study on 200 Thai dry skulls (100 males, 100 females), the cranium length and width values were 164.02±6.76 mm, 138.68±5.33 mm (CRI: 84.55) in females and 172.64±6.23 mm, 144.44±5.69 mm (CRI: 83.66) in males, respectively. In the same study, orbital width=38.23±2.10 mm and length 33.57±1.55 mm in women. (OI: 113.88). Orbital width and length in males were 40.49±1.82, respectively; It was reported as 34.69±1.73 mm (OI: 116.71). The CRI value for men obtained according to the data in the study is close to the results of our study and is within the confidence interval. The CRI value in females is close to our study results. According to the data in the study, we found that the OI obtained was close to the confidence interval in women and higher in males.

Ramamoorthy et al. (18) in their study of 70 South Indian populations, reported the cranial length and width values as follows: length for females 170.5±6.84 mm, width 128±6.15 mm (CRI: 75.07) and length for males 178.3±8.13 mm, the width is 13±6.22 mm (CRI: 74.59). In the same study, orbital height in males was 34.1±2.42 mm; the width was reported as 45.1±4.90 mm (OI: 132.25), while in women this length was reported as 34.6±1.69 mm and width as 43.8 mm. It was seen that the CRI and OI values obtained according to the data in the study were quite different from our study.

Sangvichien et al. (19) in their study on 101 Thai dry skulls (66 men and 35 women), the cranium length in men was 175.68±6.83 mm; reported its width as 145.82±5.20 mm (CRI: 83.00). In females, cranium length and width were 168.80±7.18, respectively; It is 144.66±5.29 mm (CRI: 85.69). In the same study, orbital width in men was 40.10±1.89; its length is 33.44±2.33 mm (OI: 119.91). In females, this width was reported as 38.09±2.25 mm and length as 32.89±2.28 mm (OI: 115.81).

Marinescu et al. (20) made osteometric measurements an adult modern Romanian population sample. In this study, cranial length was 174.1 and cranial width was 144.1 in men (CRI: 82.76); The orbital length is 33.1, and the orbital width is 39.9 mm (OI: 120.54). In the same study, cranial length was 166.7 mm and cranial width was 138.4 mm (CRI: 83.02) in women; The orbital length was reported as 32.6 mm and the orbital width as 38.1 mm (OI: 116.87). According to the results obtained from the study data, while the CRI results in men and women were within the confidence interval, it was seen that the OI in both men

and women was higher than the index in our study.

Toneva et al. (21) made measurements similar to our study on cranial CT images of 393 (169 males and 224 females) Bulgarian adults. In this study, cranial length was 185.50±7.09 mm and width: was 137.93±7.34 mm in men (CRI: 74.35); right orbital width was reported as 41.18±2.07 mm and left orbital width as 41.29±2.12 mm. In the same study, cranial length was 175.61±6.07 mm and cranial width was 134.56±6.15 (CRI: 76.62) mm in women; right orbital width was reported as 39.66±1.80 mm and left orbital width 39.96±1.96 mm. Orbital length calculation points in the study were not included in the discussion because they were not the same as our study. The CRI obtained from the data in the study was lower than our index values in both women and men.

Rooppakhun et al. (22) 91 on computed tomography images of Thai dry skulls (56 males, 35 females), cranial length 173±4.74 mm, width 144.13±5.45 (CRI: 83.31) and orbital width (left) 40.95±1.86 mm, orbital width (right) in males while it was 41.43±1.75 mm; Cranial length was reported as 165.15±6.61 mm, width 140.83±5.40 mm (CRI: 85.27) and orbital width as right 39.66±2.00 mm, left 39.36±2.30 mm in women. The orbital length measurement was not performed in this study. According to the results obtained from the study data, the CRI results in men were within the confidence interval, while the index in women was higher. It has been shown again by studies that the values of CRI and OI vary according to gender and both indices are large in men.

Ulcay et al. (23) measured both foramen magnum and cranium dimensions in their study of 60 dry bones belonging to the Turkish population without gender discrimination. They reported the length of the cranium as 162.45±6.20 mm and the width as 129.45±4.99 mm. According to the reported values, CRI:79.68. In our study, we found the length and width values of the cranium to be close to the present study. The CRI in our study and our results were very close to each other closeness of the results supports the existence of race-specific cranium size. Bones from the Turkish population were used in both studies. It was observed that the values of CRI and OI showed both racial and gender specific differences.

The results of our study were compared with craniometric studies performed in different and same races. It was observed that the OI and CRI values of men and women in the studies were different. Cranial and orbital dimensions in similar breeds were close to each other.

CONCLUSION

To the best of our knowledge, our study is the first in the literature to prove that the cranium size, which is important in forensic medicine, can be reached through the orbital dimension, and that this is proven by validity-reliability analysis.

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

Ethical approval: *Since the skull in the form of dry bone in the anatomy laboratory was used in the study, the decision of the ethics committee was not required. However, Permission was obtained from Erciyes University Faculty of Medicine Anatomy Department.*

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MEDICAL RECORDS-International Medical Journal

Research Article

The Use of Botulinum Toxin in Temporomandibular Disorders: A Bibliometric Study

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Abstract

Aim: Botulinum toxin injections are an important issue that is widely used, and many scientific articles have been published in patients with temporomandibular joint disorders (TMD). The aim of this study was to evaluate the status of activity the use of botulinum toxin in TMD during the period 1978-2023.

Material and Methods: Articles published until April 1, 2023 were searched in Web of Science. The top 50 articles with the highest citations and suitable for the study topic were selected among the totally 299 articles.

Results: Even though the articles published about botulinum injection in TMD have increased in recent years, there is no regular increase over the years. The most cited article was published in 2015 and the number of citations in Web of Science was 194. While there was no difference in productivity among the authors, the most productive country was the United States. Türkiye was found to be above the average among other countries.

Conclusion: This bibliometric study of the top 50 most-cited papers in Web of Science the use of botulinum toxin in TMD recognized a quantitative and qualitative analysis of this very favorable research field.

Keywords: Botulinum toxin, bibliometrics, temporomandibular disorders

INTRODUCTION

Temporomandibular joint disorders (TMD) are a complex disorder involving muscles and bones with an incidence of approximately 15% in the population. According to the American Academy of Orofacial Pain, TMD are divided into two groups. These are the myogenous type, which is related to the masticatory muscles, and the arthrogenous type, which is related to the temporomandibular joint. In both types, the aim is to eliminate the symptoms of the patients and to ensure that mandibular movements occur within physiological limits (1-3).

Botulinum toxin was discovered by Justinus Kerner in 1817 it was used for the treatment of strabismus in the 1980s, for the treatment of hemifacial spasm in the 1990s, and for cosmetic purposes after the beginning of the 2000s. In the following years, its use for cosmetic purposes in the facial area has increased rapidly. The patients mostly complain of orofacial pain in TMD. Studies have shown that botulinum toxin injections are more effective than placebo in muscular dysfunction disorders that cause TMD (4-8).

Bibliometrics is a set of literature reviews of articles published on related topics to show areas such as the historical process, the country of publication and the authors who published them. It aims to measure the impact of an article based on the number of citations it has received, which is generally accepted as one of the measures of the importance of the article. Bibliometric analysis shows current approaches to the subject, as well

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as the relationship between authors and the impact of the field and guides current research (9-12).

TMD are an important area in dentistry. Treatments or deficiencies in this field have always been the subject of research for dentistry. The lack of a bibliometric analysis on botulinum toxin injections in TMD may be a deficiency for the development and interaction of this field. Considering this deficiency, the aim of this study is to evaluate the development and status of scientific activity in the relevant field between 1978 and 2023 through bibliometric analysis of scientific articles and to shed light on current research. The aim of this study is to conduct a bibliometric analysis of the articles published on botulinum injection used in TMD.

MATERIAL AND METHOD

The characteristics of the publications in the scientific literature on the use of botox in TMD, such as authors, study design, study years and number of citations are presented in the form of bibliometric analysis.

Keywords were created to determine the selection criteria for this bibliometric analysis. When selecting search words related to the topic, keywords were selected to select the most broadly relevant articles. The selected free keywords, synonyms and indexing for appropriate topics were identified from https://www.ncbi.nlm.nih.gov/mesh.

When synonyms for TMD and Botox were examined, common words were identified and searched by typing in Web of Science (Clarivate Analytics, 1500 Spring Garden St, Philadelphia, United States of America).

Articles published until April 1, 2023, were searched with the formulation (ALL=(temporomandibular)) AND ALL=(botulinum) in the Web of Science (WOS).

The first 50 articles with the highest number of citations and appropriate to the study topic were selected of the 299 articles that emerged because of the search. The selected articles were transferred to an excel file to create a draft.

RESULTS

Fifty of the first 78 most highly cited articles on the subject published in WOS until April 1, 2023, were selected. The most cited article was published in 2015 and the number of citations in WOS was 194. The least cited article was published in 2017 and the number of citations was 21. The average number of citations of the top 50 most highly cited articles was 52.68. The number of citations and names of the articles are shown in Table 1.

Table 1. The 50 most-cited papers on the use of botulinum toxin in temporomandibular disorders

Rank	Paper	Number of Citations (WOS)	All databases' citations	Paper type
1	Gauer RL, Semidey MJ. Diagnosis and treatment of temporomandibular disorders. Am Fam Physician. 2015 Mar 15;91(6):378-86.	194	211	Article
2	Romero-Reyes M, Uyanik JM. Orofacial pain management: current perspectives. J Pain Res. 2014 Feb 21;7:99-115.	135	169	Review
3	Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. Laryngoscope. 2001 Feb;111(2):218-26.	127	141	Article
4	Wieckiewicz M, Boening K, Wiland P, Shiau YY, Paradowska-Stolarz A. Reported concepts for the treatment modalities and pain management of temporomandibular disorders. J Headache Pain. 2015;16:106.	122	133	Review
5	Guarda-Nardini L, Manfredini D, Salamone M, Salmaso L, Tonello S, Ferronato G. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. Cranio. 2008 Apr;26(2):126-35.	102	114	Article
6	Durham J, Newton-John TR, Zakrzewska JM. Temporomandibular disorders. BMJ. 2015 Mar 12;350:h1154.	81	85	Review
7	Ernberg M, Hedenberg-Magnusson B, List T, Svensson P. Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: a randomized, controlled, double-blind multicenter study. Pain. 2011 Sep;152(9):1988-1996.	81	91	Article
8	Calixtre LB, Moreira RF, Franchini GH, Alburquerque-Sendín F, Oliveira AB. Manual therapy for the management of pain and limited range of motion in subjects with signs and symptoms of temporomandibular disorder: a systematic review of randomised controlled trials. J Oral Rehabil. 2015 Nov;42(11):847-61.	78	83	Review
9	Kurtoglu C, Gur OH, Kurkcu M, Sertdemir Y, Guler-Uysal F, Uysal H. Effect of botulinum toxin-A in myofascial pain patients with or without functional disc displacement. J Oral Maxillofac Surg. 2008 Aug;66(8):1644-51.	71	79	Article

10	Freund B, Schwartz M, Symington JM. Botulinum toxin: new treatment for temporomandibular disorders. Br J Oral Maxillofac Surg. 2000 Oct;38(5):466-71.	70	72	Article
11	Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. J Pain. 2002 Feb;3(1):21-7.	68	76	Article
12	Guarda-Nardini L, Stecco A, Stecco C, Masiero S, Manfredini D. Myofascial pain of the jaw muscles: comparison of short-term effectiveness of botulinum toxin injections and fascial manipulation technique. Cranio. 2012 Apr;30(2):95-102.	67	70	Article
13	Schwartz M, Freund B. Treatment of temporomandibular disorders with botulinum toxin. Clin J Pain. 2002 Nov-Dec;18(6 Suppl):S198-203.	64	65	Article
14	Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. Cochrane Database Syst Rev. 2010 Oct 6;(10):CD004715.	62	64	Review
15	Sidebottom AJ. Current thinking in temporomandibular joint management. Br J Oral Maxillofac Surg. 2009 Mar;47(2):91-4.	62	67	Article
16	Nixdorf DR, Heo G, Major PW. Randomized controlled trial of botulinum toxin A for chronic myogenous orofacial pain. Pain. 2002 Oct;99(3):465-473.	61	66	Article
17	Freund B, Schwartz M, Symington JM. The use of botulinum toxin for the treatment of temporomandibular disorders: preliminary findings. J Oral Maxillofac Surg. 1999 Aug;57(8):916-20; discussion 920-1.	56	60	Article
18	Ivanhoe CB, Lai JM, Francisco GE. Bruxism after brain injury: successful treatment with botulinum toxin-A. Arch Phys Med Rehabil. 1997 Nov;78(11):1272-3.	56	59	Article
19	Raphael KG, Janal MN, Sirois DA, Dubrovsky B, Wigren PE, Klausner JJ, Krieger AC, Lavigne GJ. Masticatory muscle sleep background electromyographic activity is elevated in myofascial temporomandibular disorder patients. J Oral Rehabil. 2013 Dec;40(12):883-91.	54	56	Article
20	De Boever JA, Nilner M, Orthlieb JD, Steenks MH; Educational Committee of the European Academy of Craniomandibular Disorders. Recommendations by the EACD for examination, diagnosis, and management of patients with temporomandibular disorders and orofacial pain by the general dental practitioner. J Orofac Pain. 2008 Summer;22(3):268-78.	51	54	Review
21	Bakke M, Møller E, Werdelin LM, Dalager T, Kitai N, Kreiborg S. Treatment of severe temporomandibular joint clicking with botulinum toxin in the lateral pterygoid muscle in two cases of anterior disc displacement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Dec;100(6):693-700.	46	51	Article
22	Lacković Z, Filipović B, Matak I, Helyes Z. Activity of botulinum toxin type A in cranial dura: implications for treatment of migraine and other headaches. Br J Pharmacol. 2016 Jan;173(2):279-91.	45	47	Article
23	Beddis H, Pemberton M, Davies S. Sleep bruxism: an overview for clinicians. Br Dent J. 2018 Sep 28;225(6):497-501.	43	46	Article
24	Song PC, Schwartz J, Blitzer A. The emerging role of botulinum toxin in the treatment of temporomandibular disorders. Oral Dis. 2007 May;13(3):253-60.	43	45	Review
25	Daelen B, Thorwirth V, Koch A. Treatment of recurrent dislocation of the temporomandibular joint with type A botulinum toxin. Int J Oral Maxillofac Surg. 1997 Dec;26(6):458-60.	43	43	Article
26	Fu KY, Chen HM, Sun ZP, Zhang ZK, Ma XC. Long-term efficacy of botulinum toxin type A for the treatment of habitual dislocation of the temporomandibular joint. Br J Oral Maxillofac Surg. 2010 Jun;48(4):281-4.	40	43	Article
27	Ihde SK, Konstantinovic VS. The therapeutic use of botulinum toxin in cervical and maxillofacial conditions: an evidence-based review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Aug;104(2):e1-11.	40	42	Review
28	Shim YJ, Lee MK, Kato T, Park HU, Heo K, Kim ST. Effects of botulinum toxin on jaw motor events during sleep in sleep bruxism patients: a polysomnographic evaluation. J Clin Sleep Med. 2014 Mar 15;10(3):291-8.	39	44	Article

29	Majid OW. Clinical use of botulinum toxins in oral and maxillofacial surgery. Int J Oral Maxillofac Surg. 2010 Mar;39(3):197-207.	36	37	Review
30	Liddell A, Perez DE. Temporomandibular joint dislocation. Oral Maxillofac Surg Clin North Am. 2015 Feb;27(1):125-36.	35	37	Article
31	Pihut M, Ferendiuk E, Szewczyk M, Kasprzyk K, Wieckiewicz M. The efficiency of botulinum toxin type A for the treatment of masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headache. J Headache Pain. 2016;17:29.	34	39	Article
32	De la Torre Canales G, Câmara-Souza MB, do Amaral CF, Garcia RC, Manfredini D. Is there enough evidence to use botulinum toxin injections for bruxism management? A systematic literature review. Clin Oral Investig. 2017 Apr;21(3):727-734.	33	36	Review
33	Chen YW, Chiu YW, Chen CY, Chuang SK. Botulinum toxin therapy for temporomandibular joint disorders: a systematic review of randomized controlled trials. Int J Oral Maxillofac Surg. 2015 Aug;44(8):1018-26.	33	36	Review
34	Raphael KG, Tadinada A, Bradshaw JM, Janal MN, Sirois DA, Chan KC, Lurie AG. Osteopenic consequences of botulinum toxin injections in the masticatory muscles: a pilot study. J Oral Rehabil. 2014 Aug;41(8):555-63.	33	34	Article
35	Martínez-Pérez D, García Ruiz-Espiga P. Recurrent temporomandibular joint dislocation treated with botulinum toxin: report of 3 cases. J Oral Maxillofac Surg. 2004 Feb;62(2):244-6.	33	37	Case Report
36	Sycha T, Kranz G, Auff E, Schnider P. Botulinum toxin in the treatment of rare head and neck pain syndromes: a systematic review of the literature. J Neurol. 2004 Feb;251 Suppl 1:I19-30.	31	33	Article
37	Freund BJ, Schwartz M. Relief of tension-type headache symptoms in subjects with temporomandibular disorders treated with botulinum toxin-A. Headache. 2002 Nov-Dec;42(10):1033-7.	31	35	Article
38	Moore AP, Wood GD. Medical treatment of recurrent temporomandibular joint dislocation using botulinum toxin A. Br Dent J. 1997 Dec 13-27;183(11-12):415-7.	30	32	Article
39	Monroy PG, da Fonseca MA. The use of botulinum toxin-a in the treatment of severe bruxism in a patient with autism: a case report. Spec Care Dentist. 2006 Jan-Feb;26(1):37-9.	29	31	Article
40	Ghurye S, McMillan R. Orofacial pain - an update on diagnosis and management. Br Dent J. 2017 Dec;223(9):639-647.	28	31	Article
41	Awan KH. The therapeutic usage of botulinum toxin (Botox) in non-cosmetic head and neck conditions - An evidence based review. Saudi Pharm J. 2017 Jan;25(1):18-24.	28	29	Review
42	Santana-Mora U, López-Ratón M, Mora MJ, Cadarso-Suárez C, López-Cedrún J, Santana-Penín U. Surface raw electromyography has a moderate discriminatory capacity for differentiating between healthy individuals and those with TMD: a diagnostic study. J Electromyogr Kinesiol. 2014 Jun;24(3):332-40.	27	29	Article
43	Zhang LD, Liu Q, Zou DR, Yu LF. Occlusal force characteristics of masseteric muscles after intramuscular injection of botulinum toxin A(BTX - A)for treatment of temporomandibular disorder. Br J Oral Maxillofac Surg. 2016 Sep;54(7):736-40.	26	28	Article
44	Güven O. Management of chronic recurrent temporomandibular joint dislocations: a retrospective study. J Craniomaxillofac Surg. 2009 Jan;37(1):24-9.	26	27	Article
45	Mor N, Tang C, Blitzer A. Temporomandibular Myofacial Pain Treated with Botulinum Toxin Injection. Toxins (Basel). 2015 Jul 24;7(8):2791-800.	25	32	Review
46	Vázquez Bouso O, Forteza González G, Mommsen J, Grau VG, Rodríguez Fernández J, Mateos Micas M. Neurogenic temporomandibular joint dislocation treated with botulinum toxin: report of 4 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Mar;109(3):e33-7.	25	25	Article
47	Almukhtar RM, Fabi SG. The Masseter Muscle and Its Role in Facial Contouring, Aging, and Quality of Life: A Literature Review. Plast Reconstr Surg. 2019 Jan;143(1):39e-48e.	24	25	Review

48	Tinastepe N, Küçük BB, Oral K. Botulinum toxin for the treatment of bruxism. Cranio. 2015 Oct;33(4):291-8.	23	28	Review
49	Abouelhuda AM, Khalifa AK, Kim YK, Hegazy SA. Non-invasive different modalities of treatment for temporomandibular disorders: review of literature. J Korean Assoc Oral Maxillofac Surg. 2018 Apr;44(2):43-51.	22	27	Review
50	Patel AA, Lerner MZ, Blitzer A. IncobotulinumtoxinA Injection for Temporomandibular Joint Disorder. Ann Otol Rhinol Laryngol. 2017 Apr;126(4):328-333.	21	21	Article

The journal with the highest JCR®IF-2021 rate of published articles is BMJ-British Medical Journal with 96.216. Of the top 50 most cited articles, 37.5% of the journals are Q1 status journals, and it was determined as the group with the highest status with 12 of the 32 journals published. The journals and JCR®IF-2021 of the publications are shown in Table 2.

The top three most cited articles were written in the United States and the most cited authors was identified as Gauer and Semidey. No more than one article by an institution or author was identified in the top 50 most cited articles. Author information and institutional information are shown in Table 3.

While the United States is the country with the highest number of 50 articles, the fact that the second highest number is the United Kingdom shows that the publications do not belong to a continent. A total of 21 different countries were included in the study. Distribution of the countries where articles were published is shown in Figure 1.

Table 2. The journals and JCR®IF-2021 of the publications

Journal Name	Paper Numbers	JCR® IF2021	Quartile Category
AMERICAN FAMILY PHYSICIAN	1	5.305	Q1
ANNALS OF OTOLOGY RHINOLOGY AND LARYNGOLOGY	1	1.973	Q3
ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION	1	4.06	Q1
BMJ-BRITISH MEDICAL JOURNAL	1	96.216	Q1
BRITISH DENTAL JOURNAL	3	2.727	Q3
BRITISH JOURNAL OF ORAL & MAXILLOFACIAL SURGERY	4	2.018	Q3
BRITISH JOURNAL OF PHARMACOLOGY	1	9.473	Q1
CLINICAL JOURNAL OF PAIN	1	3.423	Q2
CLINICAL ORAL INVESTIGATIONS	1	3.607	Q2
COCHRANE DATABASE OF SYSTEMATIC REVIEWS	1	11.874	Q1
CRANIO-THE JOURNAL OF CRANIOMANDIBULAR & SLEEP PRACTICE	3	1.67	Q4
HEADACHE	1	5.311	Q1
INTERNATIONAL JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY	3	2.986	Q2
JOURNAL OF CLINICAL SLEEP MEDICINE	1	4.324	Q2
JOURNAL OF CRANIO-MAXILLOFACIAL SURGERY	1	3.192	Q2
JOURNAL OF ELECTROMYOGRAPHY AND KINESIOLOGY	1	2.641	Q2
JOURNAL OF HEADACHE AND PAIN	2	8.588	Q1
JOURNAL OF NEUROLOGY	1	6.682	Q1
JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY	3	2.136	Q4
JOURNAL OF ORAL REHABILITATION	3	3.558	Q2
JOURNAL OF OROFACIAL PAIN	1	2.824	Q1
JOURNAL OF PAIN	1	5.383	Q1
JOURNAL OF PAIN RESEARCH	1	2.832	Q3
JOURNAL OF THE KOREAN ASSOCIATION OF ORAL AND MAXILLOFACIAL SURGEONS (Emerging Sources Citation Index)	1	-	-
LARYNGOSCOPE	1	2.97	Q2
ORAL AND MAXILLOFACIAL SURGERY CLINICS OF NORTH AMERICA	1	3.13	Q2
ORAL DISEASES	1	4.068	Q1
ORAL SURGERY ORAL MEDICINE ORAL PATHOLOGY ORAL RADIOLOGY AND ENDODONTOLOGY	3	1.457 (year 2011)	Q2 (year 2011)
PAIN	2	7.926	Q1
PLASTIC AND RECONSTRUCTIVE SURGERY	1	5.169	Q1
SAUDI PHARMACEUTICAL JOURNAL	1	4.562	Q2
SPECIAL CARE IN DENTISTRY (Emerging Sources Citation Index)	1	-	-
TOXINS	1	5.075	Q3

Table 3. Institutes and countries of the most cited authors

First Author	Institution	Country	Number of citations
Gauer, RL	Womack Army Medical Center	US	194
Romero-Reyes, M	New York University College of Dentistry	US	135
Blitzer, A	St. Luke's-Roosevelt Hospital Center	US	127
Wieckiewicz, M	Wroclaw Medical University	Poland	122
Guarda-Nardini, L	University of Padova	Italy	102
Durham, J	Newcastle University	UK	81
Ernberg, M	Karolinska Institutet	Sweden	81
Calixtre, LB	ederal University of São Carlos	Brazil	78
Kurtoglu, C	Cukurova University	Türkiye	71
Freund, B	University of Toronto	Canada	70

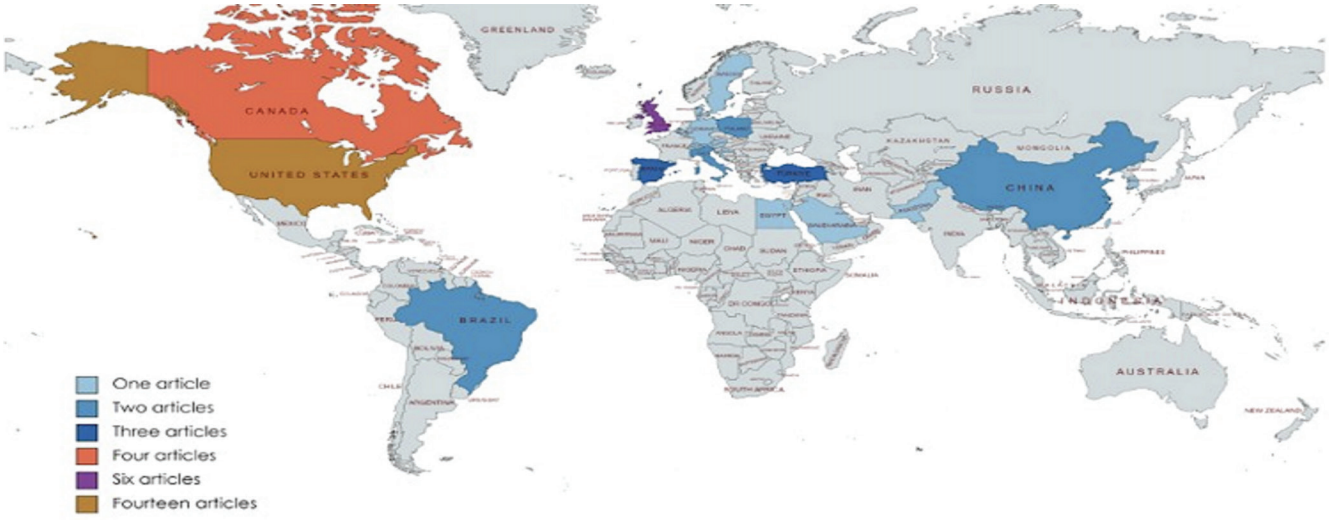

Figure 1. Contribution of each country in the distribution of the use of Botulinum Toxin in Temporomandibular Disorders articles

DISCUSSION

Since bibliometric studies on the use of botulinum toxin in TMD have not been identified in the literature and to fill the gap in this field, this study aims to evaluate the scientific studies conducted between 1978-2023. This study was conducted by selecting search words ("temporomandibular and "botulinum") to find and evaluate relevant articles in the WOS database.

The application of botulinum toxin for aesthetic purposes after the 2000s has intensified the studies in this field. When we look at the years of the 50 most cited articles about botulinum injection in TMD, it is seen that there has been an increase in recent years. The year with the highest number of publications was 2015. At the same time, the most cited Gauer and Semidey's (1) article was published in 2015.

When we evaluate the countries of the authors, it is seen that the United States holds the majority on this subject. 14 of the top 50 articles were published in the United States, followed by 6 articles from the United Kingdom. The United States is not only numerically productive, but also the country with the top 3 most cited articles. Türkiye ranked above the average among the 21 countries with total publications with 3 articles published.

While first 40 articles evaluated were identified as articles in the Science Citation Index-Expanded database except 1, the article published by Monroy and da Fonseca (13) was identified as Emerging Sources Citation Index as a category in the journal Special Care in Dentistry. Most of the published studies were identified as 66% research articles, 1 was identified as 2% case report and 32% as review articles.

It is a natural process that the citation rates of articles increase as the period of publication increases. However, this literature review shows that the most cited article was published in 2015 with 194 citations, while an article published in 1997 received 30 citations. It can be said that many issues such as the subject matter of the articles and the methods of their production affect the citation rates.

CONCLUSION

Although the number of articles published in the field of botulinum use in TMD has increased over the years, an order cannot be mentioned. Research articles are considered to receive more citations than other types of articles. The use of botulinum in TMD can be published by many journals in the Q1-Q2 WOS category.

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MEDICAL RECORDS-International Medical Journal

Research Article

Determination of Antioxidant and Anticancer Activities of *C. sativa* Leaf Extracts on MCF-7 Human Breast Cancer Cell Line

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Abstract

Aim: In this study, it was aimed to determine the total phenolic content, flavonoid content, and antioxidant activity of *Castanea sativa Mill*. (chestnut) leaf extract and their anti-proliferative effect on MCF-7 cell line.

Material and Methods: The antioxidant properties of the extract were determined using the total phenolic content, total flavonoid content, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity. In addition, the anti-proliferative effect was determined by XTT method in MCF-7 breast cell line. The leaf extract used was applied at different concentrations for 24 hours, 48 hours and 72 hours and the results were evaluated with the Graphpad Prism software program.

Results: In this study, it was revealed that the total phenolic contents of ethanolic extracts of chestnut leaf 58.22 mg GAE/g. Total flavonoid content was 64.62 mg QE/g. The DPPH activity of the leaf extract of chestnut was 80.06%. Moreover, findings showed that Chestnut leaf extract had cytotoxic effect against breast cancer cells depends on concentration and time. The 24h, 48h and 72h most effective IC50 dose were 100.1 µL ,193 µL 15.23 µL, respectively. The study showed that the ethanolic extract of chestnut has anticancer activity by supporting its antiproliferative effect in MCF-7 breast cancer cells.

Conclusion: Findings from this study indicated that ethanol extract of Castanea sativa leaf could potential as medicinal drug in breast cancer treatment.

Keywords: Antioxidant properties, anticancer, chestnut, *C. sativa*, MCF-7

INTRODUCTION

Cancer is a vast group of diseases which begin a tissue or an organ of the body when uncontrollably dividing cells growing and spread another part of body or organs (1). Cancer caused about 9.6 million deaths at the world in 2018 and mortality rate approximately 20.2% (2). Furthermore, it is predicted that 19.3 million new cancer patients could occur annually by 2025 (3). Breast cancer is affecting one in 20 globally and as many as one in eight in high-income countries (4). Surgery, chemotherapy, radiotherapy, hormone therapy is generally used for cancer treatments, but these have more side effects (5). Drug resistance is one of the most important problems for cancer patients. For this reason, several anticancer and anti-infective agents developed from biologically active plants which are widely used to treat a cancer disease (6), because it has minor side-effects, low cost, and high availability. So, it is thought that plants will continue to be the best source to produce drugs used in the treatment of different diseases in the past, present and future (7).

Secondary metabolites produced by plants are generally responsible for the biological properties of plant species used in the world (8). Compounds such as alkaloids, tannins, flavonoids and phenolics found in plants are therapeutic for human health (9). Antioxidants are important for prevent of several diseases like cancer, malaria, neurodegenerative disease (10). The use of antioxidants obtained from low-cost products obtained

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from forest products in the food, medicine and cosmetics sector is very important in terms of the sustainable use of large amounts of waste that cause environmental pollution and the production of valuable products (11).

Castanea sativa (Chestnut) which important trees because of renowned value in forest and agricultural economy naturally occurs in Turkey (12). Chestnut which are rich in carbohydrates and essential unsaturated fatty acids, starch and minerals contain flavonoids and tannins, with gallic acid as the main phenolic representative of hydrolysable tannins (13). The chestnut shells and leaves rich in bioactive compounds (14). Chestnut leaves are used for curing diarrhea and coughs in folk medicine (15), some studies showed the antioxidant potential of phenolic compounds from shells of chestnut (16). Differences among species/cultivars have shown in various studies (13) and it also shown to chestnuts from different geographic locations (17). Different cultivation techniques (soil, nutrients, minerals, irrigation, diseases and pests), climatic, environmental conditions and storage time influence nutritional composition and quality of chestnut (12).

Polyphenols and flavonoids which are found naturally in various medicinal herbs and dietary plants, have been shown to potent antioxidant, anti-inflammatory, biological effects such as anticancer (18) activities. Polyphenols with a lower molecular weight are thought to have more effective biological activity (19). Plant-based antioxidants and anti-inflammatories can prevent inflammatory disease progression or frequency (20). The antioxidant and anti-inflammatory effects of various plants have recently gained the attention (21). Great interest is about more specific information on the different chestnut cultivars because antioxidant and nutraceutical properties of chestnuts and so more studies will be needed to further support their health benefits (22).

In this context, the possible anticancer effect of dry chestnut bark extract, which has a low molecular weight, on six human cancer cell lines (DU 145, PC-3, LNCaP, MDA-MB-231, MCF-7 and Hep G2) was evaluated. It has been determined that it has an inhibitory effect on viability (14). The formation of triterpenoid saponins in the sweet chestnut heartwood of Chestnut and their potential to chemoprevent breast cancer have been reported to be valuable supplements to prevent such diseases (23). Ethanolic extract of the membrane layer of Chestnut, has more antimicrobial activity compared to the water extract (24). Chestnut wood, bark and leaf extracts have photoprotective, neuroprotective, cardioprotective and antioxidant properties for the prevention of chronic and degenerative diseases (25). Therefore, chestnut leaves are used as treatment for curing cough and diarrhea, and these also have antioxidant properties of phenolics from burs (26) natural ingredients such as plant extracts. So, the aim of this study is to determine the antioxidant properties of ethanol extract of Chestnut leaves and to determine the cytotoxic effect of the extract on human breast (MCF-7) cancer cell lines.

MATERIAL AND METHOD

The study protocol was approved by the Ethics Committee of KTO Karatay University Non- Pharmaceutical and Medical Device Research Ethics Committee (Decision No. 2023–045, dated 31.03.2023). .

Plant material

Chestnut leaves were obtained from local chestnut forest in Türkiye in June 2020. After the plant leaves were dried in the shade, they were made ready for extraction.

Plant extraction

The plant extraction was carried out by Downey et al. (2007) method (27). Chestnut leaves were extracted with orbital shaker at room temperature in the dark. The mixture was filtered with Whatman filter paper no1 and then the clear filtrate was removed from ethanol 70% at 40 °C using a rotary evaporator. The crude extracts obtained were weighed to calculate the extraction efficiency. These extracts were lyophilized with lyophilized device. After that, the extracts were weighed in accordance with the doses and prepared by dissolving in sterile water and stored at + 4°C to be applied to the cells.

Total phenolic content

Total phenolics content of Chestnut was determined by using the methods given in the literature (28) involving Folin–Ciocalteu reagent and gallic acid as a standard with some modifications. The solution of extract (0.25 mL) was mixed with diluted Folin-Ciocalteu reagent (1 mL, 1:9) and shake it vigorously then incubate 3 min at room temperature. After incubation, sodium carbonate solution (0.75 mL, 1%) added in the solution and mixed thoroughly. After a 2 h incubation at room temperature, the sample absorbance measured at 760 nm by Multiskan Sky Microplate Spectrophotometer (Thermo Fisher Scientific). The results were expressed as equivalents of mg catechol/100g of fresh weight material (mg GAE/g).

Total flavonoid content

Aluminum chloride colorimetric method was used to determine the total flavonoid content of Chestnut (29). In order to calculate the total flavonoid, the standard calibration curve was made using quercetin. Quercetin stock solution was dissolved in methanol and serial dilutions ranging from 5–200 µg/mL were prepared from this solution. 0.6 mL of diluted standard quercetin solutions or extract were mixed separately with 0.6 mL of 2% aluminum chloride. All mixtures were then incubated at room temperature for 60 minutes and read against the blank with a Multiskan Sky Microplate Spectrophotometer (Thermo Fisher Scientific) at a wavelength of 420 nm. The concentration of the total flavonoid content of the sample was calculated from the calibration chart (Y = 0.0162x + 0.0044, $R2$ = 0.999) and expressed as mg quercetin equivalent (QE)/g dried plant material. All determinations were performed in triplicate.

Free radical scavenging activity (DPPH)

Chestnut leaf extract was analyzed using a 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical method according to Cheng et al. (2006) (30). A stock solution of DPPH (200 µM) in ethanol was prepared. The reaction mixture containing 100 µL of DPPH and 100 µL of diluted Chestnut in 96-well plates was incubated at 37°C for 30 minutes. Then, absorbance was measured at 515 nm with a Multiskan Sky Microplate Spectrophotometer (Thermo Fisher Scientific). Gallic acid was used as a positive control. The percent DPPH radical scavenging activity was calculated as follows:

$$Percent\ radical\ scavenging\ activity = \left\{1 - \frac{(sample - blank)}{(control - blank)}\right\} \times 100$$

Gallic acid showed 95% radical scavenging activity at 20 µM.

Cell culture

MCF-7 breast cancer cell lines (ATCC® HTB-22™) was obtained from American Type Culture Collection (Rockville, MD, USA). MCF-7 cells were maintained in RPMI 1640 medium which has broad applicability to support the proliferation of MCF-7 cell line. RPMI 1640 medium was prepared by adding 10% Fetal Bovine Serum (FBS) and 0.1% gentamicin. Cells were proliferated at 37°C in a humidified atmosphere of 5% CO2 incubator by changing the medium for every 24 to 48 h. The cells were counted by staining with trypan blue to evaluate whether the cells had grown in sufficient number and cell viability.

Assessment of Cell Viability

The XTT assay was used to measure metabolic activity of chestnut leaf extract exerted inhibitory activity towards the MCF-7 cells. XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) is a tetrazolium-based compound which used to determine a colorimetric detection of viable mammalian cells. The assay is supported to extracellular reduction of XTT compound by NADH via by trans-plasma membrane electron transport and an electron mediator. Cells were seeded (1×10^4 cells/mL), in a final volume of 200 µL, in a 96-well microplate and treated with different concentrations of *C. sativa* extracts (1000, 500, 250,125, 62,5, 31,25, 15,62, 7,81, 3,9, 1,95 µM) for 24h, 48h, 72h. 100 µL of XTT solution (0.25 mg/mL) was added to each well according to the manufacturer's instructions and further incubated for 4h at 37 °C. The absorbance was measured UV-Vis Spectrophotometer (Multiskan Sky Microplate, Thermo Fisher Scientific, Waltham, Massachusetts, ABD). IC_{50} values were calculated with linear regression plots as the sample concentration which resulted in 50% reduction of absorbance compared to controlled (untreated) cells by Graphpad Prism 9.2.0 software (La Jolla, San Diego, CA, USA). Each concentration of *C. sativa* extracts was independently assayed with three replicates.

RESULTS

Total phenolic, flavonoid content and DPPH activity

In this study, it was revealed that the total phenolic contents of methanolic extracts of *C. sativa* leaves 58.22 mg GAE/ g. Total flavonoid content was 64.62 mg QE/ g. The DPPH activity of the leaf extract of *C. sativa* was 80.06%.

Morphological analysis of MCF-7 cells

The optical microscope (Nicon E100, Japan) micrographs shows that morphological changes of MCF-7 cells treated with *C. sativa* leaf extracts and the control group without plant extract applied to cells. The trinocular inverted microscope (Nicon TS2, Japan) at 20x magnification was used to acquire morphological images of MCF-7 cells. The image results showed chestnut extract exhibited morphological changes such as cell shrinkage and cell separation in MCF-7 cells, thereby significantly inhibiting cell proliferation (Figure 1).

MCF-7 cells which were treated with chestnut extract were generally reduced in nuclear dimensions, the prominent round cells than control groups. In addition, there was abundant cell debris in the medium of treated groups (Figure 1 b and d).

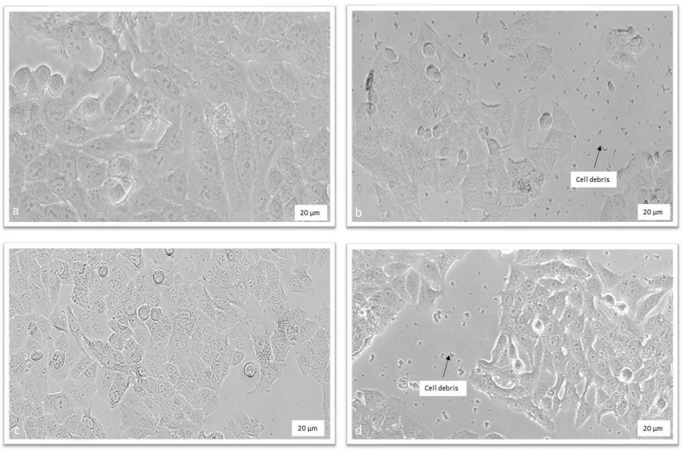

Figure 1. MCF-7 cell line images after treatments with (a) 48h Control group (b) 48h treatment group (c) 72h treatment group (d) 72h control group

Cell viability determination

Cytotoxic effect of *C. sativa* leaf extract on MCF-7 human breast cancer cell line was assessed. Cells were treated with decreasing concentrations of extracts (1000, 500, 250,125, 62,5, 31,25, 15,62, 7,81, 3,9, 1,95 µM) for 24h, 48h, 72h and the cytotoxic effect on cell viability was assessed by XTT assay. Results showed that the extracts possess cytotoxic effect on MCF-7 cell line. Cell viability decreased in a dose and time-dependent manner. The most effective dose in which killed 50% of the cell viability (IC_{50}) was 100.1µL; 193,0 µL; 15,23 µL for 24h, 48h and 72h, respectively.

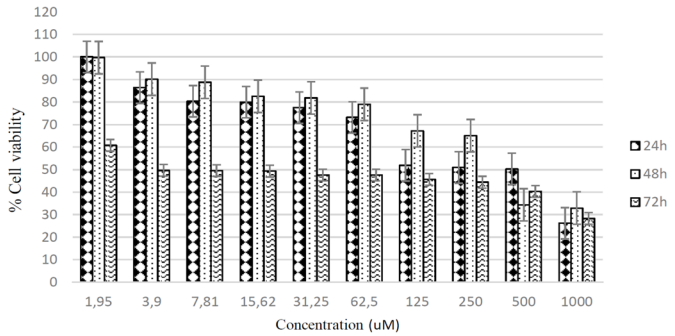

Figure 2. Effect of the *C. sativa* extract on the viability of MCF-7 cells assessed with the XTT assay depend on on 24h, 48h and 72h treatment

MCF-7 cancer cell viability was 50.29 % on 250 µL and 500 µL concentration of chestnut treatment on 24h while it was 26.15% on 1000 µL. Therefore, cell viability was 68.09% on 250 µL concentration and 47.18% on 500 µL concentration on 48h treatment while it was 42.76% on 1000 µL concentration. It was 68.09% on 250 µL; and 47.18% on 500 µL; 42.76% on 1000 µL concentrations of chestnut treatment on 48h. The cell viability was 60.72% on 1,95 µL concentration, 49.66% on 3.9 µL concentration, 49.56% on 81 µL, 49.33% on 15,62 µL conc.47.59% 31.25 µL conc., 47.58% on 62.5 µL concentration, 45.63% on 125 µL concentration, 44.40% on 250µL concentration, 40.34% on 500 µL concentration, and 28.32% on 1000 µL concentration on 72h treatment.

DISCUSSION

Chemotherapy is one of the most common methods for cancer treatment today, but most chemotherapeutic drugs cannot target the cytotoxicity of tumor cells. This situation causes multiple side effects and poor prognosis (31). In order to minimize negative side, studies on natural ingredients such as plant extracts have been used to treat many pathological conditions (6,32,33). The composition of the extracts obtained from plant tissues is related to the extraction procedure and the solvent that was used (34). In many studies, it has been reported that ethanolic extracts are important in revealing compounds with more biologically active compounds than aqueous extracts (35). In this sense several studies supported chestnut has significant antioxidant activity (11,36,37). Therefore, Genovessa et al. (2021) determined that the phenolic content of *C. sativa's* aqueous and ethanolic fruit content of ethanolic extract was 84uM gallic acid and flavonoid content of 16.73 catechin, while the phenolic content of aqueous aqueous extract was 35uM gallic acid and flavonoid content was 5.26uM catechin. The result of the study ethanolic extract of the phenolic and flavonoid compounds are richer than aqueous extract and also the antioxidant activity was that it is high on it. In this study we conducted with chestnut leaf, the total phenolic content was determined as 58.22 mg GAE/g, and the total flavonoid content as 64.62 mg QE/g. These results are in agreement with the study presented above. Polyphenols especially low molecular weight which found in phenolic acid and flavonoid classes (38) are phytochemicals provides powerful biological actions like anticancer activity (19) For this reason, we decided to assess the possible potential anticancer effect of chestnut leaves ethanolic extract on MCF-7 breast cancer cell line. There are various studies in the literature showing the antiproliferative effect of chestnut for different types of cancer (23,25,39). On the other hand, Lenzi et al. (2017), reported that chestnut extract did not have an antiproliferative effect on human T leukemia cells (40). In a study about using the ethanolic extract of chestnut on MCF-7 breast cancer cells, it was suggested that it caused a decrease in the level of ROS in cancer cells and that this extract may have potential anticancer activity (24). Result of the study showed that the ethanolic extract of chestnut has anticancer activity by supporting its antiproliferative effect in MCF-7 breast cancer cells. Besides, studies that chestnut shell extract was able to inhibit cell viability of different cancer cell lines (14).

LIMITATIONS

The limitation of our study is that in vitro studies cannot be predicted based on possible activity in vivo. Due to financial concerns, we could not perform this study in experimental animals with breast cancer. Further research is now required to further understand the full interaction of the relevant signaling pathways.

CONCLUSION

The ethanolic extract of *C. sativa* leaves is already known to be a rich source of phenolic and flavonoid compounds. The antioxidant capacity, total phenolic content, total flavonoid content and data on MCF-7 cells are evaluated as a whole, it is seen that chestnut leaf can be considered as a source of natural antioxidants. In this aspect, the results of the study are a step towards new studies on chestnut. The findings obtained in this study can be concluded that chestnut leaves offer anticancer potential on breast cancer. Based on these findings, chestnut leaves may be helpful against MCF-7 breast cancer cell and further research study may be design for finding the best molecular mechanism behind it.

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Research Article

Can Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios Predict the Risk of Developing New Ischemic Lesions After Carotid Stenting?

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Abstract

Aim: It has been reported that the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are associated with carotid artery stenosis rate, risk of restenosis after stenting, and clinical outcome after an ischemic stroke, and are also predictive markers. The objective of this study is to evaluate whether NLR and PLR values and the associated temporal changes are indicators of the risk for newly developing ischemic lesions.

Material and Methods: Patients who underwent stenting in our clinic between November 2019 and January 2022 and who had a complete blood count and a diffusion magnetic resonance imaging scan before and after the procedure, were included in the study and evaluated in two groups; patients with and without newly developing ischemic lesions.

Results: Newly developing ischemic lesions were detected in 27 of the 50 patients included in the study. There was no difference in baseline and 48th-hour NLR and PLR rates and the temporal variation of these rates between patients with and without newly developing ischemic lesions. Erythrocyte distribution width (RDW) and hemoglobin (HGB) values were higher in the without newly developing ischemic lesions group at 48 hours, but there was only a significant difference between the RDW temporal change between the two groups. In the correlation analysis, no significant correlation was found between NLR, PLR, and their temporal changes, ipsilateral and contralateral stenosis rates, age, and residual stenosis rates.

Conclusion: There was no significant relationship between the development of newly developing ischemic lesions and NLR and PLR values and the associated temporal changes.

Keywords: Carotid stenosis, stents, neutrophil, lymphocyte, platelet, red cell distribution width

INTRODUCTION

Atherosclerosis, a systemic inflammatory disease affecting arterial vessels, is one of the common causes of carotid artery stenosis and ischemic stroke (1,2). Although its incidence varies depending on the etiological classification used, carotid artery stenosis is said to cause 15% of all ischemic strokes and transient ischemic attacks (TIA) on average (2,3).

Current guidelines recommend carotid stenting (CAS) for the treatment of carotid stenosis as an alternative to carotid endarterectomy (CEA) in suitable patients (4). It is known that the frequency of minor ischemic stroke is slightly higher in carotid stenting (4). It is also known that after CAS, new ischemic lesions may develop without clinical signs. The studies that addressed newly onset ischemic lesions developing after the CAS procedure by diffusion magnetic resonance imaging (dMRI) reported the incidence of new lesions in a wide range between 18% and 72% (5,6).

It is known that neutrophils and platelets have an important role in the pathophysiology of atherosclerosis, an inflammatory disease (1,7).

Given that these parameters are an indicator of inflammation and are associated with prognosis, it

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was speculated that evaluating them within the scope of neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) would serve as a better indicator instead of evaluating them individually (8,9). It has been reported that NLR and PLR predict clinical outcomes in many diseases such as cardiovascular, rheumatological and oncological diseases and intensive care unit patients (9,10). Additionally, NLR and PLR were successfully used as a marker in predicting the third-month clinical outcome in acute ischemic stroke (11,12). In studies evaluating the relationship between NLR and PLR values and carotid stenosis rate, plaque morphology, clinical outcome after stenting, and restenosis risk, NLR and PLR values have generally been reported to be good predictive markers (9,13,14).

We could not find a study in the literature that evaluated the relationship between NLR and PLR and the risk of ischemic lesion development after carotid stenting. In the current study, it was aimed to evaluate the relationship between NLR and PLR values and their temporal changes, which were found to be good predictive markers in studies of carotid artery disease ischemic strokes, and the risk of developing newly onset ischemic lesions after carotid stent placement.

MATERIAL AND METHOD

After receiving the ethics committee's approval, the files of patients who underwent carotid stenting at our clinic between November 2019 and January 2022 were retrospectively reviewed (2022/245, 11.10.2022). Patients with symptomatic ICA stenosis of 50% or more and patients with asymptomatic ICA stenosis of 70% or more were included in the study. Of 118 patients who had carotid stenting during the study period, 45 were excluded from the study due to lack of control blood count examination and 23 because control dMRI was not performed, and 50 patients were included in the study. The study comprised patients who were older than 18 and who had undergone a complete blood count and dMRI before and within 48 hours (24-48 hours) of the procedure. Patients who had acute stent insertion, whose data could not be accessed, and who missed their follow-up visits were excluded from the study.

Patients' age, gender, vascular risk factors, stented ICA side, ipsilateral and contralateral stenosis rates, and whether they were symptomatic or not were noted. ICA stenosis rates were calculated from DSA images according to the NASCET method. Patients who had a stroke or TIA on the same side as the stenosis within the last six months were considered symptomatic.

Patients who underwent carotid stenting had been receiving dual antiplatelet therapy (acetylsalicylic acid and clopidogrel or ticagrelor) for at least five days. There were no patients receiving anticoagulant therapy. Statin therapy was initiated in patients with hyperlipidemia. Whether a balloon angioplasty was performed or not, at what stage it was performed and residual stenosis rates were noted. The patients were split into two groups as those with newly developing ischemic lesions and those without newly developing ischemic lesions in the dMRIs at the 48th-hour post-procedure. Entry data of the patients were expressed as NLR1, PLR1 and RDW1, and 48th hour values were expressed as NLR2, PLR2 and RDW2. The temporal variation in these values was specified as NLR2-NLR1, PLR2-PLR1 and RDW2-RDW1.

Statistical Analysis

Data were evaluated with SPSS 21.0 (IBM Corp., Armonk, NY, U.S., 2012) software. Categorical variables as numbers and percentages; numerical data were expressed as mean±standard deviation (SD). Whether the data met the criteria for normal distribution was evaluated with the Shapiro wilk test. Independent sample t-test or Mann-Whitney U test was used to compare two independent groups. Spearmen and Pearson correlation analysis test was used to determine the level and direction of the relationship between dependent variables. Chi-square test was used to evaluate the relationship between categorical variables. Significance level was accepted as $p<0.05$.

RESULTS

Among the 118 patients who had carotid stenting during the study date range, 50 patients who met the inclusion criteria were included in the study. In the 48th-hour dMRI examination, newly developing ischemic lesions were detected in 27 patients (54%), but not in 23 (46%) patients.

Age and gender information, vascular risk factors and procedures-related data of the patients in both groups are given in Table 1. The mean age of the patients with newly developing ischemic lesions was significantly higher than that of the patients without newly developing ischemic lesions ($p=0.017$). The two groups did not differ from one another in terms of other variables.

The data pertaining to the complete blood counts of the patients performed both before and 48 hours after the stenting are given in Table 2. When the postoperative complete blood count data was compared, the HGB2 and RDW2 values in patients with newly developing ischemic lesions were significantly lower than those without newly developing ischemic lesions (respectively $p= 0.032, 0.000$). When the HGB change values were compared between the two groups, no significant difference was found. Comparing the RDW change values, it was discovered that patients without newly developing ischemic lesions had much higher values ($p=0.000$). Between the groups, there was no significant difference in NLR1, NLR2, PLR1 and PLR2 values. In addition, regarding the temporal variations in NLR and PLR values, there was similarly no significant difference between the groups.

In the correlation analysis, no significant correlation was found between NLR, PLR, and their temporal changes, ipsilateral and contralateral stenosis rates, age, and residual stenosis rates (Table 3).

Table 1. Comparison of vascular risk factors, demographic data and procedural data

	New ischemic lesions Yes (27)	New ischemic lesions No (23)	p
Age	71.03±8.02 (54-90)	64.13±11.65	0.017*[1]
Gender M/F (%)	15 (55.6) / 12 (44.4)	18 (78.3) / 5 (21.7)	0.091[2]
HT yes/no (%)	23 (85.2) / 4 (14.8)	14 (60.9) / 9 (39.1)	0.051[2]
DM yes/no (%)	16 (59.3) / 11 (40.7)	8 (34.8) / 15 (65.2)	0.084[2]
HL yes/no (%)	17 (63) / 10 (37)	17 (73.9) / 6 (26.1)	0.408[2]
CAD yes/no (%)	12 (44.4) /15 (55.6)	9 (39.1) / 14 (60.9)	0.704[2]
Previous stroke history (%)	9 (33.3) / 18 (66.7)	6 (26.1) / 17 (73.9)	0.577[2]
Smoker yes/no	12 (44.4) /15 (55.6)	13 (56.5) / 10 (43.5)	0.395[2]
Symptomatic/ asymptomatic (%)	22 (81.5) / 5 (18.5)	18 (78.3) / 5 (21.7)	1.000[3]
Stenosis rate	75.37±12.69(55-90)	79.73±11.44 (61-95)	0.211[1]
Contralateral stenosis rate	27.70±32.96(0-100)	18.69±22.62 (0-80)	0.270[1]
Left/Right	16/11	16/7	0.449[2]
Angioplasty yes/no	18/9	19/4	0.200[2]
Residual stenosis rate	14.22±10.46	11.04±10.65	0.294[1]

HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia,
CAD: coronary artery disease
*p<0.05 [1]Independent Sample T Test, [2]Chi Square test, [3]Fisher Exact test

Table 2. Comparison of the blood count parameters of the patients

New ischemic lesions	Yes	No	p
WBC1 ($10^3/mm^3$)	7.79±1.79	8.32±1.83	0.312[1]
HGB1	12.75±2.02	13.47±1.67	0.181[1]
Neutrophil1 ($10^3/mm^3$)	5.06±1.46	5.19±1.25	0.742[1]
Lymphocyte1 ($10^3/mm^3$)	1.84±.87	2.03±0.82	0.424[1]
Platelet1 ($10^3/mm^3$)	252.37±91.31	242.60±57.72	0.861[2]
RDW1	14.04±1.45	13.61±1.93	0.073[2]
WBC2 (10^3/mm3)	8.92±2.46	8.88±2.16	0.958[1]
HGB2 ($10^3/mm^3$)	11.78±1.29	12.66±1.50	0.032*[1]
Neutrophil2 48th hour ($10^3/mm^3$)	6.02±2.17	6.29±1.76	0.643[1]
Lymphocyte2 48th hour ($10^3/mm^3$)	1.88±0.85	1.64±0.80	0.318[1]
Platelet2 48th hour ($10^3/mm^3$)	230.14±56.91	212.30±81.25	0.368[1]
RDW2 48th hour	13.50±0.77	16.33±3.99	0.000*[2]
NLR1	3.27±1.48	2.96±1.53	0.472[1]
PLR1	163.87±105.47	141.43±61.41	0.633[1]
NLR2	4.68±5.94	4.75±3.60	0.158[2]
PLR2	162.01±108.98	149.54±69.28	0.704[2]
NLR2-NLR1	1.47±6.67	1.79±4.14	0.083[2]
PLR2-PLR1	-1.80±158.42	10.19±94.41	0.397[2]
RDW2-RDW1	-0.55±1.63	2.63±4.57	0.000*[2]

WBC: White blood cells HGB: Hemoglobin, RDW: Red cell distribution width, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio,
*P<0.05 [1]Independent Sample T test, [2]Mann Whitney U test

Table 3. Correlation analysis

Pearson correlation		NLR	PLR	NLR2-NLR1	PLR2-PLR1
Stenosis rate	r	-0.045	-0.167	0.025	0.142
	p	0.758	0.246	0.862	0.325
Contralateral stenosis rate	r	0.153	0.024	-0.139	-0.128
	p	0.287	0.871	0.335	0.374
Residual stenosis rate	r	0.078	0.069	-0.045	0.028
	p	0.589	0.634	0.755	0.845
Age	r	-0.70	-0.46	0.195	0.037
	p	0.631	0.750	0.175	0.796

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio

DISCUSSION

In this study, no significant correlation was found between the development of newly developing ischemic lesions after carotid stenting, pre-procedural and 48th-hour NLR and PLR values, and the temporal changes of these rates.

Hyun et al. (15) reported a significant relationship between carotid intima thickness and NLR values in patients who had suffered a stroke due to carotid artery disease. Corriere et al. (13) reported that there was a significant relationship between NLR values and the detection of plaque in the carotid artery. Jiang et al. (16) reported a significant correlation between the NLR value and the rate of carotid stenosis in patients who underwent digital subtraction angiography (DSA). In our study, however, no significant relationship was observed between the rate of carotid stenosis and NLR.

In another study, Deşer et al. (17) found that NLR and PLR values were significantly higher in patients with >70% stenosis and detected a significant relationship between stroke risk after CEA and increased PLR values. In a study by Varım et al. (14), mean PLR was found to be significantly higher in patients with stenosis greater than 50% in symptomatic patients and more than 80% in asymptomatic patients. In our study, however, no significant relationship was observed between the rate of carotid stenosis and PLR.

Keskin et al. (18) evaluated patients who underwent carotid stenting and reported that there was an independent relationship between mortality and major cardiovascular events and the systemic immune-inflammation index. On the other hand, in the study reported by Zhengze Dai et al. (19), a significant relationship was found between stent restenosis and NLR value in asymptomatic patients, but not in symptomatic patients. Yet in another study, stent restenosis was found to be positively correlated with NLR (20). In our study, only the relationship between silent new ischemic lesions and NLR and PLR was evaluated, and no significant relationship was found.

It is known that the risk of a periprocedural stroke increases in carotid stenting in patients aged over 70 (21). In our study, the mean age of the patients with newly developing ischemic lesions was significantly higher, which was consistent with the literature.

Furere et al. (22) reported a significant relationship between carotid intima media thickness and RDW and concluded that a high RDW value is an indicator of severe carotid atherosclerosis. Similarly, in another study, a significant relationship was found between elevated RDW values and the risk of having a symptomatic plaque (23). Studies that investigated the RDW values in patients who have suffered an ischemic stroke have also reported a relationship between RDW values and the severity and clinical outcome of the stroke (24). In our study, no correlation was observed between RDW and the rate of carotid stenosis. It was observed that the postoperative RDW increase was significantly higher in patients who did not develop new ischemic lesions. Although it is difficult to explain this situation, it may be related to the younger age of the patients who do not develop new ischemic lesions.

Limitations of the Study

Apart from its strengths, such as being the first study that addressed the relationship between the development of newly onset ischemic lesions after the CAS procedure and NLR and PLR values, there were also some limitations, such as its retrospective nature and its relatively small sample size.

CONCLUSION

Contrary to what has been hypothesized initially, no significant relationship was found between the development of newly onset ischemic lesions after carotid stenting and the NLR and PLR values and the associated temporal changes. These findings may be attributed to the retrospective nature of the study and its relatively small sample size. Hence, large-scale randomized controlled studies are needed.

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MEDICAL RECORDS-International Medical Journal

Research Article

Investigation of Insulin-Like Growth Factor 1 Receptor Expression in Sacrococcygeal Pilonidal Sinus

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Abstract

Aim: This study aims to determine the role of IGF-1R in the sacrococcygeal pilonidal sinus (PS) etiology and evaluate the findings regarding its contribution to treatment.

Material and Methods: The general structure of skin and connective tissue components in healthy and lesioned tissue sections of sacrococcygeal PS cases was evaluated by Masson's trichrome staining. In addition, the expression of IGF-1R protein in healthy and pilonidal sinus tissue was determined by immunohistochemical staining.

Results: It was observed that the epidermis of the pilonidal sinus was thinned compared to the healthy area, and the hair follicle structures and connective tissue components deteriorated. IGF-1R expression was significantly decreased in basal keratinocytes in sacrococcygeal PS tissues.

Conclusion: It is thought that IGF-1R may be involved in the etiology of sacrococcygeal PS, and more data is needed in terms of its contribution to treatment.

Keywords: Sacrococcygeal pilonidal sinus, IGF-1R, keratinocytes

INTRODUCTION

Pilonidal sinus is a relatively common dermatological soft tissue disease that affects both the pediatric population and adults (1). It is twice as common in men as in women and is a suppurative condition that usually occurs between the ages of 15 and 30. The pilonidal sinus is formed under the skin of the sacrococcygeal region, and the acute form presents as a tension-generating abscess, while the chronic condition causes intermittent discharge (2). The disease, which is common among young people, significantly affects the quality of life and causes low self-esteem. Despite its partially known pathophysiology and the numerous treatment modalities available, pilonidal cysts still pose a significant problem in general surgery (3).

The pilonidal sinus originates from a congenital skin cleft caused by hair growth (4). The skin covering the sacral pilonidal sinus contains unusually deep hairy papillae. Although the follicles are separate from the sinus, they may be abnormally large, and each may carry more than one hair. None of these features are observed in the sacral skin of normal controls. Many factors affect the hair follicle's growth, and systemic factors such as hormones and environmental factors are some of them (5). A healthy skin and follicle structure (Figure 1/a) is also schematized. Although factors such as BMP, Wnt, and FGF are thought to be effective in hair growth (6), literature information on the role of insulin-like growth factors is negligible.

Epidermal stem cells are keratinocytes located in the basal layer of the epidermis and mediate epidermal homeostasis. Signaling through the insulin-like growth factor (IGF-1) receptor (IGF-1R), IGF-1 has been identified as an essential regulator of rodent skin development and differentiation. However, the role of IGF-1/IGF-1R

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signaling in human keratinocytes is not fully understood. In epithelialization models using human keratinocytes in three-dimensional cultures, it has been observed that loss of IGF-1/IGF-1R signaling causes decreased skin thickness and impaired stem cell homeostasis (7). Loesch et al. demonstrated that IGF-1R controls DNA damage repair genes in human keratinocytes (8).

Although information on skin structure and related skin diseases can be found in the literature regarding IGF-1 and IGF-1R, no data has been found regarding its role in the development of pilonidal sinus. Therefore, while planning our study, we thought that an evaluation of the histopathology of the disease would provide information for future studies on this subject and add new data to the literature. We hypothesized that IGF-1R could also be involved in the etiology of pilonidal sinus and show changes at the tissue level, mainly based on the accepted assumptions on this subject.

MATERIAL AND METHOD

Tissue Preparation

Between 2012 and 2018, sacrococcygeal pilonidal sinus cases were diagnosed with hematoxylin-eosin staining from the excisional skin tissues admitted to the Pathology Laboratory of Bozok University Hospital were evaluated in terms of material adequacy, and tissues with and without lesions were obtained. The experimental groups of our study; Group 1 (n=10): Lesioned regions of sacrococcygeal pilonidal sinus cases diagnosed by excisional skin biopsies, Group 2 (n=10): Tissues from non-lesional areas obtained from excisional skin biopsies of the same patients were formed. The study was initiated with the permission of the Akdeniz University Clinical Research Ethics Committee, numbered 08.03.2023/KAEK-198.

Sections of 5 µm thickness were taken with a microtome from healthy and lesionless areas of sacrococcygeal pilonidal sinus cases and embedded in paraffin. They were placed on a superfrost slide and kept in an oven at 56°C overnight to apply the immunohistochemical staining method.

Immunohistochemical Staining

Sections were rehydrated by passing through xylol and alcohol series (100%, 90%, 80%, 70%) for deparaffinization. To remove antigenic masking, it was boiled in citrate buffer (100244; Merck) and incubated with hydrogen peroxide (18312; Sigma) to remove endogenous peroxidase activity. Sections treated with UV blocking (TA-125-UB Thermo Scientific) to prevent non-specific immunoglobulin binding were incubated with IGF-1R primary antibody (Biocare; sku 414-110917) and appropriate secondary antibody (Vector anti Mouse; BA-9200). After making the reaction visible with DAB chromogen (D4168; Sigma) and counterstaining the sections with Mayer's Hematoxylin (109249, Merck), dehydrated sections were passed through alcohol series (70%, 80%, 90%, 100%), and xylol. After that closed with entellan. In these sections, the expression levels and localizations of the IGF-1R protein in the intact and lesioned tissues of the patients were tried to be determined. In addition, the tissues were subjected to Masson's trichrome staining, a unique connective tissue stain, to make histopathological evaluations between the groups and examine the connective tissue changes. Sections taken on the slide were kept in an oven at 56°C overnight, then deparaffinized and stained following the protocol of Masson's trichrome staining kit (GBL-5022). Sections were passed through an alcohol series and xylol for dehydration and then covered with entellan. Sections by photographing the Olympus CX43 Microscope (Japan) to visualize the localization of the IGF-1R protein.

H-Score Analysing

The marker's immunohistochemical staining power was examined with Histoscore (H-score). H-score was calculated by a semi-quantitative assessment of both the intensity of staining (graded as non-staining; -/+, weak; +, median; ++, strong; +++) using adjacent normal mucosa as the median and the percentage of the positive cells.

Statistical Analysis

The staining of six sections taken for all subjects in each group was repeated three times. Six different areas were photographed on three randomly selected slides for each subject and measured with Image J (1.52 R, National Institutes of Health, USA). The measurements were evaluated with GraphPad Prism 9 (GraphPad Software, USA) using the student t-test. The difference between the groups ($p<0.05$) was considered significant. The drawings in Figure 1 were made using the BioRender medical illustration program.

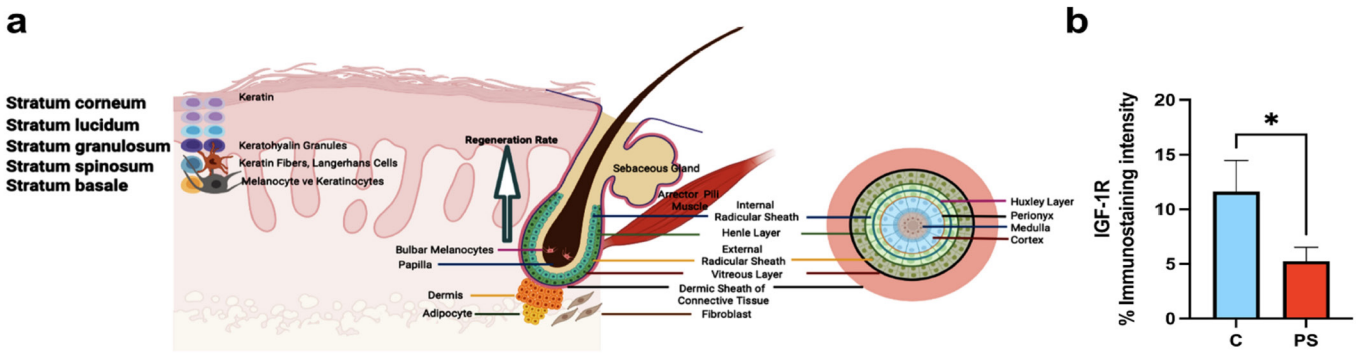

Figure 1. a: Drawing showing a healthy epidermis and the layers of the hair structure and the cells they contain (the author S.A. drew with the Biorender program), **b:** IGF-1R staining intensity graph; C: control, PS: pilonidal sinus

RESULTS

When the general tissue structure is examined with Masson's trichrome staining, the healthy epidermis (Fig.2/a and b) and the pilonidal sinus epidermal area (Fig.2/c) are compared, and a thin epidermis was observed in the PS. With Masson's trichrome staining, the medulla of the healthy hair structure was stained yellow, the sheath structures red, and the collagen fibers blue (Fig.2/a,b). In the PS, blood vessels in the connective tissue (Fig.2/c,d) and muscle/keratin fibrils stained light red (Fig.2/c,d), and collagen fibers stained light blue (Fig.2/c,d) were disorganized and thin in the pilonidal sinus, and draining material in the was located on the epidermal surface (Fig.2/c). Hair sheath structures were also scattered (Fig.2/d) in the PS. Hair follicles and cysts were embedded in the connective tissue in the PS tissues (Fig.2/d).

Immunohistochemically, IGF-1R staining was intense in melanized keratinocytes (Fig.3/a), cells located in the stratum basale in healthy tissues. Melanocytes were negatively stained (Fig.3/a). Staining was weak in gland structures (Fig.3/b). The staining of the basal line keratinocytes in the pilonidal sinus was significantly weakened and was negative in other structures and melanocytes (Fig.3/c). While bulbar melanocytes of hair follicles expressed IGF-1R in the healthy follicle (Fig.3/b), staining intensity was decreased in pilonidal sinus follicles (Fig.3/d). IGF-1R tissue staining intensity of pilonidal sinus cases was significantly reduced when compared to healthy skin ($p<0.05$) (Fig.1/b). The staining power of the markers of the examined tissues is shown in (Figure 4).

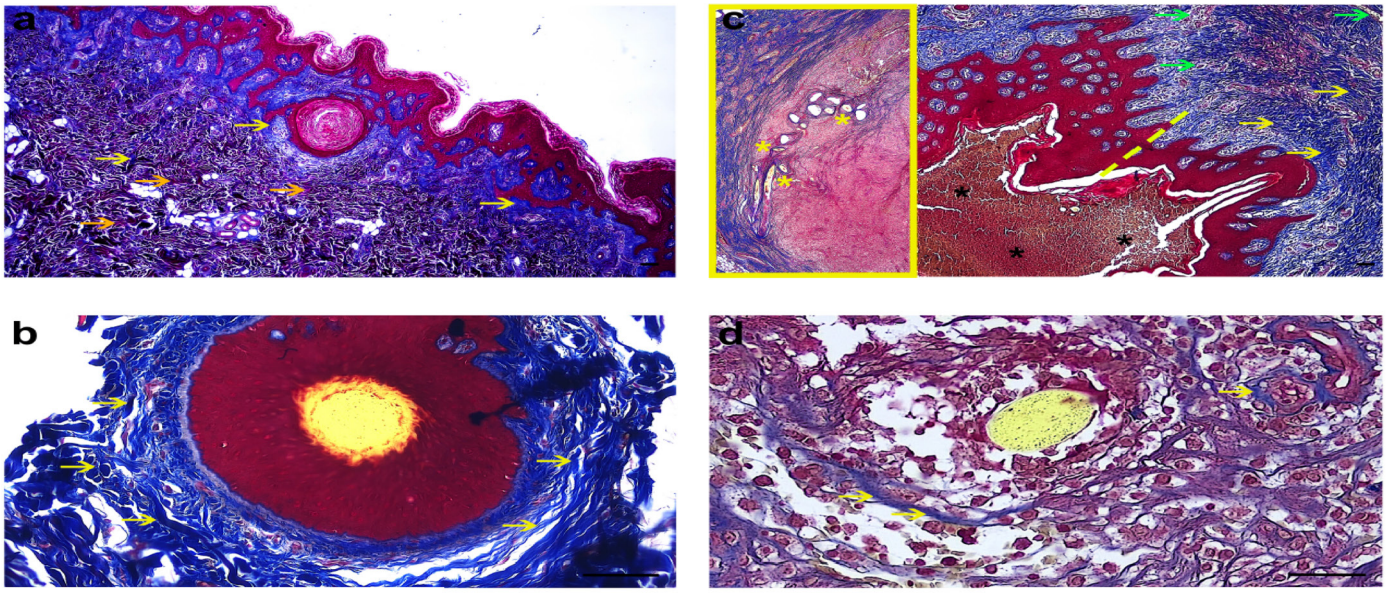

Figure 2. Masson's trichrome staining (a-d): over the yellow line; healthy skin, below the yellow line; epidermal area of pilonidal sinus, green arrows; blood vessel, orange arrows; muscle/keratin fibrils, yellow arrows; collagen fibers, black asterisks; inflammatory draining material, yellow asterisks; hair follicle and cysts, N: negative control, magnification; 5x,20x, scale bar; 50uu

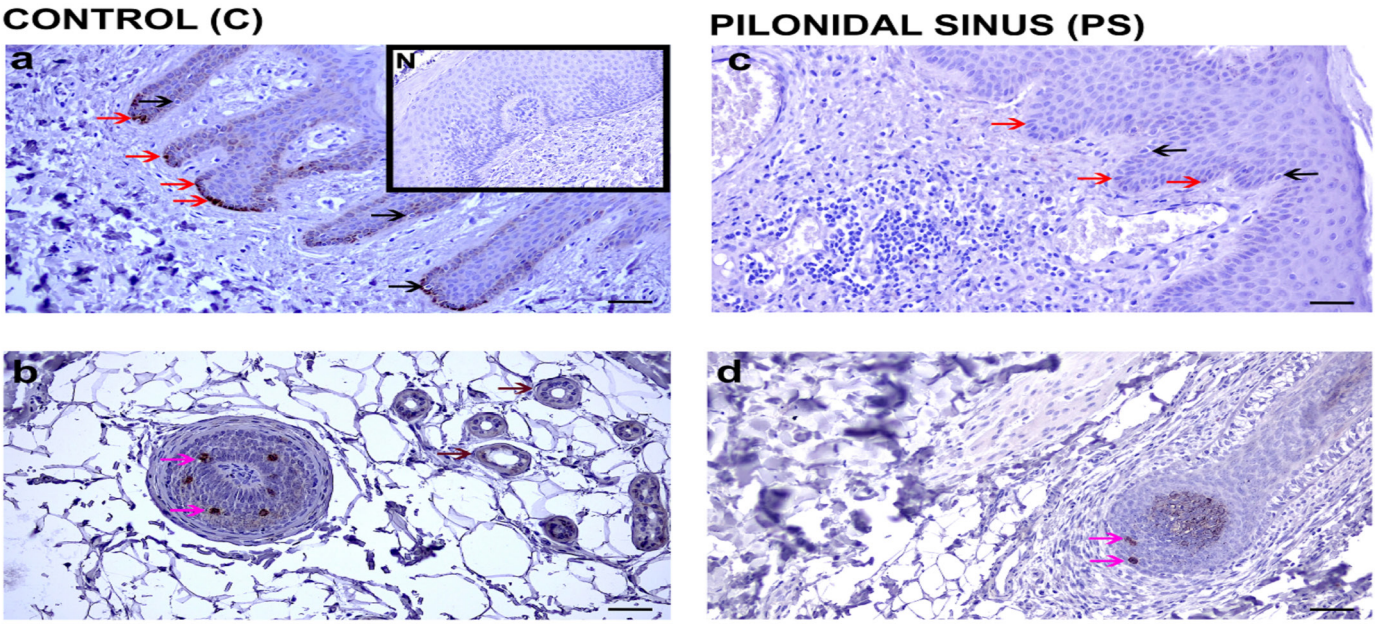

Figure 3. Immunohistochemical staining of IGF-1R (a-d): red arrows; melanized keratinocytes, black arrows; epidermal melanocytes, pink arrows; bulbar melanocytes, brown arrows; gland structures, N: negative control, magnification; 20x, scale bar; 50uu

H-SCORE		Control	PS
IGF-1R	Epithelium	(++)	(-)/(+)
	Keratinocytes	(+++)	(-)/(+)
	Melanocytes	(-)/(+)	(-)/(+)
	Muscles	(+)	(-)/(+)
	Glands	(+)	(-)/(+)
	Stroma	(++)	(+)
Masson's Trichrome Staining	Keratin	(+++)	(+)
	Collagen	(+++)	(++)
	Hair follicle	(+++)	(++)

Figure 4. Immunohistochemical staining power of markers (H-Score): non-staining; -/+, weak; +, median; ++, strong; +++

DISCUSSION

Pilonidal name; comes from the Latin pilus, meaning "hair," and nidus meaning "nest". The term "pilonidal disease" was coined by Hodges in 1880. It was defined by Mayo in 1833 and Anderson in 1847. During the wars, many US soldiers were diagnosed with the pilonidal disease, which has long been associated with driving, also known as "Jeep disease" (1). It was also named a sacrococcygeal cyst, often considering the congenital etiology of the disease (9).

In addressing the pathogenesis of pilonidal sinus disease, Karydakis attributed the hair regrowth process to three main factors: invasive, loose hair growth, a repulsive force that causes hair to settle, and the skin area around the birth cleft being too weak to prevent hair penetration. The sinus begins from a small midline opening lined by stratified squamous epithelium, and it is characterized by abscesses containing a sinus, hair, a cystic cavity lined with epithelial tissue, and a blunt-ended channel lined with granulation tissue (10). Loose hairs entering the subcutaneous tissues at the gluteal cleft are believed to cause foreign body response (11). Neutrophils and leukocytes are the structures found around abscesses in plasma cells and sometimes macrophages (10).

Although it is frequently seen in the sacrococcygeal region, it can sometimes be seen in the armpit, groin, between the fingers, navel, nose, breast area, suprapubic region, clitoris, foreskin, penis, occiput, and feet. In the sinus, the force from rubbing the skin at the base of the spine causes the hairs to sink below the surface. The hair forms small cavities or pits, enlarged hair follicles that become sinuses. Bacteria and debris enter this sterile area, causing local inflammation and the formation of pus-filled abscesses. In the chronic condition, the sinus becomes an open cavity that constantly drains a small amount of fluid (12).

Although there are many surgical techniques for treatment, no single method provides therapeutic success (3). It is widely believed that the ideal scenario in treating pilonidal sinus should be a technique with minimal excision, a low recurrence rate, a short hospital stay, a rapid return to normal life, and minimal scarring with minimal work loss (13). Moreover, It stands out in studies that indicate that extensive surgical procedures such as Z-plasty, rotated flap, or wide excision are unnecessary. There are studies advocating the view that marsupialization, which is a simple and accurate technique, gives excellent results with minimal recurrence (9).

After infection, the hair may penetrate the sinus wall or remain outside the sinus (14). Stelzner used light microscopy to indicate that hairs from pilonidal pits have a hook structure and suggested that hair migration is unidirectional. Dahl et al. confirmed the hook morphology and showed that the proposed sharp tips contribute to hair puncturing the skin, meaning hook formation prevents retraction. Gosselink et al. On the other hand, he states that the direction of the hair scales probably encourages the hair to be driven deeper into the tissue (15-17).

The hair, which is one of the skin appendages, and the hair follicle to which it is attached develop from hair follicle stem cells, which undergo growth, regression, and rest periods under the influence of external and internal factors and constitute one of the most typical examples of the stem cell niche. Hair growth cells surround the dermal papilla, and the crosstalk between mesenchymal cells and epithelial cells begins during embryogenesis when hairs first appear. After the first hair follicle is formed, the lifelong cycle of construction and destruction begins (5). Although there is information in the literature that pilonidal sinus formation is associated with structural weakness and skin inflammation, there is not enough data on the role of IGF-1R. For this reason, studies that will contribute to clarifying its histopathology will contribute to discovering unknown aspects. Our research observed that the connective tissue structure in which the hair follicle was located weakened, and the epidermis structure was thinned in the sinus region. Our findings support the hypothetical mechanism considering that proinflammatory cells are involved in this area.

The cells found in the stratum basale, located at the base of the epidermis layers of the skin, are cuboidal and mitotically active stem cells that continuously produce keratinocytes. Keratinocytes are the predominant cell type of the epidermis and originate from the basal layer, produce keratin, and are responsible for forming the epidermal water barrier by making and secreting lipids. Keratinocytes also have roles such as vitamin D synthesis and calcium absorption via UVB light activation. This layer also contains melanocytes. Melanocytes are derived

from neural crest cells. They are located between the cells of the stratum basale and produce melanin, which is associated with skin pigmentation. Long processes transfer melanin granules from melanocytes into the basal keratinocyte cytoplasm. Melanin is transferred to neighboring keratinocytes by "pigment donation" (18).

One of the vital growth factors found in the skin layers is insulin-like growth factor (IGF) (19). The IGF system contains three ligands (IGF-1, IGF-2, and insulin) belonging to a phylogenetically ancient peptide family involved in mammalian growth, development, metabolism, and cellular processes such as proliferation, survival, cell migration, and differentiation (20). IGF-1 is the primary regulator of longitudinal growth. IGF-2 is expressed in many tissues to regulate human pre-and and postnatal development (21). Deviations in the system of IGF-1, which has a high structural similarity to insulin, can be associated with various pathological conditions, including cancer. Insulin and its synthetic analogs are known to have IGF-IR binding affinity and mitogenic potential (22). IGF-1R has also been shown to interact with estrogen receptor signaling and cell-cell adhesion complexes (23). In BALB/c-3T3 fibroblasts, IGF-1 is required for cell cycle progression from G1 to S (DNA synthesis) phase, and its stimulatory role in cell proliferation is well established (24). It has been reported that epidermal basal keratinocytes are IGF-1 negative but IGF-IR positive. IGF-1 is thought to be an autocrine regulator of epidermal differentiation. The distribution of IGF-1R in the hair follicle indicates that they may be a morphogen rather than a mitogen in these regions because the IGF-IR of proliferating cells, not differentiated cells, is negative. Also, the expression of IGF-1R by the dermal papilla appears to be turned off during the transition from anagen to catagen. This implies a regulatory role for IGF-1 during the hair cycle (25). IGF-1 mRNA is expressed in the stratum granulosum of the epidermis and by dermal fibroblasts.

In human skin, epidermal keratinocytes do not express IGF-1, IGF-1R in keratinocytes is activated by IGF-1 secreted from dermal fibroblasts. Expression of IGF-1 is silenced in aged fibroblasts in vitro, and IGF-1 may be an essential component in the development of aging-associated non-melanoma skin cancer. Decreased expression of IGF-1 in aging skin is associated with an inappropriate UVB response in geriatric cases (26). In addition, mice's skin and epidermis layers carrying the gene mutations encoding IGF-1R are much thinner than the wild type. IGF-1/IGF-1R signaling plays a critical role during development. IGF-1 knockout mice die soon after birth, and these animals' skin barrier function and hair formation are impaired. In addition to a thinner skin formation, skin abnormalities are observed, including an impaired epidermis structure (27). Epidermal thickening develops in patients with acromegaly. It is thought that this situation may be related to promoting keratinocyte proliferation due to the increased secretion of IGF-1 mediated by growth hormone (28).

In studies of different systems, the hypothesis that insulin/IGF-1 signaling is involved in chronic inflammatory processes was demonstrated by Partridge et al. in insulin receptor substrate-1 deficient mice fully protected from age-related ulcerative dermatitis (29). Studies also strongly support the concept that IGF-1R activation in monocytes/macrophages controls the balance between proinflammatory and non-inflammatory macrophage populations during the development of skin inflammation (30).

When our study findings are evaluated together with the literature information mentioned above, It shows that IGF-1R is intensely expressed in healthy tissue, especially in keratinocytes. Keratinocytes have been associated with the modulation of UVB and skin aging in studies related to cancer. It appears to be important in maintaining a healthy skin structure. Moreover, IGF-1R is essential in keeping skin thickness, and the downregulation of its expression results in thin skin texture. We can say that we support Karydakisin's statement that a vulnerable skin structure and an impaired hair organization hypothetically play a role in the hair-settling process in pilonidal sinus formation. Because in our study, it was observed that IGF-1R, which is predominantly expressed in keratinocytes, is depressed in the pilonidal sinus, and maintaining a healthy skin structure may be interrupted in this case. Again, it can be said that this situation may support the formation of weak hair structure by disrupting the growth, production, and destruction diagram of the hair. On the other hand, this deterioration in growth factors is thought to be closely related to the worsening of epithelial organization and sinus formation. It has also been suggested that the IGF-1R receptor, which plays a role in the inflammatory process, may support an impaired anti-inflammatory response in these patients. We believe that a clear decision on whether IGF-1R replacement applications will improve the process in these patients can be made with more studies on the effects of IGF-1R.

CONCLUSION

In summary, when all findings and literature information are combined, it is thought that IGF-1R depression may be involved in the formation of the sacrococcygeal pilonidal sinus concerning the deterioration of the general organization of basal keratinocytes and the skin. However, more studies are needed on whether IGF-1R replacements can contribute to treatment.

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MEDICAL RECORDS-International Medical Journal

Research Article

Classification of Bovine Cumulus-Oocyte Complexes with Convolutional Neural Networks

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Abstract

Aim: Determining oocyte quality is crucial for successful fertilization and embryonic development, and there is a serious correlation between live birth rates and oocyte quality. Parameters such as the regular/irregular formation of the cumulus cell layer around the oocyte, the number of cumulus cell layers and the homogeneity of the appearance of the ooplasm are used to determine the quality of the oocytes to be used in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) methods.

Material and Methods: In this study, classification processes have been carried out using convolutional neural networks (CNN), a deep learning method, on the images of the cumulus-oocyte complex selected based on the theoretical knowledge and professional experience of embryologists. A convolutional neural network with a depth of 4 is used. In each depth level, one convolution, one ReLU and one max-pooling layer are included. The designed network architecture is trained using the Adam optimization algorithm. The cumulus-oocyte complexes (n=400) used in the study were obtained by using the oocyte aspiration method from the ovaries of the bovine slaughtered at the slaughterhouse.

Results: The CNN-based classification model developed in this study showed promising results in classifying three-class image data in terms of cumulus-oocyte complex classification. The classification model achieved high accuracy, precision, and sensitivity values on the test dataset.

Conclusion: Continuous research and optimization of the model can further improve its performance and benefit the field of cumulus-oocyte complexes classification and oocyte quality assessment.

Keywords: Cumulus-oocyte complexes, convolutional neural networks, classification, oocyte quality

INTRODUCTION

Infertility is a reproductive issue affecting millions of people worldwide (1). IVF and ICSI methods, which are applied in the centers of Assisted Reproductive Technologies (ART) are among the most common treatment methods for infertility today. These methods also used in animal breeding and biotechnology centers. After ovulation induction under clinician supervision, oocyte aspiration is performed on the day determined by the clinician for obtaining oocytes to be used in IVF and ICSI methods. The collected oocyte(s) are examined microscopically by the embryologist. High-quality oocytes are selected for fertilization based on various criteria and morphological classifications. Oocyte quality is crucial for successful fertilization and embryonic development (2). There is a serious correlation between oocyte quality and live birth rates. In order to select high-quality oocytes to improve the ability to select the best single embryo with the highest implantation potential, minimize the likelihood of multiple pregnancies due to multiple embryo transfers, increase pregnancy rates, and achieve an increase in live birth rates, oocyte classification must be done without causing doubt. In determining the quality of oocytes to be used in IVF and ICSI methods, morphological parameters related to

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the cumulus-oocyte complex structure, oocyte cytoplasm, polar body, meiotic spindle properties, perivitelline space, and zona pellucida can be used (3).

Cumulus cells are critical for oocyte maturation, ovulation, and fertilization (4). Many studies have shown that the presence of cumulus cells is a requirement for oocytes to gain developmental abilities in vitro. Cumulus cells also support energy production in the cumulus-oocyte complex (5) and play a role in protecting oocytes from damage that reactive oxygen species (ROS) can cause (6). Recent studies suggest that the mitochondrial function of cumulus cells can directly affect the reproductive capacity (7,8). The number of cumulus cell layers surrounding the oocyte is an essential factor in determining oocyte quality (4). Oocyte quality is generally evaluated based on the structure of cumulus-oocyte complexes. This method is simple and provides information about oocyte quality. Embryologists and researchers evaluate the cumulus-oocyte complex by looking at parameters such as the regular/irregular formation of the cumulus cell layer around the oocyte, the number of cumulus cell layers, and the homogeneity of the ooplasm's appearance (9,10). They use their theoretical knowledge and professional experience to select the most ideal oocytes.

However, the professional experience required for oocyte selection, which is heavily based on subjective opinions, is a challenging and time-consuming process. Although the observational experiences accumulated cumulatively over the years are precious, human error margins, time-consuming protocols, and high-cost equipment encountered in every traditional method cannot be ignored. ART methods have significantly improved over the past 30 years but success rates have not reached desired levels and remain relatively low. Minimizing human intervention in oocytes and embryos, increases the viability of these highly sensitive cells and reduces the rate of human errors.

In recent years, machine learning (ML) methods have been widely used in biomedical imaging. ML is the field of study that gives computers the ability to learn from data without explicitly writing code (11). ML gives computers the ability to "learn from experience," a trait naturally found in humans. Machine learning algorithms use computational methods to "learn" information directly from data without relying on a predetermined equation model. As the number of samples available for learning increases, the algorithms adaptively improve their performance. ML is fundamentally about predicting the future based on past experience (12,13).

Convolutional Neural Network (CNN) is a specialized form of ML methods, is a very important tool for medical image classification. This method is widely used for classifying images obtained from various medical imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (USG), and microscopic imaging. By its nature, CNN has image-shaped inputs and automatically performs feature extraction from images (11,14). Upon reviewing these studies, almost all of them focus on segmenting oocytes, and the studies addressing the classification problem using CNN are quite insufficient.

The classification of medical images with highly detailed structures is often a time-consuming and high-attention task, making it prone to human errors. The classification success may vary depending on the workload and experience of the staff performing the classification. However, artificial intelligence methods like CNN, which can learn from data, can perform classification tasks faster and with higher accuracy rates. We believe that an artificial intelligence approach trained on hundreds of oocytes can reliably predict classification of cumulus-oocyte complex and oocyte quality without human intervention. In our literature review, we have not come across a study classifying the cumulus-oocyte complex, an important criterion in determining high-quality oocytes to be applied in ART procedures, using artificial intelligence methods.

This study is expected to be a pioneering study in the literature and lay the groundwork for the integration of artificial intelligence into ART. The image data obtained of this study will be useful in increasing the originality and sensitivity of future studies on this subject and will shed light on scientific research.

MATERIAL AND METHOD

Oocyte Aspiration and Collection of Cumulus-Oocyte Complexes

This study was conducted with the approval of the Ege University Animal Experiments Local Ethics Committee, numbered 2021-045, stating that ethical committee approval is not required according to the Ministry regulations. Ovaries were obtained as waste material from animals slaughtered for human consumption at various commercial slaughterhouses in accordance with international meat production guidelines.

Ovaries collected at different times were placed in thermos flasks containing a transport medium immediately after slaughter and brought to the laboratory within a maximum of 3 hours. Sterile PBS, adjusted to a temperature of 20-25°C and supplemented with Penicillin (50-100 IU/ml) and Amphotericin-B (50 ng/ml), was used as the transport medium. The transport medium was freshly prepared for each study. The ovaries brought to the laboratory were washed twice with 0.9% NaCl to remove blood and transport medium and then dried with a drying paper before proceeding to the aspiration process. Follicles with a diameter of 2-10 mm in the ovaries were aspirated with 5-10 ml sterile needle-tipped syringes varying in thickness from 26-20-Gauge (Ayset, Adana, Türkiye; Berika, Konya, Türkiye; Beybi, İstanbul, Türkiye). The follicular fluid obtained by aspiration was collected in 50 ml Falcon tubes. The tubes containing the collected follicular fluid were left at room temperature for 20 minutes to allow the cumulus-oocyte complexes to settle at the bottom. At the end of this period, the cumulus-oocyte complexes that settled at the bottom of the tube in the follicular fluid were taken with the help of a Pasteur pipette and transferred to 90x15 mm Petri dishes (Figure 1).

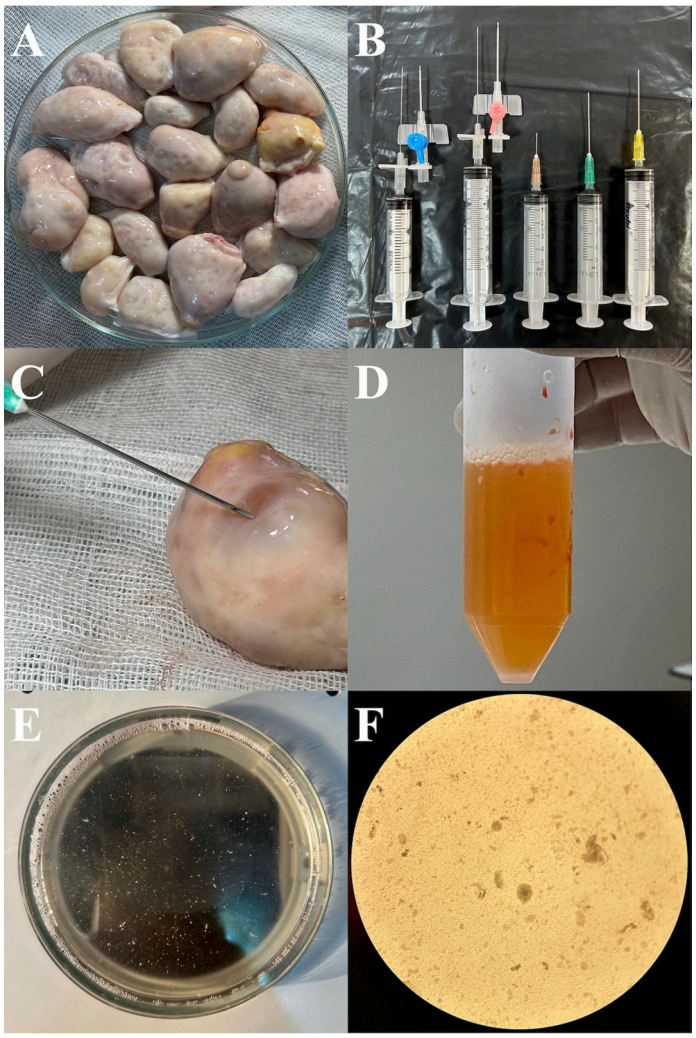

Figure 1. Obtaining cumulus-oocyte complexes from bovine ovaries with photographs from current study **A.** Specimens from bovine ovaries **B.** Injectors with various needle sizes **C.** Aspiration process **D.** Aspirated material in Falcon tube **E.** Examination under a stereo microscope **F.** Imaging and analysis

Cumulus-Oocyte Complex Classification

A total of 400 cumulus-oocyte complexes were classified under the Olympus SC50 digital camera attached to the Olympus SZ61 Stereo Microscope with WHSZ10X-H/22 eyepieces. The classification was performed by embryologists on the research team, considering the number and appearance of cumulus cell layers surrounding the oocyte and the characteristics of the oocyte and oocyte cytoplasm, based on the features described in the literature (15-17). Accordingly: Cumulus-oocyte complexes surrounded by at least five layers of compact cumulus cells, with transparent, homogeneous, and bright cytoplasm were classified as Good Quality (Category A) (n=100). Cumulus-oocyte complexes surrounded by 3-5 layers of compact cumulus cells, with slightly granular, dark-colored cytoplasm were classified as Medium Quality (Category B) (n=100). Cumulus-oocyte complexes surrounded by 1-2 layers of sparse irregular cumulus cells, with granular, dark-colored cytoplasm were classified as Poor Quality (Category C) (n=100) (Figure 2).

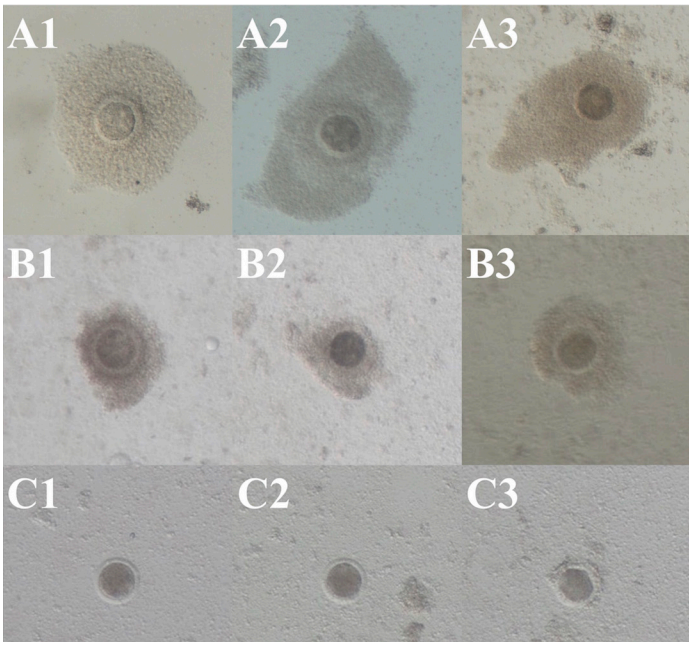

Figure 2. The classification of cumulus-oocyte complexes with representative images from the training set **A1-3.** Good quality (category A) **B1-3.** Medium quality (category B) **C1-3.** Poor quality (category C)

Data Set

For the preparation of data sets to be used in artificial intelligence training, digital images of each cumulus-oocyte complex in categories A, B, and C were obtained with one hundred images per category. To test and evaluate the performance of the deep learning method, 100 cumulus-oocyte complexes, which were never used in artificial intelligence training, were classified by embryologists on the research team, considering the features described in the literature (15-17), and their digital images were obtained from the images taken with the the stereo microscope.

Cumulus-Oocyte Complex Classification with Convolutional Neural Networks

In this study, the classification process was performed using convolutional neural networks on images divided into 3 different classes. 75% of the 400 images from different classes were used for the training of the designed CNN model, while 25% were used for testing. In the training set, there were 100 images for each of the classes A, B, and C, while in the test set, there were 34 images for class A and 33 images for classes B and C. Sample images from different classes are given in Figure 3 below.

The CNN architecture used in the study for classifying images is given in Figure 4 below. The designed architecture has an input size of 128x128x3 and an output consisting of 3 neurons. The Rectified Linear Unit (ReLU) activation function was used as the activation function for each convolutional layer in the architecture, which consists of 4 convolutional layers. A max-pooling layer was used after each convolutional layer in the architecture, and a fully connected layer consisting of 128 neurons was placed between the last convolutional layer and the output layer. The CNN model training was carried out with the ADAM

optimization algorithm in 200 epochs, and the batch size was set to 64.

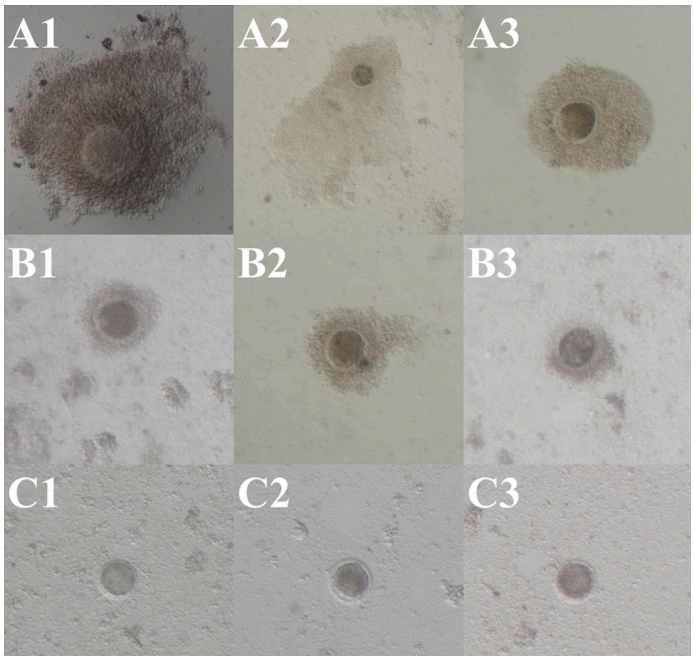

Figure 3. Sample images from the test set representing the classification of cumulus-oocyte complexes as good quality (A1-3). medium quality (B1-3), and low quality (C1-3)

In this study, data augmentation was performed on the training set to prevent overfitting and achieve better performance by increasing the relatively small number of data for deep CNN model training. For the test set, only original images were used. The data augmentation process was carried out within the flow shown in Figure 5 below. Each image follows the process shown in Figure 5 before being applied to the network for training. During the augmentation process, horizontal and vertical flip operations are applied to the images with a probability of p=0.5. Then, after performing a rotation operation with a random angle between -30 and +30 degrees, the brightness of the image is changed with a random coefficient between 0.5 and 1.5. Finally, each color channel of the images is shifted randomly between -20 and 20. This process can help the model generalize more broadly against color changes by altering the color distributions of the images.

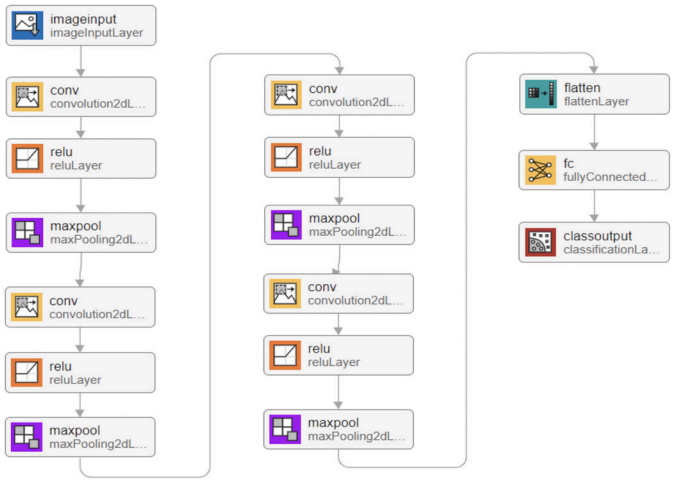

Figure 4. Proposed CNN model

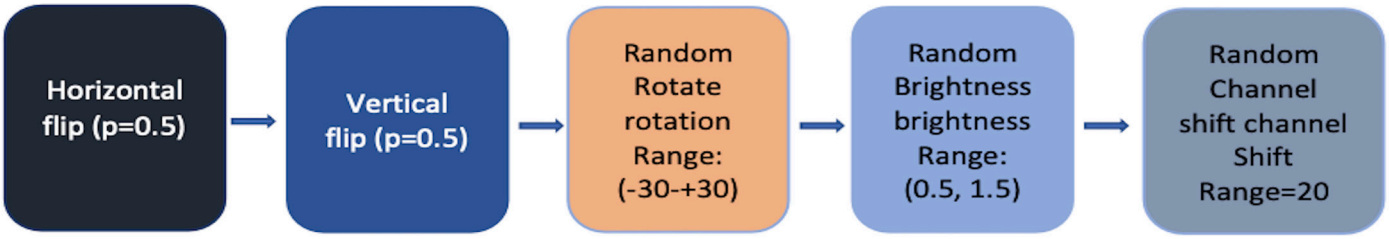

Figure 5. Data augmentation process

RESULTS

The confusion matrices obtained for the test set are given in Table 1. According to the confusion matrix, the model made 32 correct predictions for Class A, with only 2 incorrect predictions. For Class B, 24 correct predictions were made, while 7 and 2 incorrect predictions were made for Class A and C, respectively. Finally, 32 correct predictions were obtained for Class C, and only 1 incorrect prediction was made for Class B.

Table 1. Confusion matrix for the test set

Confusion matrix				
		Predicted		
Class		A	B	C
Actual	A	32	0	2
	B	7	24	2
	C	0	1	32

It can be seen that the CNN model is successful in classifying 3-class image data. High accuracy rates were obtained especially for Class A and C, while an acceptable accuracy rate was achieved for Class B. These results indicate that CNN-based classification methods are reliable and effective tools for oocyte quality and classification.

Table 2 presents the precision, recall (sensitivity), and accuracy metric measurement results calculated using the confusion matrices. In this study, the performance of the classification model on data belonging to three different classes was evaluated. The model's success was measured using accuracy, precision, and sensitivity metrics. The accuracy value obtained on the test set was calculated to be 0.8800.

The precision values calculated for Class A are 0.8205; for Class B, 0.9600; and for Class C, 0.8888. These results show that the model makes predictions with the highest

precision value for Class B and the lowest precision value for Class A. The macro average of precision values was found to be 0.8898.

Table 2. Metric measurement results

Metrics	A	B	C	Macro average
Precision	0.8205	0.9600	0.8889	0.8898
Recall	0.9412	0.7273	0.9697	0.8794
Overall accuracy			0.8800	

Sensitivity values were calculated as 0.9412 for Class A, 0.7273 for Class B, and 0.9697 for Class C. The model detects true positives with the highest sensitivity value for Class C and the lowest sensitivity value for Class B. The macro average of sensitivity values is 0.8794.

DISCUSSION

Human ART and animal reproductive technologies have been developing intensively, especially in recent years. For both species, gamete cells are of particular importance as the focus of reproductive biotechnologies. All processes, from in vivo derivation of cumulus-oocyte complexes to in vitro maturation of oocytes, and from fertilization to live birth were human-dependent (15). The integration of artificial intelligence into ART, where success is highly proportional to the knowledge, experience, and manipulation abilities of human beings, has been developed with innovative results. However, the human dependence persists, and there remains a need to develop artificial intelligence applications in reproductive biotechnologies for both humans and animals. In addition, considering the acceleration of the livestock industry of economically valuable animals or the improvement of their products, and the protection of rare species and animal welfare, the magnitude of the need for artificial intelligence applications to be integrated into animal reproductive technologies can be understood in order to make rapid and effective results commercially viable (18).

The process of distinguishing those with the highest viability among oocytes and embryos is based on the analysis of their morphological criteria. Attempts to characterize morphological features associated with oocyte/embryo quality to produce a full-term pregnancy have long been significant, but limited success due to several reasons remains a major barrier. While cellular and molecular analyzes can provide new clues for defining more objective criteria of quality, many of these approaches are incompatible with cell viability (19).

Artificial intelligence applications that minimize human intervention and have the potential to self-develop the established standards and can be applied directly in vivo or in vitro have become essential for acquiring competent oocytes/embryos. Due to the recent acceleration in the capacity to extract tissue descriptors from a given image, there has been increasing interest in the use of artificial intelligence-based methods that select oocyte/embryo by scoring over digital images. Firuzinia et al. and Targosz et al. have performed oocyte segmentation using pretrained networks, Resnet and MobileNet (20-21). Similarly, Athanasiou et al. have carried out oocyte segmentation using U-net (22). Raudonis et al. designed a 5-class model using AlexNet and Vgg16 to classify embryos based on the number of cells within the embryo in their study (23). Kragh and colleagues predicted the inner cell mass (ICM) and trophectoderm (TE) grades from a single frame in time-lapse imaging using CNN (24). Monge and Beltran classified seven distinct species of avian Eimeria oocytes using their designed CNN (25).

To the best of our knowledge for the first time in the literature, the images of cumulus-oocyte complexes selected based on the theoretical knowledge and professional experience of embryologists were classified using CNN, a deep learning method, which has 4 depths, has convolution, ReLU and maximum pooling layer at each depth level, and has a designed network architecture trained with Adam optimization algorithm. The results obtained from the classification model developed in this study were aimed to demonstrate the effectiveness of the CNN-based approach in categorizing image data divided into three classes, especially related to oocyte quality and classification.

As shown in Table 1, our results demonstrate the effectiveness of the CNN-based approach for this application, as the model achieved high accuracy rates for Class A and C, and an acceptable accuracy rate for Class B. This indicates that CNN-based classification methods are reliable and effective tools for such applications. Analyzing the performance metrics presented in Table 2, the model's precision and sensitivity values were evaluated for each class. The highest precision value was achieved for Class B, whereas the lowest precision value was observed for Class A. This suggests that the model is more likely to make accurate predictions for Class B, while improvements can be made for Class A. The sensitivity values revealed that the model detects true positives with the highest sensitivity for Class C and the lowest sensitivity for Class B. This indicates that the model can effectively identify true positives for Class C, but has room for improvement in detecting true positives for Class B. Despite the high accuracy, precision, and sensitivity values obtained on the test dataset, the lower sensitivity for Class B and lower precision for Class A indicate that further refinements are required for these classes. Nevertheless, the overall performance of the current model indicates the potential of CNN-based methods as reliable and effective tools for tasks involving oocyte quality assessment and classification.

Due to the limited number of studies, this study is expected to make a significant contribution to the literature. The dataset obtained from this study will fulfill the needs required in this field. However, reviewing the sample size and class balance of the dataset should be considered for future studies to enhance the model's performance. This may involve increasing the number of

samples for underrepresented classes, ensuring a more balanced dataset, and potentially improving classification performance. Additionally, exploring feature engineering methods could lead to more accurate and reliable classification results. Investigating various preprocessing techniques, such as image augmentation, denoising, and normalization, may improve the model's ability to extract relevant features from the image data. Furthermore, the implementation of different CNN architectures or the use of ensemble methods might also enhance the model's performance (26).

In summary, our CNN-based classification model demonstrated promising results in classifying three-class image data related to oocyte quality and classification. While improvements can be made for specific classes, the overall performance of the model indicates that CNN-based approaches are reliable and effective tools for such tasks. Continued research and optimization of the model can further enhance its performance, ultimately benefiting the field of oocyte quality assessment and classification.

CONCLUSION

The classification model developed in this study achieved high accuracy, precision, and sensitivity values on the test dataset. However, it is important to note that the model shows lower sensitivity for Class B and lower precision for Class A. This indicates that further improvements are needed for these classes. In future studies, reviewing the sample size and class balance of the dataset and considering feature engineering methods might be beneficial to further increase the model's performance.

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Conflict of Interest: *The authors declare that they have no conflict of interests.*

Ethical approval: *This study was conducted with the approval of the Ege University Animal Experiments Local Ethics Committee, numbered 2021-045, stating that ethical committee approval is not required according to the Ministry regulations.*

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Author's Contribution: *Conception of the study: C.Ş., K.D.K., C.T., A.G., T.Ç. Acquisition of study materials: C.Ş., K.D.K., C.T., A.G. Acquisition of microscopic images: C.Ş., K.D.K., C.T., A.G. Analysis and interpretation of microscopic data: C.Ş., K.D.K., C.T., A.G., T.Ç. Acquisition, analysis and interpretation of computer-based data: E.Ö., O.E., M.K.G. Drafting of the manuscript: A.G., T.Ç., E.Ö., O.E., M.K.G. Revising the manuscript critically for important intellectual content: A.G., T.Ç., O.E., M.G.K. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

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Research Article

Invention Arising From Surgical Service Needs; Stoma Bag Cover

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Abstract

Aim: In cases such as colostomies, enterocutaneous fistulas and catheters leaking fluid from the environment; the use of stoma bags is necessary. The aim of this study; it is to present the invention called "stoma bag cover" that can be used instead of laborious applications such as opening the stoma bag completely to make an enema or puncturing the bag for drainage.

Material and Methods: Stoma bag cover is a cover that can be placed in the anterior middle part of the stoma bags and provides an opening through which catheters can come out. In addition, in order to prevent leakage around the drain, there is a nylon structure prepared with a purse-shaped thread around the inside of the cover. By knotting this nylon structure after the drain or catheter is passed through the thread at the end, the space that will cause leakage around the drain is eliminated. In addition, if the need for the opening in the stoma bag ends, the cover is designed to be closed and leakproof.

Results: Stoma bag cover; it provides a more practical and effective mechanism for applications that are sometimes insufficient to prevent leakage, such as tying and taping applied to drains removed from the stoma bag. In addition, this invention is a valve mechanism that can enable some necessary applications without opening the stoma bag completely without contamination.

Conclusion: It is expected that this invention will provide healthier results and comfort compared to previous applications, both by providing ease of application and reducing contamination.

Keywords: Colostomy, stoma bag, drains, stoma bag cover

INTRODUCTION

Every year, tens of thousands of people in the world go through stoma formation. The most common conditions requiring stoma surgery are colorectal cancer, bladder cancer, ulcerative colitis and Crohn disease (1). This distinction is important primarily because of its features such as pre-operative location marking and the relative inadequacy of patient preparation for emergency surgeries. Although many patients cope with stoma, they experience considerable difficulty and distress, this situation is more common in emergency stomas; one study found that 51% of patients had their colostomy done in an emergency operation and without planning and preparation for a stoma (2).

Stoma formation is a simple surgical intervention, but its results are not only limited to a spectrum of morbidity expressed with difficulty in care and an uncomfortable life, but also life-threatening complications can occur. In retrospective studies, the most common complications are dermatitis-skin irritation, parastomal pain and partial necrosis, prolapse, stenosis and parastomal hernia. Again, in unit-based evaluations, the general surgery service was found to be the unit with the highest number of complications, followed by gynecology, surgical oncology, pediatric surgery and trauma units, respectively (3,4).

Drains, as stomas are indispensable in many surgical interventions, are mostly used after surgery and in some cases to control bleeding and leakage without surgery and to remove body fluids, and today they are an indispensable part of treatment. Drains are used to control postoperative leakage and bleeding, to prevent fluid accumulation in the operation site, to prevent loculation and abscess formation, and to facilitate wound healing. In cases such as intra-abdominal collection, abscess, ascites, pleural effusion, it

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is placed percutaneously in body cavities accompanied by radiological imaging (5).

Although drains are one of the most preferred tools today due to the benefits they provide, the use of drains brings with it some problems (6). The efficiency of the drain, its ability to prolong the hospitalization period, the need for antibiotic use, etc. are among these (7). There are also problems such as pain in the area, fear, difficulty sleeping with the drain, the need for dressing around the drain, etc. in general terms, patient discomfort, especially in patients who need long-term drainage (5).

Stoma bags are designed for colostomies and ileostomies created after gastrointestinal surgeries and urostomies created after urological surgery and are commercially available as transparent or opaque. In order to fix the stoma bag to the patient's body, the so-called stoma adapter can be used as a separate adapter from the bag or adjacent to the bag depending on the product variety on the market. The stoma adapter is cut in a suitable width according to the width of the stoma and the stoma bag is then closed (8).

The use of stoma bags is not only limited to colostomy and ileostomies and urostomies created after surgery, but also for formations such as enterocutaneous fistula; It is useful to prevent skin erosion and contamination. In addition, although it is not mentioned in the literature, it is encountered in surgical services that stoma bags are used by creating various mechanisms for drains and catheters that leak fluid around and contaminate the dressing, or in other words, wet it and cause contamination and prepare the ground for infection.

The aim of this study; while making use of stoma bags to prevent contamination and infection, it is to reveal the equipment called “stoma bag cover”, which contributes to clinical practice in terms of ease of dressing, patient comfort and hygiene, instead of open and troublesome mechanisms that are open to contamination and its benefits.

MATERIAL AND METHOD

For the solution of the difficulties that are often overlooked in surgical services; that the stoma is removed from the bag and tightly tied around it, and applications such as tying and taping to prevent the stoma from leaking will be applied in a more practical and effective way; In addition, in order to prevent uncontrolled separation of the stoma bag from the adapter in order to prevent contamination in interventions such as enema from the stoma, a valve mechanism called “stoma bag cover” was introduced during the search for an effective solution to this need of surgical services. The main feature of this mechanism is; the stoma bag cover is an independent part of the stoma bag structure and can be used by the part of the stoma bag cover to be attached to the stoma bag on the patient. This mechanism becomes usable after the connection with the inside of the stoma bag is made by puncturing through the line where the lid opening is and will be pierced by the person. There is a cylindrical nylon structure inside the stoma bag lid that can fit into the closed lid volume. The fact that this structure has a thread mechanism at the end, which is used to knot the nylon by shrinking, is another basic feature of this cover that provides its functionality. The stoma bag cover is opened and closed with the help of the segment to be held during opening and closing; It can be closed again safely and easily thanks to the presence of a compatible segment that prevents leakage when the cover is closed. It also includes additional features that are carefully designed to ensure that the segments forming it can be easily closed again when the process is finished, by means of the connection extension that prevents the cover from being completely separated from each other during opening and closing.

This equipment, which is useful in patient-based trials in the clinic, can be produced from the same materials (polyurethane) as all kinds of stoma bags and adapters in the market, with any manufacturer team and equipment capable of producing stoma bags and adapters. Patent procedures have been started by the by the Patent and National Trademark Institution; the process continues with the application number 2021/006679.

RESULTS

Products called stoma bags and stoma adapters have already been used for a long time. The stoma bag cover is used by sticking it to the surfaces of the stoma bags (Figure 1, Figure 2). On the floor of the cover is the part of the stoma bag cover to be attached to the stoma bag on the patient. After the stoma bag is adhered to the appropriate place on the surface of the bag, the flap of the stoma bag is opened with the help of the segment to be held during opening and closing, while the flap is on the stoma bag. Since the opened cover is connected to the floor by the connection extension, it is not completely separated; It provides ease of closing again when the process is finished. After opening the lid of the stoma bag, it is seen that there is a nylon structure inside the cylindrical lid that can fit into the closed lid volume. At the end of this structure, there is a thread for knotting the nylon by shrinking it. Before this mechanism is knotted and tightened, a hole is drilled on the surface of the bag at the point where the stoma bag lid is attached to the bag, through the line where the lid opening is and will be pierced by the person, in order to provide a passage between the lid and the bag. After the hole is opened, the stoma bag is intervened with enemas, etc. At the end of the process, the nylon structure is knotted. Then the cover is closed tightly with the help of the segment to be held during opening and closing. The compatible segment, which prevents leakage when the lid is closed, is present in the lid mechanism and ensures safe closing at the end of the process.

Apart from enema etc. interventions, drains can also be removed through the hole opened in the stoma bag. After the drain is removed from the hole, the nylon structure inside the stoma bag cover and the thread mechanism at the end are knotted and the mechanism becomes usable

by tightening the drain with a knot. If the need ends, the knot is loosened; then the drain is removed or the drain stays in place and the stoma bag can be removed and a new stoma bag inserted. If the drain is pulled, the thread is knotted again and the cover is tightly closed.

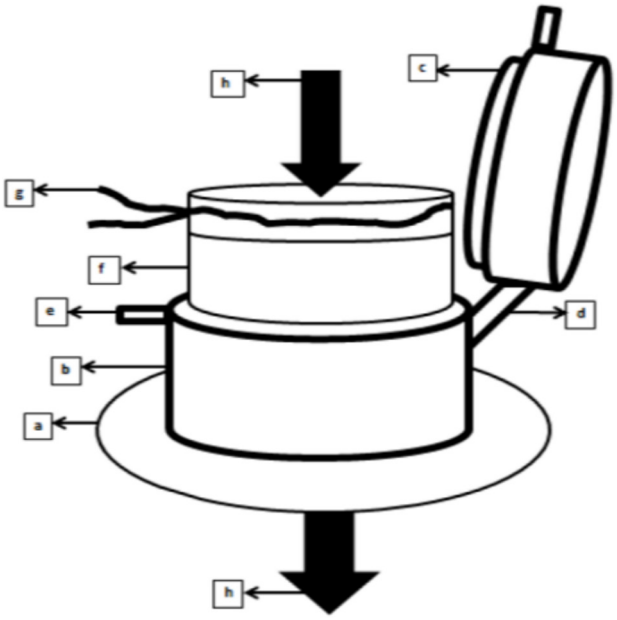

Figure 1. Stoma bag cover, open view **a.** The part of the stoma bag cover on the floor of the cover to be attached to the stoma bag on the patient **b.** Stoma Bag Cover **c.** Compatible segment that prevents leakage when the lid is closed **d.** Connection extension that connects the cover to the floor and prevents it from being completely separated and provides ease of closing when the process is finished **e.** Segment to be held during opening and closing **f.** After the stoma bag cover is opened, the nylon structure inside the cylindrical cover and can fit into the closed cover volume **g.** Thread for knotting the nylon at the end of the nylon structure by shrinking it **h.** The line on the bag surface at the point where the stoma bag cover is attached to the bag, where the flap opening is to allow passage between the cap and the bag and to be pierced by the person.

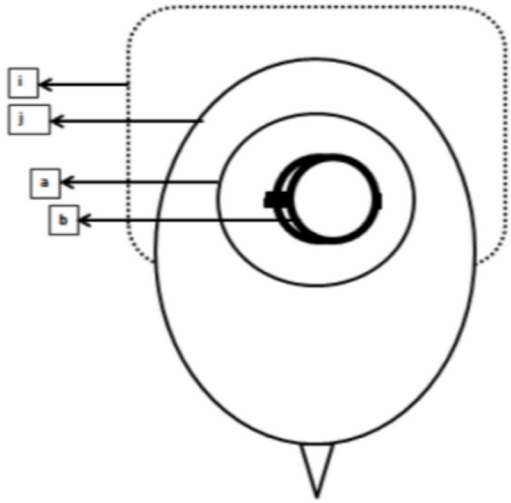

Figure 2. The view of the stoma bag cover while it is on the stoma bag **a.** The part of the stoma bag cover on the floor of the cover to be attached to the stoma bag on the patient **b.** Stoma Bag Cover **i.** Stoma adapter (any market product) **j.** Stoma bag (any market product)

DISCUSSION

In addition to the routine care and cleaning of stomas, intervention by enema through the stomal opening in cases of constipation, subileus and ileus or to give luminal contrast for imaging is a frequently applied practice in general surgery and emergency surgery units (9,10). Sometimes due to clinical necessities, in surgeries where a double-barreled stoma is opened from the proximal intestinal loops, in order to prevent the development of short bowel syndrome by ensuring the continuity of the gastrointestinal passage, in some surgical services in such patients, the intestinal fluid from the proximal stomal opening is given through a foley catheter or a feeding catheter from the distal end of the stoma. Ans can also be provided to participate in digestion. Sometimes, leakage may occur around the drain in the drains placed in the patient after the surgery, the drains placed in interventional radiology, acid drainage catheter, etc. Contamination, which sometimes occurs due to abundant drainage and sometimes due to insufficient functioning of the drain, cannot be adequately prevented despite frequent dressings, and an effective solution is required to control this drainage fluid (11,12). For this, sticking a stoma bag over the drain outlet and removing the drain from the bag is not uncommon in clinical practice.

When enema needs to be made from a stoma, the stoma bag is opened by separating it from the adapter. After the enema, the enema fluid and if the enema works, the fecal contents are scattered around. In one-piece stoma bags where the adapter is not separate, this process is performed by separating the bag from the skin where it is completely adhered. This invites epidermal and dermal injuries that may occur on the skin, on top of contamination with the intestinal contents in other types of stoma bags and contamination to the environment. In order to prevent short bowel syndrome in stomas with double barrels opened from the proximal, it is an application used in surgical services to ensure the continuation of intestinal content from the proximal anus to the distal anna. For this purpose, a catheter is placed in the distal stomal ann; the ends of such catheters and the ends of various drain and drainage catheters on which a bag is attached because it leaks around; In clinical practice, the bag is punctured to remove it from the stoma bag. In order to prevent leaks around the bag hole, various suture materials, threads and tapes are used to tightly connect the hole created in the bag and the drain/catheter that comes out of it, however, leakage and contamination from the puncture site of the bag continues (Figure 3). Although it is difficult to create this mechanism in terms of time and effort, if a leakproof condition can be achieved, patients stay as much as possible so that the mechanism does not deteriorate, and their mobilization is inevitably restricted. This, in turn, invites secondary complications such as deep vein thrombosis, decubitus wounds, etc., which cannot be predicted at first glance.

Although such special applications arising from the needs of surgical service bring various secondary problems such as contamination of the procedure area with intestinal

Figure 3. Stoma bag placed in the drain outlet area in order to prevent leakage around the drain, but it is seen that the leak continues from the outlet hole of the drain bag

contents, ineffective mechanisms, and ignoring patient comfort, while being performed under current conditions, the desired results are not always achieved with the mechanisms that are tried to be created.

The stoma bag cover is designed to facilitate the mechanism to be applied in a more practical and effective way, such as binding and taping applied to the drains removed from the stoma bag, in a more practical and effective way, and also to prevent contamination and to provide hygienic conditions more easily when enema is required.

CONCLUSION

With this invention, it is aimed to achieve better results with a comfortable mechanism for the procedures that are performed by puncturing stoma bags or separating them from their adapters, which cause a lot of time and effort, as its benefits can be seen in patient-based trials in the clinic. In this way, in addition to the standard use of stoma bags, it is expected that various bag arrangements, which are tried to be applied to facilitate the treatment process, will be made more efficient, and a more hygienic, more effective process that causes less comorbidity in patients.

As a result, it is expected that this invention will provide healthier results and comfort compared to previous applications, both by providing ease of application and reducing contamination.

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Ethical approval: *Ethics committee approval is not required.*

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Research Article

Prediction of Short or Long Length of Stay COVID-19 by Machine Learning

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Abstract

Aim: The aim of this study is to utilize machine learning techniques to accurately predict the length of stay for Covid-19 patients, based on basic clinical parameters.

Material and Methods: The study examined seven key variables, namely age, gender, length of hospitalization, c-reactive protein, ferritin, lymphocyte count, and the COVID-19 Reporting and Data System (CORADS), in a cohort of 118 adult patients who were admitted to the hospital with a diagnosis of Covid-19 during the period of November 2020 to January 2021. The data set is partitioned into a training and validation set comprising 80% of the data and a test set comprising 20% of the data in a random manner. The present study employed the caret package in the R programming language to develop machine learning models aimed at predicting the length of stay (short or long) in a given context. The performance metrics of these models were subsequently documented.

Results: The k-nearest neighbor model produced the best results among the various models. As per the model, the evaluation outcomes for the estimation of hospitalizations lasting for 5 days or less and those exceeding 5 days are as follows: The accuracy rate was 0.92 (95% CI, 0.73-0.99), the no-information rate was 0.67, the Kappa rate was 0.82, and the F1 score was 0.89 (p=0.0048).

Conclusion: By applying machine learning into Covid-19, length of stay estimates can be made with more accuracy, allowing for more effective patient management.

Keywords: COVID-19, machine learning, R programming, length of stay, accuracy, management

INTRODUCTION

The ongoing COVID-19 pandemic, now approaching its third year, persists in its global dissemination. During the initial wave of the pandemic, all nations have demonstrated a lack of capability in effectively managing the outbreak (1). The current pandemic has resulted in prolonged and unforeseeable hospitalizations due to Covid-19, posing a challenge in the management of patients with pre-existing chronic or severe conditions, as well as those requiring hospitalization and subsequent monitoring (2). The COVID-19 pandemic serves as a reminder of the critical importance of proficient bed capacity management for all illnesses, particularly in the context of outbreaks that require prompt implementation of action plans (3). The challenge of managing the overwhelming demand for hospitalizations during the pandemic, which exceeded the capacity of health facilities, required a proficient integration of scarce data and vague indicators.

In healthcare facilities where there are constraints on bed availability and patient capacity, it is imperative to develop a comprehensive strategy and ascertain whether patients will be admitted for a brief or extended duration. It is advisable to implement pre-hospital interventions to mitigate the duration of hospitalization, commonly referred to as length of stay (LoS) (4). Thus, efficient management can be facilitated by ensuring the effective circulation of all hospital items, including people and logistics, particularly in the context of acute and complex events (5).

Today, machine learning is gaining prominence as a scientific approach capable of effectively forecasting the likelihood of various phenomena or events and their corresponding risk rates

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(6). The employment of machine learning methods and models has become ubiquitous in various domains of the battle against Covid-19, including but not limited to the prediction of disease transmission, mortality rates, and the development of vaccines (7). Consequently, any performance data obtained through the utilization of machine learning models pertaining to Covid-19's length of stay (LoS) will make a substantial contribution to the management of hospitalizations.

The objective of this study was to evaluate the efficacy of machine learning (ML) models in predicting the requirement of short-term or long-term hospitalization of patients based on their basic demographic, biochemical, and imaging data.

MATERIAL AND METHOD

The present study is a retrospective and observational investigation that was carried out at the Ministry of Health Ordu University Training and Research Hospital, following the acquisition of requisite approvals from the pertinent ethics committee and institution.

Patient Selection

The study sample comprises of individuals who are 18 years of age or older and who sought medical attention at our healthcare facility for Covid-19 infection during the period spanning from November 2020 to January 2021, and subsequently required hospitalization. A cohort of patients was identified through a full review of the health information management system (HIMS).

Data Types and Preparation

The demographic and descriptive information pertaining to the patients identified by HIMS was completely documented. This included details such as age, gender, and other relevant factors. The dates pertaining to the hospitalization and subsequent discharge were properly recorded. Based on WHO data spanning the last two decades (1996-2014), the average hospital stay duration in Turkey is 5.1 days (8). Therefore, in our study design, we defined the parameters of low and long-term hospitalization as stays of less than or greater than 5 days, respectively. A new categorical variable named "LOSClass" was introduced into the data set by categorizing individuals based on the duration of their hospitalization. Specifically, those who were hospitalized for 5 days or less were assigned a categorical designation of "1", while those who were hospitalized for more than 5 days were assigned a categorical designation of "2". The length of stay variable, expressed in numeric form, was removed from the dataset. Biochemical markers such as C-reactive protein (CRP), ferritin, and lymphocyte levels were incorporated into the study. In addition, the thoracic computed tomography (CT) scans acquired at the time of submission were recorded, along with the imaging dates and the Covid-19 Reporting and Data System (CORADS) assessments as indicated in the CT reports. The superiority of the CORADS scoring system in predicting the severity of pulmonary involvement, as well as in forecasting prognosis and length of stay (LoS), has been demonstrated in comparison to other proposed scoring systems (9). These findings have been included in the dataset. Upon reevaluation of the public health management system, the PCR outcomes for the detection of COVID-19 were reaffirmed.

Statistical Analysis and Machine Learning

Basic statistical and machine learning analyses were performed using Jamovi version 2.3.16 (10,11) and RStudio version 4.2.0 of the R programming language (11). The caret package (version 6.0-93) in the R programming language was employed for the implementation of a machine learning methodology (12). The caret package available in the R programming language appears to be adequate for the implementation of a machine learning system, as it is capable of performing intricate regression and classification analyses. (13). The train() method is used by the related package to construct a predictive model. The packages "party, physc, tidyverse, and dplyr" were used for ML analysis in addition to caret. A flowchart of the plan for the study is shown in Figure 1.

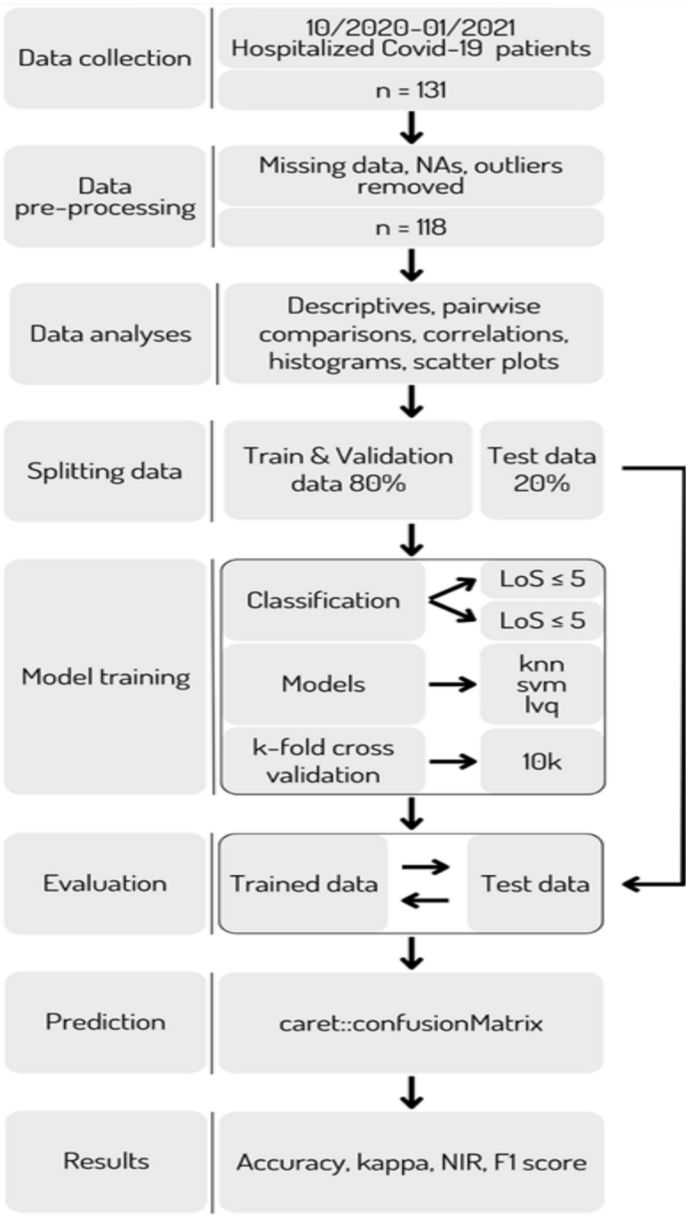

Figure 1. Flow-chart of the study. NA: not available, LoS: length of stay, knn: k-nearest neighbor, lvq: learning vector quantization, svm: support vector machine, NIR: no-information rate

Model Implementation and Evaluation

The labels of all data assigned based on the length of stay categories. The labeled dataset was split into two parts randomly as follows: 80% of the observations were randomly assigned to the training and validation set and the independent test set is 20%.

The k-fold cross validation is a robust and secure internal validation approach to obtain fair results. However, avoiding the potential bias of cross-validation several medical studies use the external validation which is known as independent test (14). We prefer same independent test approach with cross validation. In this paper, the 80% parts of all dataset is used for model training and validation process. The rest of dataset, namely 20% is unseen data and used for external independent testing to evaluate the model performance.

Again, our method applied optimally defined classifier parameters. Cross-validation tuning of hyperparameters requires lengthy training durations and yielded comparable accuracy performance (±1%) for our dataset. Therefore, we preferred to use the system's optimal hyperparameters.

For model training, we used the classification models k-nearest neighbor (method: knn), learning vector quantization (method: lvq), and support vector machine (method: svm). Given the limited size of our dataset, we employed the k-fold cross-validation technique, a widely utilized approach for model evaluation (15) that is favored for its ability to yield unbiased performance outcomes. Specifically, we opted for a 10-fold cross-validation strategy.

Subsequently, the predictive values of each model were calculated, and the performance metrics of each model were assessed through using of the "confusionMatrix" function from the caret package. The evaluation encompassed measures such as accuracy, kappa, no information rate (NIR), and p significance findings. Kappa indicates the degree of agreement between two groups of categorical data, relative to what would be predicted by chance alone. A score of 1 (one) represents total agreement, whereas a score of 0 (zero) represents disagreement (16).

The term NIR, which is also referred to as the base rate, pertains to the proportion of the "most popular state" that is determined through the validation of the test set using machine learning models. It is an accuracy paradox caused by repeatedly "incorrect" estimations of the observational variables (17). It is a crucial requirement for test performance, and when estimating using a good model, the accuracy rate is predicted to be significantly higher than NIR, that is, the p value should be less than 0.05 according to the 95% confidence interval.

RESULTS

A total of 131 patients who met the criteria for the specified time period were identified. During the data preprocessing stage, any missing data and NAs were eliminated. Furthermore, based on the boxplots generated during the initial analysis of the data, it was ascertained that the variables harbored outlier values, and the related observations were eliminated from the study. The final version of the dataset comprised a total of 118 observations. In the final version of the dataset, the category classification of the dependent variable was analyzed, and no class imbalance was found (Script 1).

Script 1. A section showing the process of removing outliers from the dataset, the number of observations obtained after removing all outliers, and the LOSClass table. df: dataset, FERR: ferritin

```
#An example of removing the outliers from a
variable

quartiles <- quantile(df$FERR,
       probs=c(.25, .75), na.rm =
       FALSE)
       IQR <- IQR(df$FERR)
       Lower <- quartiles[1] - 1.5*IQR
       Upper <- quartiles[2] + 1.5*IQR


df <- subset(df, df$FERR > Lower &
df$FERR
      < Upper)



#Dimension of the final dataset
> dim(df)
[1] 118   7

#Table of the LoSClass
> table(df$LOSClass)
 1  2
58 60
```

Tables 1 and 2 present the descriptive statistics of the dataset. The sample's average age was 67.69 years with a standard deviation of 14.63. There were 57 female patients and 61 male patients, as revealed by the distribution of gender. The percentage and quantitative distributions of CORADS scores, whose median value was 5 (five), are shown in Table 3.

The scatter and histogram graphs of the numerical variables in the final version of the dataset, along with the correlation values calculated using the “pairs.panel” function of the "psych" package, are shown in Figure 2.

The data presented in this figure indicates a weak correlation (r=0.20) between CRP and ferritin levels. This correlation was not statistically significant (p = 0.033). With the exception of lymphocyte levels, Pearson's correlation analysis of the numerical data with CORADS, which is ordinal data, revealed significant relationships with the other three numerical data. We discovered the following correlations: r=-0.343 with age (p<0.001), r=0.252 with ferritin (p<0.001), r=0.252 with CRP (p<0.001), and r=-0.126 with lymphocytes (p=0.174).

Table 1. Descriptive statistics of numeric variables

		95% CI					
	Mean	Lower	Upper	SD	Min	Max	Calc W
AGE	67.69	65.03	70.36	14.63	30	96	0.165
CRP	8.45	7.30	9.61	6.32	0.200	27.4	<0.001
LYM	1211.80	1107.05	1316.54	574.53	240	2740	<0.001
FERR	407.29	353.55	461.04	294.82	13.600	1195.0	<0.001

CRP: c-reactive protein, FERR: ferritin, LYM: lymphocyte, CI: confidence interval, SD: standard deviation, Min: minimum, Max: maximum, Calc W: p value of Shapiro-Wilk test

Table 2. Age-related descriptive data according to gender and length of stay classification

				95% CI				
Sex	LOSClass	N	Mean	Lower	Upper	SD	Min	Max
Female	1	27	63.8	57.6	70.0	15.6	30	96
	2	30	71.9	67.5	76.4	12.0	42	95
Male	1	31	67.2	61.0	73.3	16.7	39	92
	2	30	67.5	62.5	72.5	13.4	31	88
Total	-	118	67.7	65.0	70.4	14.6	30	96

LOSClass: length of stay classification, N: number, CI: confidence interval, SD: standard deviation, Min: minimum, Max: maximum Note: The CI of the mean assumes sample means follow a t-distribution with N - 1 degrees of freedom

Table 3. Frequencies of CORADS

CORADS	Counts	% of Total	Cumulative %
1	1	0.8 %	0.8 %
2	9	7.6 %	8.5 %
3	18	15.3 %	23.7 %
4	21	17.8 %	41.5 %
5	69	58.5 %	100.0 %

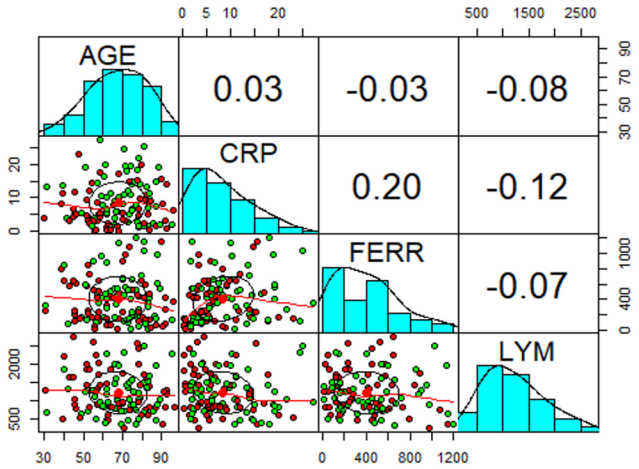

Figure 2. Histograms of numerical data and outcomes of pairwise comparisons. The ordinates and coordinates of each variable's values are shown on the side or top of the box bearing the variable's name. Moreover, scatter plots and correlation coefficients are located inside the boxes where the two variables overlap. CRP: c-reactive protein, FERR: ferritin, LYM: lymphocyte

Following the random splitting of the dataset (referred to as "df" in the analysis) into the two parts of 80% and 20%, two distinct sub-datasets were created, which were respectively named "x_train" and "x_test" in the analysis. The training set consisted of 94 observations, while the test set contained 24 observations. The number of length of stays (LoS) in both groups exhibited comparable. In the training set, there are 50 (fifty) observations for 5 days or less, and 44 (forty-four) observations for longer than 5 days. In the test set, the number of observations for 5 days or less was 8 and the number of observations over 5 days was 16 (Script 2).

Script 2. The process of splitting the data set into a training set and a test set by 80 percent and 20 percent, respectively. Additionally, the distribution of newly formed sets' values according to LOSClass

```
#Producing the train and the test samples

set.seed(2022)
split <- sample(1:nrow(df),
   as.integer(0.8*nrow(df)), F)

train1 <- df[split,]
test1 <- df[-split,]

x_train <- train1
x_test <- test1

y_train <- factor(train1[,"LOSClass"],
levels=c(1,2))
y_test <-  factor(test1[,"LOSClass"],
levels=c(1,2))

#The tables according to LOSClass of the train
and test datasets
> table(x_train$LOSClass)
 1  2
50 44
> table(x_test$LOSClass)
 1  2
 8 16
```

The results for the confusion matrix were obtained after model training and prediction computations. Script 3 includes an example model code.

Script 3. The coding and outcomes of knn model's performance

```
set.seed(2022)
knn.fit <- train(x_train, y_train,
     method = "knn",
     preProcess = c("center", "scale"),
     tuneLength = 10,
     trControl = trainControl(method =
     "cv", number=10))
predknn <- predict(knn.fit, x_test)
confknn <-
     confusionMatrix(as.factor(predknn),
     as.factor(y_test), mode="everything")
> confknn
Confusion Matrix and Statistics
          Reference
Prediction   1  2
        1    8  2
        2    0 14
              Accuracy:  0.9167
                95% CI:  (0.73, 0.9897)
  No Information Rate:  0.6667
  P-Value [Acc > NIR]:  0.004871
                 Kappa:  0.8235
       Mcnemar's Test:  0.479500
              P-Value:
          Sensitivity:  1.0000
          Specificity:  0.8750
       Pos Pred Value:  0.8000
       Neg Pred Value:  1.0000
            Precision:  0.8000
               Recall:  1.0000
                   F1:  0.8889
           Prevalence:  0.3333
       Detection Rate:  0.3333
 Detection Prevalence:  0.4167
    Balanced Accuracy:  0.9375
     'Positive' Class:   1
```

The performance outcomes of ML models were evaluated with special attention given to accuracy, kappa, NIR, F1 scores, and p significant values. Upon examination of the performance metrics presented in Table 4, it was determined that the accuracy of the knn model was 0.92, with a 95% confidence interval ranging from 0.73 to 1.00 and a p-value of 0.0048. Despite achieving a 0.75 accuracy level in the SVM model, the statistical significance of the p value was not established. The lvq model exhibited poor performance in terms of both accuracy and p values.

The Kappa value, commonly referred to as Cohen's Kappa, is a statistical measure that evaluates the level of agreement between two random categorical variables in terms of their predicted and true labels. Its values range from -1 to 1. Inconsistency is typically attributed to results that fall below 0.6, whereas a higher degree of congruity is associated with values closer to 1 (one). (18). The results of our study indicate that among the models tested, the knn model exhibited the highest Kappa value, which was recorded at 0.82.

On the contrary, the F1 score denotes the ability of the test to predict the true. In cases where there exists an imbalance among classes, the employment of this metric takes precedence over accuracy measurements (19). Although the dataset exhibits no class imbalance, the KNN model's F1 score is notably high, suggesting that it is a reliable model.

The McNemar test is utilized to ascertain whether incorrect data is incidental or if it manifests with a specific frequency. Thus, it is advisable not to reject the null hypothesis as errors are expected to occur consistently (20). The McNemar's test outcome pertaining to our knn model yielded a p-value of 0.48, thereby confirming the null hypothesis.

Table 4. Results of the models by confussionMatrix function

Models	ACC	95% CI	NIR	Kappa	F1 Score	p value [ACC>NIR]	McNemar's Test p value
knn	0.92	0.73-0.99	0.67	0.82	0.89	**0.0048**	0.48
lvq	0.5	0.44-0.84	0.67	0.14	0.33	0.59	0.28
svm	0.75	0.53-0.90	0.67	0.52	0.72	0.26	0.04

knn: k-nearest neighbors, lvq: learning vector quantization, svm: support vector machines, ACC: accuracy, CI: confidence interval, NIR: no information rate. Significant p-values between Accuracy and NIR are shown in bold

DISCUSSION

The present study used a machine learning (ML) approach to categorically evaluate hospitalization duration (≤5 days or >5 days) for Covid-19 patients. The findings revealed a noteworthy accuracy rate exceeding 90%. No statistically significant results were observed in the remaining two machine learning models. Additional findings regarding the performance of the K-Nearest Neighbors (KNN) model suggest that it is efficacious and possesses a favorable predictive capability.

The COVID-19 pandemic has resulted in a noteworthy duration of hospitalization for patients, and we will look at and discuss certain outcomes pertaining to this phenomenon. One of the most intriguing studies among these is a systematic review. In that review, encompassed a sample size of approximately 430,000 patients from 126 distinct investigations. The average length of stay (LoS) for Covid-19 was found to be 14.49 days, with a standard deviation of 7.92. The minimum and maximum durations of hospitalization were 3.5 and 53.8 days, respectively (21).

The use of blood tests and imaging scans can aid in the early determination of the probability of short or extended hospitalization. In addition to Covid-19, various factors including age, lung involvement scores, CRP, ferritin, and lymphocyte levels have been identified as significant predictors of disease severity and consequently, length of hospitalization (22). The research conducted by Oksuz et al. revealed a significant association between abnormal blood parameters and increased hospitalization duration and costs (23).

We observed that machine learning analyses of the variables of the severity of lung involvement in The existing literature on Covid-19 and the estimation of length of stay (LoS) was found to be limited. In a study involving 254 patients conducted by Chamberlin et al., a score other than CORADS was used to predict hospitalization and an accuracy of 0.77 was determined (24). In a different study by Purkayastha et al. that used a different scoring system than CORADS, the accuracy levels of the ML analysis results using the "boosting" and "bayesian" methods were 0.68 (p=0.023) and 0.77 (p=0.023), respectively (25).

The study conducted by Olivato et al. involved a sample size of 6000 patients diagnosed with Covid-19. The researchers used a machine learning approach to forecast the duration of hospitalization, regardless of the severity of lung involvement. The approach was designed to predict hospitalization periods of less than seven days or more. The achieved F1 score was 0.76; however, the values for kappa and p were not disclosed (26).

Saadatmand et al. used ML to determine the length of stay (LoS) in hospital, identifying between stays of less than seven days and those exceeding this duration. The study conducted on 112 critical care patients demonstrated that the CART model attained the highest accuracy score of 0.82 (27). In the related research, the statistical significance level was not specified, and the kappa coefficient was observed to be low, measuring at 0.48.

Finally, Alabbas et al. showed that the rf model had an accuracy score of 94.16% in a study involving 895 patients that did not include lung involvement levels (28). In the linked study, attempts were made to estimate the number of hospitalized days for seven distinct five-day groups.

CONCLUSION

In our study, we used ferritin, CRP, lymphocyte, and lung involvement scores, which are frequently requested basic tests for Covid-19, as well as age and gender to predict whether the length of stay would be short or long. Numerous biomarkers were incorporated into prediction models in the published literature, whereas lung involvement scores were rarely used. In addition, crucial prediction performance scores such as "kappa" and "p significance" were absent from the analysis outcomes. Alternatively, we believe that our relatively small sample size has an effect on the prediction models. As evidenced by the literature and other methodologies, using the ML method to determine the risk of short- and long-term hospitalization appears feasible and reasonable. We believe that the incorporation of ML coding of such data into HIMS interfaces will make substantial contributions to the management of Covid-19 patients through the assessment of short or long hospitalization risk rates.

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Research Article

Quantitative Assessment of the Pharyngeal Recess Morphometry in Anatolian Population Using 3D Models Generated from Multidetector Computed Tomography Images

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Abstract

Aim: It was aimed to analyze the detailed morphometry of the pharyngeal recess (PR) using three-dimensional (3D) models reconstructed from multidetector computed tomography (MDCT) images.

Material and Methods: This study was a retrospective analysis and performed on MDCT images of 97 patients (43 males, 54 females). 3D models of the PR were reconstructed using 3D Slicer software, enabling morphometric measurements according to established protocols. Measurements included PR depths, distances between the posterior nasal spine and torus levatorius (PNS-TL), distances between right and left TL (RTL-LTL) distances between the PNS and posterior wall of the nasopharynx (PNS-PWN), the angle (α) between the centerline of the PR and the sagittal plane. The morphologies of the PR classified into three types.

Results: The average measurements for the parameters were as follows: PR depth - 10.42 mm, distance between PNS and TL - 10.40 mm, distance between RTL and LTL - 19.13 mm, distance between PNS and PWN - 19.92 mm, and the angle (α) - 53.65°. The prevalence of PR types was 20.62%, 47.42% and 31.96% for type 1, type 2 and type 3, respectively.

Conclusion: Variations in reported measurements of the pharyngeal recess can be attributed to imaging techniques, patient positioning, anatomical differences, and sample sizes. The use of 3D models generated from MDCT datasets offers a high-resolution and comprehensive approach to understanding the PR's morphometry and spatial relationships, enabling accurate measurements and advancing our knowledge of this anatomical region.

Keywords: 3D slicer, multidetector computed tomography, nasopharyngeal carcinoma, nasopharynx, pharyngeal recess

INTRODUCTION

The pharyngeal recess (PR), also referred to as the Rosenmüller fossa, is a well-known anatomical structure that is bilaterally located in the nasopharynx, below the skull base (1). The eponymously attributed nomenclature of the PR originates from its first description in 1808 by Johann Christian Rosenmüller, a German anatomist (2). Although it is a relatively small area in the aerodigestive tract, it is clinically important as it is an anatomical region where nasopharyngeal carcinoma (NPC) malignancies originate (3).

The PR is formed by the nasopharyngeal mucosal reflection over the longus colli and surrounded by distinct anatomical structures. The eustachian tube and levator veli palatini demarcate its anterior boundary, while the posterior wall of the nasopharynx and retropharyngeal space limits posteromedialy. Laterally, the fossa is bordered by the parapharyngeal space and tensor veli palatini, also the superior border of the constrictor superior marks its inferior extent. The skull base constitutes the superior boundary of this fossa. Furthermore it is in close proximity to the internal carotid artery through its roof (4-6).

Since the primary diagnostic evidence for the NPC is asymmetry and blunting in the PR, utilization of innovative 3D imaging modalities are essential for the detailed evaluation of the area (7). The superior spatial resolution and image quality offered by MDCT, render it an

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indispensable tool for exploring the PR morphology and ultimately diagnosing the NPC (8). However, the spatial localization in bilateral symmetry of the structures that compose the PR or adjacent structures are typically not congruent within the same axial plane, thus hindering the accuracy of morphometric assessments (9). The rotational functionality provided by radiological visualization software tools may potentially address this issue by revolving the entire Digital Imaging and Communications in Medicine (DICOM) dataset around specific landmarks following the creation of three-dimensional (3D) reconstructions. Nonetheless, this recourse may not be feasible due to the absence of such tools in frequently utilized stationary software. Third-party software, which facilitate the creation of 3D reconstructions from DICOM datasets, offer the added advantage of rotational movement of radiological planes or models, thereby enabling the execution of precise morphometric analysis (10).

The diagnosis of NPC conventionally relies on the utilization of ear, nose, and throat (ENT) clinical evaluation methods, where the MRI and MDCT images acquired in the supine position are employed by ENT specialists to achieve accurate diagnosis (11). Therefore, to analyze the morphometric features of the PR, 3D digital models were reconstructed in this study using DICOM datasets of the MDCT images obtained from patients in the supine position. It was aimed to enhance the current knowledge about this crucial anatomical region, thereby facilitating diagnosis and treatment of the NPC.

MATERIAL AND METHOD

This retrospective study received approval from the local non-interventional clinical research ethics committee (Protocol no: 7.4.23/132) and adhered to the principles outlined in the Declaration of Helsinki. The dataset for this study consisted of axial MDCT images of patients screened between January 2022 and December 2022. A randomized approach was employed to select MDCT images from the archive of the Radiology Department at the Faculty of Medicine, Cukurova University. The scans were conducted using a 160-slice MDCT scanner (Toshiba Aquilion™ PRIME; Otawara, Japan) with a standard protocol of 0.6 mm collimation, 0.5 mm slice thickness, 120 kV, and 250 m. A bone window setting (Width: 2500; Level: 500) and a digital workstation (Vitrea CT workstation, Toshiba; Otawara, Japan) were used to evaluate the images. A series of 171 MDCT images from supine patients, with their head and neck in neutral position and the Frankfort horizontal plane perpendicular to the floor, were selected. After applying exclusion criteria (trauma, tumors, incomplete images, swellings or malformation of the nasopharyngeal region) 97 MDCT images were remained and anonymized. The DICOM datasets of those patients were used in the study.

Segmentation of the 3D models was carried out utilizing *3D Slicer*. In the *Segment Editor Module* thresholding was manually adjusted for the segmentation of 3D models. Two distinct segmentations were conducted: one for the bones (yellow) and the other for the soft tissue (green). The resultant 3D models of both bones and soft tissue were then merged in the same workspace. To facilitate further morphometric analysis, the anatomical landmarks were designated using the *Paint Tool*. The axial MDCT plane was manually scrolled and subsequently rotated within the x, y, z coordinates, until proper alignment was achieved with the identified anatomical landmarks (Figure 1). The sagittal plane was scrolled laterally until the bilateral components of the PR became visible. The 3D models cropped through the determined axial and sagittal planes (Figure 2) and morphometric measurements were performed in the *Markups Module.*

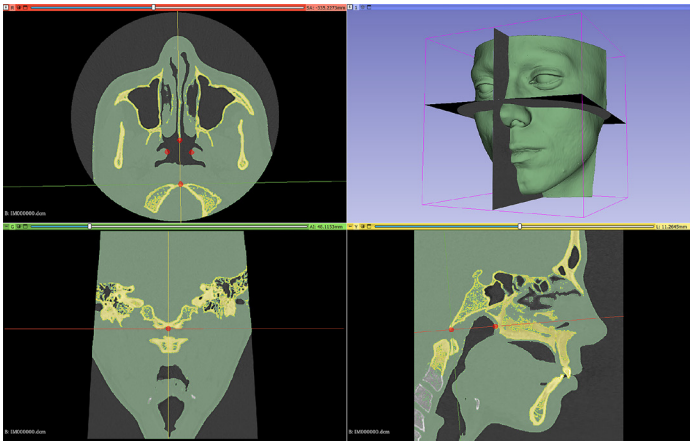

Figure 1. Landmarks were determined on axial planes (red dots). The axial plane aligned through the basion + PNS and Right PR + Left PR. The sagittal plane was aligned through the basion and PNS

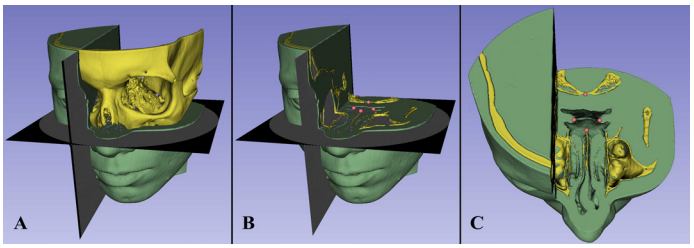

Figure 2. The sagittal plane scrolled through the lateral side (right side) until whole PR structures were viewed. Soft tissue **(A)** and the skull **(B)** were cut-out from the intersection of the planes to visualize the landmarks **(C)**

Following the identification of the relevant landmarks, morphometric measurements were carried out in accordance with established protocols (Figure 3). The distances and angles were measured three times, averaged, and the resulting mean value documented as the final value:

LPR Depth: Vertical distance to the line connecting LTL (c) with basion (d)
RPR Depth: Vertical distance to the line connecting RTL (b) with basion (d)
a-e: Distance between PNS and PWN
f-b: Distance between PNS and RTL
g-c: Distance between PNS and LTL
b-c: Distance between RTL and LTL
RPRα: The angle between the centerline of the RPR and

the sagittal plane
LPRα: The angle between the centerline of the LPR and the sagittal plane

The morphologies of the PRs were initially classified into three types: Type 1 (fossa depth <5 mm), Type 2 (fossa depth ≥ 5 mm and opening width <1 mm), and Type 3 (fossa depth ≥ 5 mm and opening width ≥1 mm).

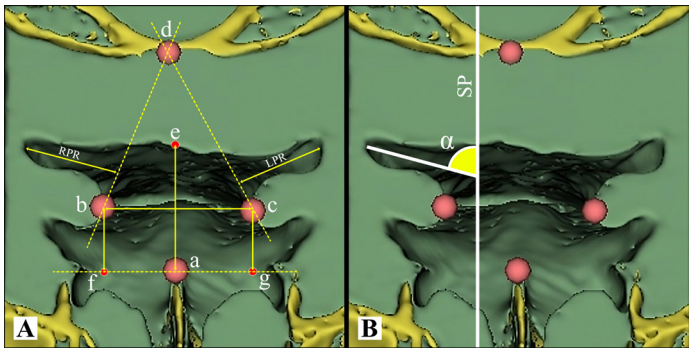

Figure 3. A. Distances were measured through the determined landmarks on finalized 3D models. **a.** Posterior nasal spine (PNS); **b.** Right torus levatorius (RTL); **c.** Left torus levatorius (LTL); **d.** Basion; **e.** Posterior wall of the nasopharynx (PWN); **f.** Projection of the RTL on the horizontal line passing through the PNS; **g.** Projection of the LTL on the horizontal line passing through the PNS. Additionally, a horizontal line passing through the PNS, and also lines connecting RTL (b) and LTL (c) with basion (e) was generated. **B. α.** The angle between the centerline of the PR and the sagittal plane (the angle of the right pharyngeal recess-RPRα was shown for representative purpose on the figure). SP: sagittal plane

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Version 20.0 statistical software package (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as mean and standard deviation and as median and minimum-maximum. The Kolmogorov–Smirnov test was employed to classify the distribution of the datasets into parametric and nonparametric data. The Mann-Whitney U test was used to compare the morphometric variables between male and female groups, while Spearman's r correlation was used to examine the relationship between variables. The Wilcoxon rank-sum test was used to analyze TL, PR, and angle parameters on both sides. The frequencies of PR types were compared by gender using a chi-square test for significance. Inter-observer reliability analysis was performed on measurements taken by two observers, with the primary observer (HE) conducting the initial measurements and the secondary observer (MT) conducting the same measurements while being blinded to the initial measurements. Intraclass correlation coefficients (ICC) were utilized to evaluate the level of agreement between the two observers and assess inter-observer reliability. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

The ICC values for each of the measurements are presented in (Table 1), indicating good to excellent inter-observer reliability, as per the evaluation of Koo and Li (2016) (12).

In this study, the DICOM datasets of 97 patients (43 males and 54 females) were analyzed. The average age of the patients was 50.77±16.72 years with a range of 22-81 years. The mean age for males and females were 54.00±15.86 years and 48.20±17.09 years, respectively. There was no significant difference observed in the age and other parameters between males and females (Table 2). The Wilcoxon rank-sum test revealed no significant differences for TL (p = 0.077) and PR (p = 0.059), but a significant difference for angle (p = 0.010). A strong positive correlation was observed between the left and right depths of the PR (Table 3). Moreover, a very strong positive correlation was found between the lengths of the TL and the depths of the PR in the same sides (Table 3).

The PR type data indicate a higher prevalence of type 2, with a frequency of 46% in males and 58.7% in females. Conversely, type 1 morphology was less common, representing 26.5% of males and 21.3% of females. Type 3 prevalence rate was 27.5% in males and 30% in females.

Table 1. Intra-observer reproducibility and reliability for each the measurements taken

Parameters	ICC (95% CI)	p
Left PR	0.933 (0.829-0.973)	<0.001
Right PR	0.921 (0.800-0.969)	<0.001
Left TL	0.860 (0.647-0.945)	<0.001
Right TL	0.871 (0.674-0.949)	<0.001
Left TL – Right TL	0.908 (0.767-0.963)	<0.001
PNS – PWN	0.928 (0.818-0.972)	<0.001
Left Angle	0.894 (0.733-0.958)	<0.001
Right Angle	0.880 (0.696-0.952)	<0.001
Type Left	0.966 (0.922-0.988)	<0.001
Type Right	0.929 (0.820-0.972)	<0.001

ICC: intraclass correlation coefficient CI: confidence interval

Table 2. Distribution of male and female morphometric measurements

Parameters	n	Total	Male	Female	p
Age	97	50.77±16.72 54.00 (22.00-81.00)	54.00±15.86 60.00 (22.00-81.00)	48.20±17.09 48.00 (22.00-78.00)	0.084
PR (mm)	97	10.42±4.35 11.50 (1.97-19.27)	10.00±5.25 11.24 (1.97-19.27)	10.76±3.49 11.56 (2.31-18.04)	0.791
PNS-TL (mm)	97	10.40±4.39 11.40 (1.89-19.27)	9.88±5.33 11.24 (1.89-19.45)	10.82±3.46 11.48 (2.18-18.04)	0.594
RTL – LTL (mm)	97	19.13±3.49 19.17 (11.97-29.61)	19.00±4.02 18.82 (11.97-29.61)	19.13±3.05 19.21 (14.03-26.78)	0.862
PNS – PWN (mm)	97	19.92±3.43 20.10 (10.03-28.45)	20.03±3.06 20.70 (10.03-24.67)	19.84±3.73 19.07 (12.49-28.45)	0.396
Angle (α) (°)	97	53.65±6.94 53.41 (39.92-72.96)	53.49±7.08 53.47 (39.92-67.03)	53.79±6.90 53.33 (41.10-72.96)	0.994
PR Types n (%)	Type 1	40 (20.62%)	23 (26.74%)	17 (15.74%)	0.169
	Type 2	92 (47.42%)	38 (44.19%)	54 (50%)	
	Type 3	62 (31.96%)	25 (29.07%)	37 (34.26%)	

Values are given as Mean±Standard Deviation and Median (Min-Max)

Table 3. Spearman correlation coefficients (r) between pairs of parameters for each side and between the left and right sides

	Age	LPR	RPR	PNS-LTL	PNS-RTL	RTL-LTL	PNS-PWN	Left α
LPR	-0.122							
PPR	-0.096	0.742**						
PNS-LTL	-0.102	0.971**	0.757**					
PNS-RTL	-0.090	0.760**	0.978**	0.775**				
RTL-LTL	-0.035	0.376**	0.347**	0.335**	0.340**			
PNS-PWN	0.281**	0.154	0.178	0.159	0.173	0.191		
Left α	-0.072	0.015	-0.197	0.036	-0.222*	-0.201*	-0.028	
Right α	-0.086	0.008	-0.136	0.041	-0.132	-0.143	0.170	0.602**

**. Correlation is significant at the 0.01 level (2-tailed)
*. Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

In this study, 3D head models generated from DICOM datasets were used. It was aimed to enhance the reproducibility of the measurements by employing accurate and clear landmarks. The utilization of reconstructed 3D models provided a comprehensive understanding of the spatial relationships between anatomical structures within the nasopharynx. These measurements carry significant implications for surgical planning, radiation therapy, and the diagnosis of various pathologies in this region. Despite substantial advancements in medical knowledge concerning the anatomy of the PR, it remains an area of paramount clinical importance due to its high prevalence in the occurrence of NPC. Early detection of NPC is essential for timely treatment, which in turn contributes to improved survival rates (13).

Cone beam computed tomography (CBCT) imaging plays a crucial role in providing detailed three-dimensional information, enabling accurate diagnosis and treatment planning in various dental applications (14). In addition, it is also more practical and less time-consuming in terms of scanning patients in the upright position (15). Sutthiprapaporn et al. (2008) highlighted the advantage

of upright positioning during CBCT scans to minimize gravitational effects that may distort PR morphology typically observed in supine MDCT imaging (16). They also stated that CBCT imaging may facilitate the early diagnosis of NPC (9). In our analysis of radiology archive images, we identified cases with distorted PR morphology, aligning with Sutthiprapaporn et al.'s (2008) findings. However, we excluded such images and opted for MDCT datasets that facilitated clear PR identification. On the other hand, diagnosis of NPC is commonly performed in ENT clinics, utilizing symptom evaluation, physical examination, biopsy analysis, and MRI or MDCT imaging for accurate assessment (13). While CBCT imaging is predominantly used in dentistry, it is not practical for the diagnosis NPC. Therefore, our study employed MDCT images which are routinely utilized in ENT clinics.

Several studies have explored the detailed understanding of the PR and parapharyngeal space by analyzing images obtained from CBCT and MDCT (4,9,17-21). Loh et al. (1991) examined the PR morphometry in MDCT images of supine patients and reported a maximum PR depth of 18.8 mm (19). In contrast, Sutthiprapaporn et al. (2008) compared CBCT and MDCT techniques and found significantly lower PR depth values in CBCT imaging (1.1 mm on the left side, 2.1 mm on the right side) compared to their MDCT imaging results (6.8 mm on the left side, 9.8 mm on the right side) (9). Takasugi et al. (2016) evaluated CT images and reported a PR depth of 14 mm in the Japanese population (21). Furthermore, in two distinct investigations scrutinizing the Anatolian populace, Erdem et al. (2020) documented PR depths of 10.3 mm for males and 11.31 mm for females, while Kaplan et al. (2022) reported a variability spanning from 7.6 to 12 mm (4,18). In another CBCT study on an Anatolian sample, Serindere et al. (2022) reported PR depths of 5.26 mm on the left side and 5.54 mm on the right side (20). Our study revealed an average PR depth of 10.42 mm (male: 10.00 mm; female: 10.76 mm). These reported values of PR depths exhibit discrepancies both between different populations and within the same population.

The literature presents variations in the spatial relationship between the TL and the PNS. Interestingly, despite utilizing the same imaging modality and studying samples from either similar or different populations, divergent results have been documented. Furthermore, consensus is yet to be reached concerning the disparity between the left and right TL distances (4,9,20). Sutthiprapaporn et al. reported that both the torus tubarius and torus levatorius extend into the nasopharynx while in upright position. They additionally noted that these structures move downward when in supine position, leading to increased distances between the left and right sides (9). With the exception of the values reported by Sutthiprapaporn et al., previous studies have reported similar findings regarding the distance between the PNS and the PWN (4,9,20). The divergent outcomes in Sutthiprapaporn et al.'s study can likely be attributed to their notably smaller sample size. The same phenomenon of sample group discrepancy may also account for the lower values reported by Sutthiprapaporn et al. for the angle between the PR and sagittal axis (9).

The pharyngeal recesses (PRs) are classified into three distinct types based on their morphological characteristics. In our study, type 2 PRs were the most prevalent, followed by type 3 and type 1. Interestingly, similar pattern was observed in the study conducted by Takasugi et al., where type 2 PRs were also the most common, albeit with potentially different frequencies (21). On the other hand, Kaplan et al. reported in 2019 that type 1 PRs were the most prevalent, followed by type 3 and type 2, while their subsequent investigation in 2022 reported an altered order of type 3, type 2, and type 1 (17,18). These variations in the prevalence and ordering of PR types observed across different studies highlight the need for further exploration and elucidation of the underlying factors contributing to these discrepancies.

CONCLUSION

The reported discrepancies of reported measurements between different populations or even within the same population can be attributed to variations in imaging techniques, patient positioning, population-specific anatomical differences, and variations in sample sizes and demographics. A thorough understanding of these factors is crucial for accurate interpretation and clinical application of morphometric knowledge involving such anatomical regions. The technique which we employed, offers several advantages in understanding the anatomical features of the region. Utilization of 3D models reconstructed from MDCT datasets provided a comprehensive and high-resolution approach. This technique allows for a detailed visualization and analysis of the PR, offering a three-dimensional perspective that enhances our understanding of its morphometry and spatial relationships. The high-resolution imaging provided by MDCT datasets may contribute to a more accurate depiction of the PR and enable a better assessment of its variability across different populations. Furthermore, the capability to rotate the 3D models in desired spatial planes and the ability to accurately position radiological planes at specific landmarks confers practicality in conducting measurements. These measurements would otherwise be challenging through conventional morphometric analysis methodologies. Therefore, our study highlights the potential benefits of using 3D models generated from MDCT datasets to further explore and elucidate the morphometric characteristics of the PR, advancing our understanding of this anatomical region.

This study has several limitations. Firstly, the analysis was based on MDCT datasets obtained from a single center, limiting the ethnic diversity of the sample and potentially affecting the generalizability of the findings to other populations. Secondly, comparisons with other studies in the literature were primarily performed

with CBCT images, rather than 3D models. Differences in imaging modalities may introduce variations in measurements and hinder direct result comparisons. Furthermore, the sample size of 97 MDCT DICOM datasets, while substantial, should be considered in the interpretation of the results. Lastly, this study focused solely on morphometric analysis and did not consider other relevant factors such as demographics, clinical data, or functional aspects. Future studies could address these limitations and adopt a multidimensional approach to enhance our understanding of the pharyngeal recess and parapharyngeal space.

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Research Article

Evaluation of Poisoning Cases Presenting to the Pediatric Emergency Department

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Abstract

Aim: Poisoning in the pediatric population often results in numerous visits to emergency services. The purpose of our study is to conduct a retrospective analysis of the demographic and epidemiological characteristics, clinical progression, laboratory findings, and prognosis of patients who presented to the pediatric emergency outpatient clinic due to poisoning.

Material and Methods: The clinical and laboratory features of patients who presented to our hospital's emergency department due to poisoning between March 2019 and March 2020 were retrospectively examined. Statistical analyses were carried out using IBM SPSS Statistics for Windows 22.0 software.

Results: The mean age of the 624 cases who presented to the pediatric emergency department due to poisoning over a one-year period was 7.9±6.2 (1.0-18.0) years, with 49.8% of them being female (n=311). It was found that the cause of poisoning in 14.6% (n=91) of the cases was a suicide attempt. Drug intoxications accounted for 54.3% (n=339) of all cases, of which 77% (n=261) involved a single drug and 23% (n=78) involved multiple drug consumption. 79.3% (n=495) of the patients, who had an admission time to hospital of 1.3±0.6 (1.0-4.0) hours, were asymptomatic upon arrival, and 71.5% (n=446) were admitted for hospitalization. 28.5% (n=178) were treated on an outpatient basis. 35.3% (n=157) of the hospitalized patients required monitoring in the intensive care unit. The mean hospital stay was determined to be 2.4±1.1 (1.0-11.0) days.

Conclusion: Drugs, especially analgesics, are the most frequent cause of poisoning in childhood. The most appropriate strategy for poisoning will be to enact preventive measures, increase societal awareness, and ensure that diagnosis and treatment are swiftly and effectively implemented.

Keywords: Poisoning, child, emergency department

INTRODUCTION

Childhood poisoning represents a significant health concern both globally and nationally, contributing to severe mortality and morbidity, with a high incidence of emergency service admissions and hospitalizations (1). The American Poison Control Center's records indicate that over two million children seek assistance from pediatric emergency services due to poisoning annually (2). Based on 2020 data from the National Poison Information Center, roughly 47% of emergency service visits due to poisoning involve children (3). In children, poisonings most commonly occur within the 1-5 age group and are typically accidental in nature (3). As the causes, types, and influencing factors of poisoning vary between countries, and even among different regions within the same country, it is essential for each nation to evaluate its unique poisoning profile and implement necessary precautions according to identified risks (4).

According to the Turkish Statistical Institute's 2019 reports, injuries and poisonings constituted the most

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frequent cause of death within the 1-17 age group (5). In 2014, the mortality rate attributed to this cause among children was reported at 69.4% (5). The 2020 data from the American Center for Disease Control and Prevention state that accidental injuries and deaths are the most prevalent causes (6). The aim of our study was to conduct a retrospective evaluation of the demographic and epidemiological characteristics, clinical progression, laboratory findings, and prognosis of patients who presented to the pediatric emergency outpatient clinic due to poisoning.

MATERIAL AND METHOD

Hospital records, clinical, and epidemiological data from patients who presented to our hospital's pediatric emergency department due to poisoning between March 2019 and March 2020 were retrospectively analyzed. The study received approval from the Hitit University Faculty of Medicine Clinical Research Ethics Committee on 08/09/2020, under decision number 325.

The study excluded food poisonings other than those caused by mushrooms and plants. Patients poisoned by drugs and substances other than drugs were considered separately. Non-drug ingestions were classified into categories such as caustic/corrosive substances, inhaled gases, plants, fungi, hydrocarbons, organophosphates, insect bites, rat poison, mercury, and naphthalene. Details recorded included the cause of poisoning (accidental or intentional), the route of administration (oral, parenteral, transdermal, inhalation, rectal), the time from poisoning to arrival at the emergency department, clinical findings, treatments administered prior to and at the emergency department, and the location and duration of follow-up.

Statistical analyses were conducted using IBM SPSS Statistics for Windows 22.0 software. Pearson's chi-square test or Fisher's exact test were employed to compare qualitative variables when the expected frequency was less than five cells. The Shapiro-Wilk test was utilized to determine whether numerical variables followed a normal distribution, and the t-test was applied to independent groups to compare normally distributed variables across two groups. The Mann Whitney U test was employed to compare non-normally distributed variables across two groups. The relationship between normally distributed variables was assessed using the Pearson correlation coefficient, while the Spearman's rank correlation coefficient was used to examine the relationship between non-normally distributed variables. A p-value less than 0.05 was deemed statistically significant.

RESULTS

Over a one-year period, the pediatric emergency service received 165,506 visits, with 624 (or 3.4%) attributed to poisonings. The mean age of these poisoning patients was 7.9±6.2 years, ranging from 1 to 18 years. Gender distribution was nearly equal, with females accounting for 49.8% (n=311) and males 50.2% (n=313). Poisoning as a result of a suicide attempt constituted 14.6% (n=91) of cases. The mean age of those attempting suicide was 15.3±1.3 years (range: 12-17 years), with females comprising 71.1% (n=64) of this subgroup. From the moment of hospital admission, averaging 1.3±0.6 hours (range: 1-4 hours) post-poisoning, 71.5% (n=446) of patients were hospitalized, while 28.5% (n=178) were treated as outpatients. Of those hospitalized, 35.3% (n=157) required intensive care, with an average hospital stay of 2.4±1.1 days (range: 1-11 days).

When grouped by age, males dominated cases under 12 years, while females were more frequent among those 12 years and older (Table 1). The mean age of those poisoned with corrosive substances (n=83) was 3.2±3.7 years (range: 1-17 years), with males accounting for 57.8% (n=48).

Table 1 : Gender distribution of the cases according to age groups

Gender	Age group		
	<6 years old (n=327) (%) (n)	6-11 years (n=51) (%) (n)	>12 years (n=238) (%) (n)
Female	41.9% (n=137)	39.2% (n=20)	62.6% (n=149)
Male	58.1% (n=190)	60.8% (n=31)	37.4% (n=89)

Table 2 outlines the causative factors of poisoning in our patients. Drugs were the most common cause (54.3%, n=339), followed by ingestion of corrosive substances (13.3%, n=83) (Table 2). Table 3 details the specific drugs involved in poisoning cases. Of those with drug-related poisoning, 77% (n=261) had ingested a single drug, and 23% (n=78) had taken multiple drugs. The mean age of single-drug ingestions was 6.5±5.9 years (range: 0-17 years), while those who took multiple drugs averaged 12.7±5.4 years (range: 1-17 years). Females attempting suicide represented 55.1% (n=43) of multiple-drug ingestions, with 16.9% (n=44) of single-drug ingestions resulting from suicide attempts. Despite no significant difference in terms of gender distribution, season, admission time and duration, hospitalization, location and duration, and treatment approach between patients poisoned by a single drug versus multiple drugs (p>0.05), their mean ages were statistically different (p=0.001).

The mean age of the 261 cases of poisoning due to suicide attempts was 15.2±1.6 years. The causative agent was drugs in 99.2% (n=259) of cases and insecticide-agricultural medicine in 0.8% (n=2).

Most admissions occurred during winter (27.2%, n=173) and spring (27.2%, n=170) months, with 24.2% (n=151) in summer and 20.8% (n=130) in autumn. Admissions were most common (48%, n=301) between 16:00-23:59, with the least occurring between 00:00-08:00 (18%, n=113). The peak referral time was immediately after ingestion was discovered. Upon presentation, 79.5% (n=495) of patients exhibited no symptoms, whereas 8.3% (n=52) reported

nausea and vomiting, and 2.4% (n=15) experienced drowsiness. Other complaints included dizziness, weakness, loss of consciousness, bodily convulsions, numbness, palpitations, inability to walk, shortness of breath, lip swelling, and body rash.

Table 2. Poisoning factors

Poisoning factors	n	%
Drug	**339**	54.3
Corrosive-caustic substance	83	13.3
Alcohol	42	6.7
Food	42	6.7
Carbon monoxide	37	5.9
Mushroom	25	4.0
Hydrocarbon	23	3.7
Insecticide-agricultural pesticide	13	2.1
Rat poison	12	1.9
Herb	5	.8
Other chemicals	2	.3
Mercury	one	.2
TOTAL	**624**	**100.0**

Table 3: Drugs causing poisoning

Active ingredient	n	%
Paracetamol	43	12.6
Diclofenac potassium	20	5.8
Ibuprofen	16	4.7
Risperidone	8	2,4
Methylphenidate hydrochloride	7	2.1
Metformin	6	1.8
Dexketoprofen	6	1.8
Sertraline	6	1.8
Valproic acid	5	1.5
Acetylsalicylic acid	5	1.5
Amoxicillin+clavulanate	5	1.5
Other	212	62.5
TOTAL	**339**	**%**

In terms of treatment, common interventions for poisoned patients included clinical monitoring, gastric lavage and administration of activated charcoal, and hydration and oxygen administration. The most frequent treatment was clinical monitoring and administration of activated charcoal-lavage (28.2%, n=176), followed by hydration therapy (25.6%, n=160). No antidotes were administered, and there were no recorded fatalities.

DISCUSSION

Poisoning, one of the primary reasons for pediatric emergency services visits, is predominantly observed in younger age groups (7). Although the mean age in our study was 7.9±6.2 years, it's significant to note that 52.4% of our cases were children under the age of 6 years. Similar findings are noted in the literature, such as a Spanish study of 2157 poisoning cases, where 67% of the patients were children younger than four years of age (8). The study conducted by Akgül et al. reported that 58.1% of the cases involved males younger than five years old, with poisonings becoming more prevalent in females above the age of 12 (9). Similarly, in a study conducted by Özdemir et al., it was found that poisoning was more common in males younger than five years old and females older than thirteen years (10). Andıran et al. reported higher rates of poisoning in males under the age of ten and females over the age of ten (11). Consistent with these studies, our data revealed that poisoning was more common in males under 12 years of age and in females over 12 years of age. Accidental poisoning in younger children and suicidal poisoning in adolescence are common, suggesting a bimodal distribution (9).

Factors influencing poisoning differ according to geography, seasons, socio-cultural characteristics, and age group (12). In our study, the most common cause of poisoning was drug intake, followed by ingestion of corrosive substances. In line with our study, a Spanish study found that 48% of poisoning cases in the emergency department resulted from drug intake (13). Poisoning typically occurs with orally taken drugs and cleaning products easily accessible to children (8,10). In our study, the most common drugs causing poisoning were analgesics (23.1%, n=79), with paracetamol (12.6%, n=43) being the most common among them. Similar to our findings, the study by Akgül et al. reported analgesics as the leading cause of poisoning (26.9%). When evaluating the drugs ingested, the most common poisonings were attributed to nonsteroidal anti-inflammatory agents (12.3%) and paracetamol group drugs (11.3%) (9). In our study, non-steroidal anti-inflammatory agents (5.8%, n=20) were the second most common cause after paracetamol (12.6%, n=43). In a national study, it was found that 75% of poisonings reported to the National Poison Center in 2003 were drug-related, with analgesics being the most common followed by antidepressants (14). An English study reported that 60% of intoxications in children aged 14 years and younger were due to drugs, a third of which were analgesics. This widespread use of over-the-counter analgesic-anti-inflammatory drugs suggests they are easily accessible and therefore more often identified as a poisoning agent.

In the study conducted by Ozdemir et al., 44.3% of cases were poisoned with corrosive substances, with non-drug agents more commonly implicated between the ages of 1-5 (10). In our study, the rate of poisoning with corrosive substances (13.3%) was found to be lower than in the

aforementioned study, and the mean age (3.2 years) was similar. Poisoning is more frequent due to children's higher activity levels at play age and the consumption of cleaning products as food.

Numerous studies in rural areas of our country have determined that poisonings are most common in the spring and summer. In contrast, a study in Sakarya reported poisonings being most common in autumn, while a study by Biçer et al. in Istanbul reported most incidences in December, and the study of Türkmenoğlu et al. found winter to be the most common time (16-18). Türkmenoğlu suggested the lower incidence of poisoning in Istanbul during the summer months was due to fewer encounters with toxic animals and pesticides in city life, and a decrease in emergency visits as families leave the city for vacation (18). According to our study results, poisoning cases are seen more frequently in the spring and winter months. This aligns with the findings from studies in our country, which suggest an increase in exposure to toxic substances from pesticides, home dyeing and cleaning activities in the spring, and a higher occurrence of carbon monoxide poisoning in the winter months (16).

Examining the admission times of patients to the emergency department in eight-hour intervals, we found the highest admission rate (48%) between 16:00 and 23:59. Studies have reported that cases of poisoning tend to visit pediatric emergency services more frequently during evening hours (18). A study in Çukurova observed the most frequent visits in the morning (19). Türkmenoğlu's study found the most common admission hours to be between 18.00 and 23.59. This is likely because families are occupied during dinner hours and may not supervise their children as closely.

In our study, the most common reason for admission was discovery of drug intake. Most of the cases (79.5%) were asymptomatic, with less frequent development of nausea, vomiting, and drowsiness. However, when comparing the admission time and age distribution of the cases, it was found that the younger the age, the shorter the time taken to reach the hospital. In a study by Akıcı et al. in Istanbul comparing children younger than six years old and older, it was observed that the group with younger children sought help earlier. This is likely because families monitor their young children more closely and notice changes sooner (20, 21).

In our study, 14.6% of all cases involved a suicide attempt. Studies report that suicide attempts increase during adolescence, with most cases involving drug-induced poisoning, more commonly in females (6). The mean age (15.3 years) and gender distribution (71% female) of cases poisoned due to suicide in our study aligned with the literature.

Most poisoning cases are asymptomatic and require only supportive treatment. In instances of toxic dose drug intake within the first hour, gastric lavage should be performed, followed by administration of activated charcoal. The most common treatment in our study was observation and administration of activated charcoal-lavage. Antidote treatment is not always possible depending on the active substance in poisonings, and despite all interventions, some patients still die. While child poisoning mortality was 4.9% between 1975 and 1984 at Hacettepe University, the increase in early admission and improved intensive care facilities in recent years have significantly reduced mortality (10). Even et al. reported that 8% of poisoning cases were treated in the pediatric intensive care unit, with only one fatality (22). Young reported a 0.7% mortality rate, and Özdemir reported 0.9% (10,23). Kondolot et al. reported no fatalities (24). In our study, no fatalities were observed among patients treated for poisoning. We believe the lack of mortality in our cases is due to easy access to transportation and early admission, as well as advanced treatment options and intensive care facilities.

CONCLUSION

In conclusion, childhood poisonings have an important place in emergency applications and poisonings with drugs, especially analgesics still take the first place, and the frequency of suicide attempts in the adolescent age group is striking. In order to prevent childhood poisoning, it is necessary to raise awareness of families, schools and the society, and especially the preference of non-opening lids for the packaging of drugs will be beneficial in preventing accidental poisoning in young children. The most correct approach in poisoning will be to take preventive measures and raise awareness of the society, and to ensure that diagnosis and treatment are implemented quickly and effectively.

LIMITATIONS

The study is retrospective and single-center. Patients with missing data could not be evaluated.

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MEDICAL RECORDS-International Medical Journal

Research Article

The effects of Q angle and Hamstring Length on Balance Performance in Patients with Lumbar Disc Hernia

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Abstract

Aim: Patellafemoral angle (Q angle) and Hamstring length are important measurements to evaluate balance. This study aims to examine the effects of Q angle and Hamstring length on balance performance in patients with lumbar intervertebral disc herniation (LDH).

Material and Methods: LDH (n=32) and control group (CG)(n=30) were included in the study. Q angles and hamstring muscle lengths of the participants were measured. Balance was evaluated with Y balance test.

Results: As a result of our study, no difference was found between LDH patients and CG groups in terms of hamstring muscle length; Q angle decreased in LDH patients and there was a negative high correlation between Q angle and R -Anterior, R-Posteromedial, R-Posterolateral values on the right and between Q angle and L-Anterior, L-Posteriolmedial, L-Posterolateral values on the left.

Conclusion: It was found that Q angle measurements decreased in LDH patients, causing genu varum and leading to impairment in balance, especially in the left anterior, anteromedial and anterolateral.

Keywords: Lumbar intervertebral disc herniation, patellafemoral angle, hamstring length, Y balance test

INTRODUCTION

Low back pain and radicular leg pain are common problems in physical medicine and rehabilitation. LDH is one of the most common causes of this type of pain (1, 2). When pain and shoulder instability develop, this process is evaluated pathologically and requires medical and/or surgical treatment. This degenerative process includes a wide variety of morphological changes, including large tears in anulus fibrosus. From these tears in the anulus fibrosus, especially from the radial tears, the nucleus pulposus herniates and LDH develops in patients (3,4). Patients with LDH experience sciatica symptoms affecting the lower extremities due to (primarily) nerve compression. These symptoms cause a decrease in knee strength (5).

Q angle has an important place in clinical evaluations and it is also frequently used to determine the condition of the lower extremity in cadavers (6). If the Q angle exceeds the limit of 15-20 degrees, it will cause injury to the knee extensor muscles and also increase the tendency of the patella to slide laterally. As a result, severe patella femoral pain will occur. Deterioration in the biomechanics of the knee joint and lower extremity also causes balance

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disorders. In the literature review, it has been reported that the Q-angle is affected by the decrease in the speed of the quadriceps muscle with physical performance (7). Postural control and balance is the body's ability to keep its centre of gravity on the base of support, an essential requirement for independent mobility in daily life (8).

Clinical results have shown that shortening of the hamstring muscle is associated with specific conditions of the lumbar spine and general dysfunction of the lumbar region (9). Although the balance of the shortening of the hamstring muscles towards the back of the individual has not been fully clarified, knowing the effects of the short hamstrings on pelvic flexion and lumbar function during forward bending may guide the understanding of the problems in the cases. The idea that short hamstrings reduce pelvic flexion range of motion (ROM) when bending forward with the knees straight is supported by the results of studies measuring the contribution of posterior pelvic tilt to straight leg lift angle (SLL) (10). The aim of this study is to examine the effects of Q angle and Hamstring length on balance performance in LDH patients.

MATERIAL AND METHOD

In the power analysis conducted to determine the sample of the study, when the analysis was made according to Type I error (α) 0.05, power (1-β) 0.80 effect size 1.3, it was found that at least 50 participants, 25 healthy individuals and 25 LDH patients, should participate in the study (11). Individuals aged between 40 and 64 with and without a diagnosis of LDH who had not undergone surgery from the low back area and who did not have implants were included in the study, while patients who had undergone surgery from the low back area, those who had neurological disorders and those who had implants in the low back area were excluded from the study. As a result, a total of 62 individuals, patients with LDH (n=32) and healthy volunteers (n=30), participated in the study. Dominant extremities of all LDH patients and the control group were the right side.

Ethical Considerations

The study was conducted with the 2023/ 241 numbered of Non- interventional Clinical disquisition Ethics Committee. Written informed concurrence was attained from each party. The study was conducted in agreement with the declaration of Helsinki.

Data Collection Process

Demographic data and measurement results of each participant informed about the study were recorded. Hamstring muscle length of the participants was measured with Sit-Reach Test and balance was measured with Y Balance Test.

Assessment of Q Angle

The Q angle is measured by drawing a line (with a tape measure) from the spina iliaca anterior superior (SIAS) to the center of the patella. A new measurement is then made from the middle of the patella to the tuberositas tibia. To find the angle Q, measure the angle between these two measurements and then subtract 180 degrees.

The normal Q angle is 14 degrees in men and 17 degrees in women. An increase in the Q angle may indicate a higher risk of knee and knee problems (13).

Hamstring Length (Sit and reach test)

Baseline® (Cooper Institute/ YMCA, AAHPERD, New York, USA) device was used to measure hamstring length. Participants were asked to get into a long sitting position. They were then asked to place the soles of their feet on the test device and lie down three times to warm up. Then, the arm lengths of the subjects on the device were determined and they were asked to reach forward as much as possible by pressing the measuring device without raising their knees. This process was done three times and the average was recorded (14).

Y Balance Test (YBT)

Dynamic balance capability was determined by using Y Balance Test. Before the measures, the participants were given instructions about how the test would be performed and they watched videos. Regarding the knowledge effect, 6 operations were made before the sanctioned measures (15). After completing the test trials, a 2- minute break was given, followed by 3 test trials in each direction. All actors performed the Y Balance Test with the side they preferred in strength test. In this test, while actors stand in balance on one bottom, they are asked to reach as important as possible in three different directions with the other bottom at the same time anterior, posterolateral and posteromedial. For this reason, this test measures the strength, stability and balance of athletes in different directions. YBT emulsion score is calculated by adding 3 directions of reach and homogenizing the results to lower extremity, while asymmetry is the difference between right and left extremity reach (16).

Statistical Analysis

SPSS 25 was used in the study for statistical analyses. Normality analysis of the data was performed according to Kolmogrov Simirnov method and the data were found to be normally distributed. Levene test was used for homogeneity of variances. Independent Samples T Test was conducted to compare dynamic balance, hamstring length and Q angles of LDH group and CG. Pearson Correlation Coefficient was used to determine the relationship of Q angle and hamstring length with balance performance. Level of significance was determined as 0.05 in the study.

RESULTS

When the demographic data of the study were examined, while mean age was 49.12 in the LDH group, it was 51.40 in the CG. Mean height was 160.12 in the LDH group, while it was 170.86 in the CG. Mean weight was 64.3 in the LDH group, while it was 70.33 in the CG. BMI values were 25 in the LDH group and 23.77 in the CG (Table 1).

Table 1. Descriptive information of the participants

Parameters	LDH N=32	CG N=30
Age (Years)	49.12±6.59	51.40±6.64
Height (cm)	160.12±6.36	170.86±9.91
Weight (kg)	64.31±10.42	70.33±18.05
BMI(kg/m2)	25.00±3.42	23.77±4.21

BMI: body mass index

Table 2 shows Q angle, Y balance test results and hamstring lengths of the participants. According to the results, significant difference was found between LDH group and CG in terms of hamstring length (t=6.728, p<.001), QA (t=-3.124, p=.003), R-Anterior (t=-4.643, p<.001), R-Posteromedial (t=-6.320, p<.001), R-Posterolateral (t=-4.989, p<.001), L-Anterior (t=-4.817, p<.001), L-Posteromedial (t=-4.848, p<.001), L-Posterolateral (t=4.532, p<.001) (Figure 1) (Table 2).

Table 2. Right and left extremity Q angle and Y balance measurement results of the participants

Parameters	LDH N=32	CG N=30	t	p
R-QA	9.56±0.80	10.46±1.38	-3.124	.003
R-Anterior (%)	99.59±12.36	116.14±15.59	-4.643	<.001
R-Posteromedial (%)	94.88±10.27	123.06±22.29	-6.320	<.001
R-Posterolateral	101.33±14.30	128.96±26.98	-4.989	<.001
L-QA	9.56±0.80	10.46±1.38	-3.124	.003
L-Anterior (%)	103.42±11.91	119.71±14.49	-4.817	<.001
L-Posteriolmedial (%)	95.41±9.82	119.96±26.06	-4.848	<.001
L-Posterolateral (%)	104.00±9.15	127.92±27.51	-4.532	<.001
Hamstring Length	14.31±5.01	-1.06±11.85	6.728	<.001

R-Anterior (Y balance): right anterior balance, R-Posteromedial: right posteromedial balance, R-Posterolateral: right posterolateral balance; L-Anterior: left anterior balance, L-Posteromedial: left posteromedial balance, L-Posterolateral: left posterolateral balance

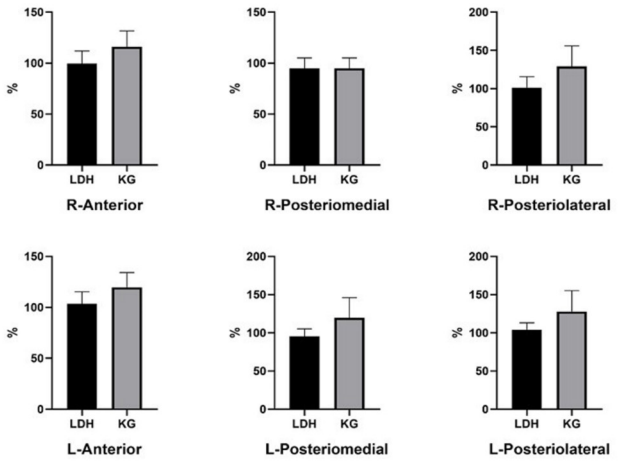

Figure 1. Comparison of Y balance performances of the participants

Table 3 shows the analysis of the relationship between participants' Q angle and hamstring length and dynamic balance performance. According to the table, negative high correlation was found between participants' Q angle and L-Anterior (r=-.564, p=.001) and L-Posterolateral (r=-.792, p=.000) (p<0.05). Negative high correlation was found between participants' Hamstring length and L-Posteromedial (r=-.719, p=.000) reach distance (p<0.05) (Table 3).

Table 3. Relationship of Q angle and hamstring length with balance performance in individuals with LDH

Variables	Q angle	Hamstring length
R-Anterior (%)	r= -.161, p=.378	r= -.186, p=.309
R-Posteromedial (%)	r= -.297, p=.099	r= .442, p=.011
R-Posterolateral	r= -.161, p=.379	r= .140, p=.446
L-Anterior (%)	r= -.564, p=.001*	r= -.180, p=.323
L-Posteriolmedial (%)	r= -.329, p=.066	r= -.719, p=.000*
L-Posterolateral (%)	r= -.792, p=.000*	r= -.560, p=.001

R-Anterior (Y balance): right anterior balance, R-Posteromedial: right posteromedial balance, R-Posterolateral: right posterolateral balance, L-Anterior: left anterior balance, L-Posteromedial: left posteromedial balance, L-Posterolateral: left posterolateral balance

DISCUSSION

In this study which aimed to find out the effects of Q angle and Hamstring length on balance performance in LDH patients, Q angle was found to decrease in LDH patients and a high negative correlation was found on the right in R-Anterior, R-Posteromedial, R-Posterolateral valıes and on the left in L-Anterior, L-Posteriolmedial, L-Posterolateral values.

The Q angle is an important mechanism in the musculoskeletal system. Changes in the Q angle cause the extensor mechanism to deteriorate and can cause balance problems by causing hypermobility and patellar instability in the knee joint (17). Although Q angle is frequently used in determining knee pathologies (18), its use in LDH patients is limited. However, it is known that knee pathologies develop secondary to the disease in LDH patients (19).

In a study conducted in literature, Q angles of individuals who are engaged in physical activity and those of sedentary individuals were compared and Q angle was found to be narrower in individuals who were physically active (20). In another study, it was reported that Q angle was associated with the strength applied by quadriceps femoris to the patella and lateral and therefore athletes could have lower Q angles (21). Due to such reasons, the effect of transmitted muscle strength will increase as Q angle gets smaller, in other words, as the angle gets narrower. In our study, it was found that anterior, posteromedial and posterolateral balance increased in the left extremity as Q angle decreased in LDH patients. However, this result was not found in the right extremity. We believe that this result was due to the fact that the left extremity was the supporting leg.

Decrease in Q angle will cause the pathology called genu verum which causes the knee to make an angle to the lateral. In this case, the load on the knee will not be evenly distributed, causing pain in the low back and knee area (22). In LDH patients, the body's centre of gravity will change and the knee will have more load due to increasing pain. In our study, we found that Q angle was lower in LDH patients (23). In this case, our study supports the literature.

If hamstrings are shorter, pelvic tilt becomes limited and looser spinal tissues will stretch (24). In addition, since hamstrings can change the transmission of force between the lower limbs and the trunk and can maintain excessive erector spine electromyography activity during dynamic activities (25), hamstring shortness will affect low back and hip functions (26). These assumptions lead to the hypothesis that hamstring shortness may affect trunk and pelvic dynamics during manual material transport.

Hamstring flexibility is considered an important component of physical fitness and plays an important role in protecting the spine (27). Shortened hamstring extensibility has been suggested as a predisposing factor for low back disorders and changes in lumbopelvic rhythm (28). In our study, we found that hamstring muscle was shorter in LDH patients when compared with CG, although not statistically significant.

CONCLUSION

As a result of the study, it was found that Q angle measurements decreased in LDH patients, leading to genu varum and as a result of this, balance was deteriorated especially in the left anterior, anteromedial and anterolateral. It is recommended that health professionals who prepare treatment protocol to LDH patients should give exercises that will specifically develop balance in these directions.

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Research Article

Investigation of the Effects of Smartphone Use on the Dominant Thumb and Wrist of University Students

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Abstract

Aim: In this study, the effects of the addiction level of smartphone use in university students on the range of motion and proprioception of the dominant hand, wrist range of motion (ROM), and thumb ROM were investigated.

Material and Methods: Wrist and thumb ROMs were measured with a manual goniometer with a sensitivity of 1 degree, and hand grip strength was measured with a hand grip dynamometer in a total of 100 volunteer university students with a mean age of 18-25. Smartphone Addiction Scale-Short Form (SAS-SF) and Patient Rated Wrist and Hand Evaluation (PRWHE) questionnaire were applied to the students. Statistical analyzes were made using the SPSS 25 program.

Results: The students' usage time of smartphones and addiction levels do not affect the hand grip strength; the increase in smartphone addiction statistically correlates with the right thumb flexion (0.016) and abduction ROMs (0.015), statistically correlated with increased pain level in daily life and statistically correlated with the decrease of the wrist radial deviation ROM (0.009). As the duration of smartphone use increases, the error rate in right thumb abduction proprioception statistically increases (0.027). In addition, we determined the statistically correlations in both thumb flexion and abduction movements.

Conclusion: We determined that the excessive usage of smartphones affects the ROM of thumb flexion and abduction, the ROM of wrist radial deviation, and the proprioception of thumb abduction, and it does not affect the hand grip strength. The findings of our research will be a source for future studies.

Keywords: Proprioception of thumb, smartphone addiction, hand grip strength, wrist ROM

INTRODUCTION

In recent times, communication tools have started to take more place in our daily lives; smartphones are also one of the most important tools. Since smartphones provide many conveniences with their applications, they are used extensively (1).

Besides the communication function, smartphones also perform many functions, such as reading books, shopping online, exchanging e-mails, sending messages, meeting new people, and providing faster access to information. Students use smartphones for many subjects, such as taking pictures of presentations or materials instead of taking (2,3).

Excessive and uncontrolled use of applications on smartphones causes addiction (1). Smartphone addiction has recently manifested itself as a widespread addiction problem around the world it seems that people are busy with a smartphone even when they have a job (4). Smartphone addiction includes being unable to stay separate from the smartphone, feeling anxious when it stays separate, spending unnecessary money despite its economically high costs, and not being able to control smartphone usage time (5).

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Since smartphones are used excessively and unconsciously, they negatively affect individuals' mental and physical health in recent times. Mental problems such as anxiety, depression, lack of attention, decreased social interaction and academic achievement, and problems in business life are observed (5,6).

As a result of unconscious and excessive use, musculoskeletal disorders originate in the head, neck, back, and hands. However, it causes numbness, loss of strength in the hands, and structural disorders in the fingers. Due to the obsession with controlling the smartphone, people experience concentration impairment and distraction, which causes accidents (3,7,8).

Smartphones offer online communication opportunities, making them an important communication tool among university students (9). However, the increase in students' smartphone usage time decreases their course concentration and negatively affects their course success. This increased usage time causes a decrease in their ability to pay attention, coordinate, problems solving, and quickly reaction (10-13).

It is also often necessary to measure proprioception to determine the cause of the resulting movement or balance problems or the effects of an intervention (14). Proprioception is defined as awareness of the mechanical and volumetric state of the body and its musculoskeletal parts. Proprioception is also critical for learning, planning, executing, and correcting motor actions (15,16). Besides, each person has a different degree of proprioception awareness. The sense of perception of hand movements is based on multi-sensory information, including touch and muscle proprioception. Proprioception disorders cause muscle coordination disorders that cause people injuries (14-16).

In this study, we investigated the addiction level of the smartphones of university student's effect on the range of motion (ROM) of the dominant hand, wrist, thumb, and the effect of proprioception alteration.

MATERIAL AND METHOD

100 volunteer university student were included in the study. The participant's average age was between 18-25, and informed consent forms were taken from the participants. Ethical approval of Malatya Turgut Özal University Non-Invasive Clinical Research Ethics Committee was obtained (2022/78).

The participants who did not have any deformity or congenital deformity in the wrist or hand were included in the study. Individuals who had wrist trauma or surgery were not included in the study. To eliminate the margin of error, 3 measurements were taken from the participants, and the average value was recorded.

Various measurements were taken from the participants' dominance and non-dominance hand. Goniometer measured the ROM while they were sitting position with placing their forearm on the table.

The most appropriate 20° of thumb flexion ROM used in daily life was determined in proprioceptive evaluation. Besides the thumb abduction, ROM was measured at the most appropriate 40° used daily, with eyes open and closed .

Ulnar and radial deviation joint movement measurement of the pivot point of the goniometer was placed in the 3rd carpometacarpal joint. The fixed arm was placed parallel to the midplane of the radius and ulna. Then the mobile arm is followed the third metacarpal bone during the motion (17).

The grip strength was measured by the "Baseline Hydraulic Hand Dynamometer." The measurements were performed while sitting and standing. In the first measurement, the shoulder was in adduction, the elbow was in 90 flexions, the forearm was in a neutral position, the wrist was measured at 0-30˚, the extension, and the ulnar deviation was calculated at 0-15˚. In the second measurement position, the shoulder was adduction while standing, the elbow was in extension, and the forearm was in the neutral position (18).

Smartphone Addiction Scale-Short Form (SAS-SF) was developed to measure individuals' smartphone addiction risk. The scale consists of 10 parts, and 6 of the query is evaluated with a Likert grade scale. The scale questions consisting of 10 items are graded with a 6-point Likert scale. Validity and reliability studies of the scale were conducted for university students. Scale scores range from 10 to 60. As the test score increases, people's smartphone addiction increases (19).

Patient Rated Wrist and Hand Evaluation (PRWHE) scale consists of 15 queries. It was performed to measure daily life disability and pain due to wrist problems by professional surgeries on wrist surgery. As the total score in the PRWHE questionnaire approaches 0, the level of pain and disability decreases, while as it approaches 100, pain and disability increase (20).

Statistical Analysis

The analysis of the data included in the research was carried out with the SPSS25 (Statistical Program in Social Sciences) program. Normal distribution was checked with the Kolmogorov Smirnow Test (21). The significance level (p) was taken as 0.05 for the comparison tests. Since the variables did not have a normal distribution (p>0.05), the analysis was continued with non-parametric test methods. Spearman rank correlation coefficient was used since the variables included in the study showed normal distribution. The Cronbach α coefficient was used to determine the reliability analysis of the scales.

RESULTS

Demographic Information

Demographic information of the participants is given in Table 1.

Table 1. Demographic information of the participants

Variable	Groups	Frequency	Percent
Gender	Male	41	41.0
	Female	59	59.0
Age	17-19 age	50	50.0
	20 age and over	50	50.0
Marital status	Single	98	98.0
	Married	2	2.0
Dominance hand	Right	90	90.0
	Left	10	10.0
How many years have you been using a smartphone?	1-5 year	32	32.0
	5-7 year	34	34.0
	8 year and over	34	34.0
Do you have a psychiatric disorder?	No	95	95.0
	Yes	5	5.0
Do you have any physical disorders?	No	97	97.0
	Yes	3	3.0
Have you had a hand operation?	No	98	98.0
	Yes	2	2.0
Do you use glasses or contact lenses?	No	49	49.0
	Yes	51	51.0
Mothers of the student's educational status	Illiterate	9	9.0
	Primary school	48	48.0
	High school	28	28.0
	University	13	13.0
	Graduate	2	2.0
Fathers of the student's educational status	Illiterate	3	3.0
	Primary school	21	21.0
	High school	38	38.0
	University	33	33.0
	Graduate	5	5.0
The tool used to access the Internet	Mobile phone	94	94.0
	Tablet	2	2.0
	Computer	4	4.0
Daily smartphone usage time	Less than 1 hour	3	3.0
	1-2 hour	10	10.0
	3-4 hour	45	45.0
	4-5 hour	29	29.0
	More than 6 hour	13	13.0
Number of cell phone checks per day	Less than 10 times	5	5.0
	11-20 times	24	24.0
	21-30 times	21	21.0
	31-40 times	27	27.0
	More than 40 times	23	23.0
The market value of the used mobile phone	2000 TL and below	19	19.0
	2001-5000 ₺	46	46.0
	5001-10000 ₺	23	23.0
	10001 TL and above	12	12.0
Most used phone time	08.00-12.00 hours	1	1.0
	12.00-18.00 hours	19	19.0
	18.00-24.00 hours	69	69.0
	24.00-08.00 hours	11	11.0
Total		**100**	**100.0**

Definitive stats of scale scores

The mean scores of the scale scores, the standard deviation values, the intervals of variation of the scale scores, and the Cronbach α reliability coefficients were calculated for the participants (Table 2).

It was determined that the ABI-SF Index ranged between 12 and 59, the average was 30.2±10.73, and the Cronbach's alpha value scale total correlation coefficient was 0.907. Besides the PRWHE Index ranged from 1 to 88, the mean was 27.98±20.45, and the Cronbach's alpha value scale total correlation coefficient was 0.913 (Table 2).

Examining the parameters of investigation

Evaluations of the relationship between the tests and grip strength

The participants included in the study were tested to determine whether there is a relationship between smartphone usage time, SAS-SF index, PRWHE Index, and hand grip strength. There was a statistically significant weak positive correlation between SAS-SF and PRWHE pain (p=0.007). It was determined that there was no statistically significant relationship between the right and left grip strength of MFUT and SAS-SF (Table 3).

Table 2. Descriptive statistics and reliability values of scale scores

Scale	Mean±sd	Median (Min-Max)	Cronbach alfa
SAS-SF	30.2±10.73	31(12-59)	0.907
PRWHE Index of pain	10.12±7.34	9(0-30)	0.913
PRWHE Index of function	9.53±9.73	7(0-39)	
PRWHE Index of daily activities	8.47±6.72	7(0-27)	
PRWHE Index	27.98±20.45	25.5(1-88)	

sd: standart deviation, SAS-SF: smartphone addiction scale-short form, PRWHE: patient rated wrist and hand evaluation

Table 3. The relationship between Mobile phone usage time, SAS-SF index, PRWHE İndex, and hand grip strength

Indexes	Value	Right hand SGS	Right hand CGS	Left hand SGS	Left hand CGS
MFUT	r	-0.065	-0.032	-0.028	0.036
	p	0.521	0.751	0.783	0.723
SAS-SF	r	-0.003	-0.079	-0.013	-0.070
	p	0.979	0.434	0.899	0.491
PRWHE	r	-0.142	-0.115	-0.136	-0.153
	p	0.162	0.258	0.180	0.132

r: sperm rank correlation coefficient, *p<0.05, SGS: standing grip strength, CGS: grip strength sitting in a chair, MFUT: mobile phone usage time, SAS-SF: smartphone addiction scale-short form, PRWHE: patient rated wrist and hand evaluation

Evaluations of the relationship between the tests and the ROM of wrist

The participants' wrist flexion, extension, radial deviation, and ulnar deviation values were analyzed. There was a negative, weak, statistically significant relationship between SAS-SF scale and right-left hand of the radial deviation. In addition there was a weak positive correlation determined between SAS-SF and left wrist extension (p<0.05) (Table 4).

Evaluations of the relationship between the tests and the ROM of thumbs

The correlation of the ROM of the thumb with the duration of smartphone use, the SAS-SF index and the PRWHE Index value were analyzed (Table 5). A positive, weak, statistically significant correlation was found between SAS-SF and the right thumb flexion and thumb abduction movement (p<0.05). There was a positive weak statistical significance that was determined between the PRWHE index and the flexion of the right thumb (p<0.05) (Table 5).

Table 4. Evaluations of the relationship between the tests and the ROM of wrist

Scales	Values	Extension of the right hand	Flexion of the right hand	Radial deviation of the right hand	Ulnar deviation of the right hand	Extension of the left hand	Flexion of the left hand	Radial deviation of the left hand	Ulnar deviation of the left hand
MFUT	r	0.128	-0.197	-0.069	0.152	-0.016	-0.175	0.167	0.081
	p	0.205	0.051	0.492	0.131	0.872	0.082	0.096	0.426
SAS-SF	r	0.121	-0.008	-0.261	0.014	**0.284**	0.141	-0.225	-0.001
	p	0.231	0.940	**0.009***	0.891	**0.004***	0.161	**0.025***	0.992
PRWHE	r	0.050	0.082	-0.154	-0.162	0.052	0.172	-0.150	-0.145
	p	0.624	0.424	0.131	0.111	0.609	0.091	0.141	0.154

r: sperm rank correlation coefficient, *p<0.05, SGS: standing grip strength, CGS: grip strength sitting in a chair, MFUT: mobile phone usage time, SAS-SF: smartphone addiction scale-short form, PRWHE: patient rated wrist and hand evaluation

Table 5. Evaluations of the relationship between the tests and the ROM of thumbs

Scales	Values	The flexion of the right thumb	The abduction of the right thumb	The flexion of the left thumb	The abduction of the left thumb
MFUT	R	-0.145	-0.149	-0.096	0.110
	P	0.150	0.138	0.341	0.277
SAS-SF	R	**0.240**	**0.244**	0.077	-0.053
	P	**0.016***	**0.015***	0.448	0.600
PRWHE	R	0.277	0.010	-0.009	-0.067
	P	**0.006***	0.921	0.927	0.513

r: sperm rank correlation coefficient, *p<0.05, SGS: standing grip strength, CGS: grip strength sitting in a chair, MFUT: mobile phone usage time, SAS-SF: smartphone addiction scale-short form, PRWHE: patient rated wrist and hand evaluation

Evaluations of the relationship between the tests and the proprioception of thumbs

The correlation of the eyes open proprioception of thumb and eyes closed proprioception of thumb with the duration of smartphone use, the SAS-SF index, and the PRWHE Index values were analyzed. In addition, the thumb proprioception correlation among themselves was analyzed (Table 6).

A positive, weak, statistically significant correlation was found between the duration of smartphone use and the eyes open proprioceptive value determined with the right thumb abduction ROM (p<0.05) (Table 6).

The eyes open right thumb flexion proprioception was correlated with, the eyes closed right thumb flexion, the eyes closed and opened right thumb abduction, the eyes closed left thumb flexion, and the eyes opened left thumb abduction (Table 6).

The eyes closed right thumb flexion proprioception was correlated with, the eyes closed and opened right thumb abduction, the eyes closed left thumb flexion, and the eyes opened and closed left thumb abduction (Table 6).

The eyes opened right thumb abduction proprioception correlated with, the eyes closed right thumb abduction and opened left thumb flexion. The eyes closed right thumb abduction proprioception was correlated with the eyes closed left thumb flexion (Table 6).

The eyes opened and closed left thumb flexion, and abduction proprioception were correlated with left thumb proprioception movements except the left flexion eyes opened proprioception and left abduction eyes closed proprioception (Table 6).

Table 6. Evaluations of the relationship between the parameters and the proprioception of thumbs

Parameters	Values	The prop. of right thumb FLX-EO	The prop. of right thumb FLX-EC	The prop. of the right thumb. ABD-EO	The prop. of the right thumb ABD-EC	The prop. of left thumb FLX-EO	The prop. of left thumb FLX-EC	The prop. of the left thumb. ABD-EO	The prop. of left thumb ABD-EC
MFUT	R	-0.025	0.035	0.221	0.062	-0.047	-0.109	-0.028	0.055
	P	0.808	0.727	0.027*	0.540	0.641	0.280	0.786	0.586
SAS-SF	R	0.002	-0.110	-0.002	-0.042	-0.227	-0.110	0.013	0.074
	P	0.986	0.275	0.981	0.681	0.023	0.274	0.902	0.464
PRWHE	R	-0.055	-0.070	-0.094	-0.026	0.023	-0.003	-0.069	0.069
	P	0.589	0.495	0.356	0.799	0.821	0.974	0.501	0.497
The prop. of right thumb FLX-EO	R		0.592	0.243	0.219	0.132	0.276	0.201	0.001*
	P		**0.001***	**0.015***	**0.029***	0.191	**0.006***	**0.044***	0.997
The prop. of right thumb FLX-EC	R			0.247	0.229	0.148	0.402	0.232	0.231
	P			**0.013***	**0.022***	0.142	**0.001***	**0.020***	**0.021***
The prop. of the right thumb. ABD-EO	R				0.552	0.248	0.165	0.104	0.079
	P				**0.001***	**0.013***	0.101	0.301	0.435
The prop. of the right thumb. ABD-EC	R					0.163	0.310	0.179	0.226
	P					0.104	0.002	0.075	0.023
The prop. of left thumb FLX-EO	R						0.543	0.274	0.195
	P						**0.001***	**0.006***	0.052
The prop. of left thumb FLX-EC	R							0.291	0.209
	P							**0.003***	**0.037***
The prop. of the left thumb. ABD-EO	R								0.319
	P								**0.001***

r: sperm rank correlation coefficient, *p<0.05, SGS: standing grip strength, CGS: grip strength sitting in a chair, MFUT: mobile phone usage time, SAS-SF: smartphone addiction scale-short form, PRWHE: patient rated wrist and hand evaluation
EO: eyes open, EC: eyes closed FLX: flexions ABD: abduction

DISCUSSION

Excessive use of smartphones for purposes other than their intended purpose may adversely affect people's physiological, psychological and social development. Excessive use of smartphones, especially by young users, causes smartphone addiction (22). In the study by Noyan et al., the students' SAS-SF mean scores were 26.17±9.64 (19). In the study of Kwon et al., this average is 25.7 (3). In our study, the mean score of the students in SAS-SF scores was found to be 30.2±10.73. The fact that the scores on this scale are close and have similar values showed that the results given in the studies in which this scale was conducted with different student groups were at the same values.

It has been determined that the frequency of smartphone use in individuals in the 18-34 age group in Turkey has reached 81% (23). Barthwal et al. found that 62.1% of students use smartphones for more than 3 hours (24). In two similar studies conducted by Jilisha et al., and Güneş et al., in which the average daily cell phone usage time was examined, the rate of use of three hours or more was found to be 71% and 73% (25,26). In the study of Noyan et al., it is seen that people are interested in their smartphones for 3-4 hours (32.9%) at most (19). In our study, similar to the results of Noyan et al., it was determined that students use their smartphones for a maximum of 3-4 hours (45%) per day.

Jilisha et al., Güneş et al., in their study, similarly found that students usually check their phones first when they get up in the morning (25,26). As a result of Sarıkaya's research on associate degree students, it is pointed out that as the frequency of checking their smartphone increases, nomophobia increases (27). In his study, Yılmaz concluded that 42.6% of students check their phones 41 times a day or more (28). In the study by Noyan et al., 38.7% of the students checked their smartphones 40 or more times; It was observed that 23.6% of them checked 20 times a day or less (19). In our study, 27% of the students checked 31-40 times, 24% 11-20 times, 23% 40 times a day, and more; It was determined that 5% of them checked their smartphones ten times or less. As a result of this situation, we think that nomophobic behaviors increase in those who check their phones 40 or more times a day.

As a result of Sarıkaya's research on associate degree students, it was determined that the nomophobia levels of students with a smartphone experience of 4-5 years and more than five years were significantly higher than those with less than one year of smartphone experience (27). As a result of their studies, Gezgin et al. and Yıldırım et al. similarly state that the level of nomophobia increases as the smartphone experience increases (29,30). In our study, when we look at the years of use of smartphones, it was determined that 34% of those who use smartphones for 5-7 years and eight years or more. The fact that the SAS-SF data is high during this period shows that the long-term use of the phone by the students increases the level of addiction.

Gay et al. developed a motion-tracking system for wrist joint position sense measurement and evaluated passive and active joint position sense for flexion and extension movements in 80 healthy individuals. They found that flexion and extension error averages 4.9° in passive and 5.9° in active movement (31).

Patterson et al. evaluated the wrist joint position sense with the goniometer they developed and found that the error amount in neutral and extension varied between 0° and 3° (32).

In our study, joint position sense was evaluated for thumb abduction and flexion movements with eyes open and eyes closed. As a result of our research found a significant relationship between the students' smartphone usage time and the right-hand thumb abduction movement and eye-open proprioceptive value. Here, the increase in ECTS is associated with abduction movement, especially in the dominant right thumb. Because the proprioception values in the right and left thumb flexion and abduction movements are correlated in the measurements with eyes open and eyes closed, we think that the right and left thumbs are affected in a parallel direction, influence not only peripheral but also central.

Smartphone users also experience pain, numbness, muscle weakness, and limitation of movement in other parts of the body, including the neck, shoulder, elbow, arm, wrist, hand, thumb, and finger. Kim et al. As a result of ultrasound evaluation, it was reported that excessive smartphone use causes thumb pain and reduces finger grip strength and hand functions (33). In the study of Eapen et al., it was determined that hand muscles are used excessively due to holding mobile devices in hand for a long time, and myofascial pain syndrome in hand may develop as a result (34). In their study, Gustafsson et al. found that numbness developed in the hands and fingers due to texting on the phone (35). Berolo et al., in their study on university students and staff, found that pain developed in the right thumb due to mobile device use (36). Inal et al., in their study, determined that the repeated use of smartphones for messaging may cause Dequervein tenosynovitis by damaging the extensor pollicis longus tendon of the thumb in addition to the tendons in the first compartment of the wrist (37). Our study was similar to the studies in the literature, and it was determined that there was a significant relationship between the students' smartphone usage time and PRWHE pain, right thumb flexion and abduction, and radial deviation values of both wrists, and it did not affect grip strength.

Choi et al., in their study on 315 students using smartphones, determined that as the duration of use of the devices increased, the problems related to the musculoskeletal system grew, and they found that the pain was also associated with the period of use of these devices (38). Turgay et al. found that students with pain in the hands/wrists at any time during the last 12 months had higher mean scores in SAS-SF than those who did not (39). In our study, there was a weak positive correlation between ABI-SF and right thumb flexion and abduction movement; There was a weak positive and statistically significant correlation between ECTS and proprioceptive value measured with right-hand thumb abduction movement with eyes open. This shows that the flexion and abduction movements of the thumb increase in direct proportion with the increase in addiction, and the increase in the duration of smartphone use also increases the error rate in thumb proprioception, that is, the sensitivity error.

CONCLUSION

In conclusion, we determined that the excessive usage of smartphones affects the ROM of thumb flexion and abduction, the ROM of wrist radial deviation, and the proprioception of thumb abduction and does not effects the hand grip strength. The findings of our research will be a source for future studies.

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Research Article

Evaluation of the Effect of COVID-19 on Patients Undergoing Orthodontic Treatment

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Abstract

Aim: COVID-19 necessitated a reassessment of existing work patterns in all professions. The aim of this study was to evaluate the physical and psychosocial effects of the pandemic on different orthodontic treatment groups.

Material and Methods: This descriptive, cross-sectional survey study evaluated data from 235 volunteers aged 18 years and older who were receiving orthodontic treatment (mean age: 23.8+5.8 years; 83 male, 152 female). The 15-item questionnaire comprised three sections: sociodemographic characteristics, the psychosocial effects during the COVID-19 pandemic, and the physical/oral symptoms in orthodontic patients who had COVID-19. Statistical significance was set at $P<0.05$.

Results: Over half (53.2%) of participants stated they attended routine orthodontic follow-up visits and felt no concern about the risk of COVID-19 transmission, while 85.9% said they were happy to receive orthodontic treatment during the pandemic. In addition, 68.1% of the participants considered the pandemic to be advantageous for orthodontic treatment, most commonly because wearing masks concealed orthodontic wires (44.3%).The most pronounced intraoral finding among patients with COVID-19 was loss of taste (5.9±4.6).

Conclusion: The COVID-19 pandemic was found to have no serious negative psychosocial effects. Mask use was reported to be the greatest advantage, while dysgeusia was one of the most common oral findings.

Keywords: COVID-19, orthodontics, pandemics, braces, clear aligner appliances

INTRODUCTION

Pandemics of varying scale and severity have occurred throughout human history. In addition to causing mass casualties, they have also wrought many economic and psychosocial consequences. Current advances in technology have made it possible for health services and personnel to reach more areas in shorter time. As a result, infection can be detected more rapidly and controlled more easily than in the past. However, international travel has also become faster, more comfortable, and more affordable, which facilitates the spread of epidemics. Therefore, it did not take long for the COVID-19 epidemic that emerged in Wuhan, China in late 2019 to spread to other continents. The World Health Organization (WHO) officially named the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection "COVID-19" on February 11, 2020 and declared it a pandemic on March 11, 2020 (1). Globally, more than 600 million cases of COVID-19 have been identified and more than 6.4 million deaths documented, with 4.2 million new cases reported between August 29 and September 4, 2022, representing a 12% decrease in the number of

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weekly cases compared to the previous week (2).

The COVID-19 pandemic, which is now in its third year, has posed a major threat to public health worldwide (3). Even when infection is controlled through effective treatment and/or vaccination, dramatic and long-term changes in lifestyle, work, and sociocultural relations are expected to affect the entire world population (4). Like other health services, dentistry has also been reshaped during this process. The COVID-19 pandemic has had a direct impact on all social environments and professions, and orthodontics is also among these occupational groups. While the physical and psychosocial effects of the pandemic are still being felt in orthodontics practice, it is estimated that some important adaptations will be reversible and some will be permanent (3).

In addition to the consequences of the pandemic for physicians, orthodontic patients' expectations from dentists, treatment priorities, and views on treatment have also changed. During the pandemic, all routine dental services were suspended in countries experiencing COVID-19 outbreaks as priority shifted to the need for organized emergency care provided by teams equipped with appropriate personal protective equipment (5). Dentistry practices pose a greater risk for the transmission of COVID-19 than many other health services because of the intense aerosol production, high viral load in the saliva of infected people, and the close face-to-face contact with patients during treatment (6). The invariable detection of SARS-CoV-2 in the oral mucosa (7) and saliva (8) of infected persons required dental health professionals and other medical personnel performing aerosol-generating procedures to be placed in the "very high risk of exposure" category (9).

Today, dental emergencies can be managed through remote triage via phone calls, e-mail, or other online methods (10). The scientific literature on tele-dentistry is extensive and mainly covers preventive dentistry practices for people living in isolated areas. While tele-dentistry in orthodontics previously encompassed diagnosis and treatment planning, it has now developed to include areas such as the follow-up of clear aligner use and the use of elastics in fixed orthodontic treatments with functional or removable appliances (10).

Compared to other branches of dentistry, the fewer emergencies in patients receiving orthodontic treatment have resulted in a different experience of the COVID-19 pandemic. The relatively long duration of orthodontic treatments and the need for regular monthly follow-up resulted in many patients having brackets or appliances at the start of the pandemic. When patients have difficulty going to their orthodontists, various problems such as soft tissue irritations, bracket failure, and noncompliance with appliance wear can occur. However, regular monthly visits may cause patients to feel uneasy about the risk of transmission involved in going to the hospital. Factors such as these led to an increase in tele-dentistry practices in orthodontics. Some patients may even consider it advantageous to undergo orthodontic treatment during the COVID-19 pandemic for reasons such as decreased socialization, more time spent at home, and the masks hiding their braces. Although the physical and psychosocial expectations of orthodontic patients have changed during COVID-19, it is important to determine the impact of the pandemic on patients at the level of public health needs. The aim of this study was to evaluate the psychosocial and physical effects of the pandemic on patients in different orthodontic treatment groups.

MATERIAL AND METHOD

This descriptive and cross-sectional study was approved by the Istanbul Medipol University Noninvasive Clinical Research Ethics Committee (E-10840098-772.02-5645). Informed consent forms explaining the study methods were signed by all individuals who participated in the study.

Study Design

The study was conducted in a single center (Istanbul Medipol University Faculty of Dentistry, Department of Orthodontics) with 235 randomly selected volunteers aged 18 and over who were undergoing orthodontic treatment. The data were obtained between February and September of 2022 using a self-administered 15-item questionnaire. In power analysis, the minimum sample size for study power of 95% with a significance level of 5% and effect size of 0.30 was calculated as 220 individuals. The survey data of 235 individuals were included in the study to increase the reliability of the results. Inclusion criteria were age of 18 years or older, voluntary participation, and no prior history of orthodontic treatment. Exclusion criteria were the presence of any craniofacial syndrome and diagnosed psychiatric problems. Questionnaire responses collected from 235 individuals (83 male and 152 female) who met the study inclusion criteria comprised the material of the study. Patients were offered no incentive or compensation for their participation.

The questionnaire included three sections. The first part asked about the participants' sociodemographic characteristics, the second part evaluated the psychosocial effects of orthodontic treatment during the COVID-19 pandemic, and the third part was a physical assessment of orthodontic patients who had COVID-19 infection. In the third section, individuals were asked to rate their intraoral findings on a Visual Analog Scale ranging from 0 to 10.

Treatments were divided into three groups, those involving fixed orthodontic treatments (brackets), clear aligners, and removable appliances.

Statistical Analysis

Descriptive statistics were used to summarize continuous variables. Frequency and percentage values were calculated as descriptive statistics for categorical variables. Relationships with categorical variables were analyzed using chi-square test or Yates continuity correction, as appropriate.

Statistical significance was set at P<0.05. Analyses were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

RESULTS

A total of 235 individuals (mean age: 23.8+5.8 years) participated in this cross-sectional study. Of the individuals surveyed, 64.7% were female (n=152) and 35.3% (n=83) were male. The distribution of clinical and sociodemographic data is shown in Table 1. Over half (53.6%) of the participants were students, while 10% stated that they were not working or studying. Approximately half of the patients started their orthodontic treatment process during the pandemic (n=120, 51.1%) and about half started before the pandemic (n=115, 48.9%). Most participants (91.5%) were undergoing fixed orthodontic treatment, 17 participants reported using clear aligners, and 7 participants were treated with removable appliances. Nearly half (46.4%) of the participants reported continuing their normal school/work routine, whereas 22.1% stated they had switched to remote education/work.

Analysis of the participants' responses to questions about the psychosocial effects of orthodontic treatment during the COVID-19 pandemic is shown in Table 2. While 53.2% of the participants stated that they attended routine orthodontic follow-up visits and were not concerned about the risk of COVID-19 transmission, 28.1% said they experienced anxiety. The majority of participants (85.9) stated that they were happy to undergo orthodontic treatment during the pandemic, and 74.9% stated that

Table 1. Distribution of clinical and sociodemographic data

	N	%
Gender		
Male	83	35.3
Female	152	64.7
Total	235	100
School/Work life		
'I am studying'	126	53.6
'I am working'	85	36.2
None	24	10.2
Beginning of orthodontic treatment		
After March 2020 when COVID-19 was seen in Turkey	120	51.1
Before March 2020 when COVID-19 was seen in Turkey	115	48.9
Type of orthodontic treatment		
Fixed orthodontic treatment	215	91.5
Clear aligners	13	5.5
Removable appliances	7	3
School/Work life routine		
Normal	109	46.4
Hybrid (normal + remote)	48	20.4
Remote	52	22.1
None	26	11.1

N: number of participants

Table 2. The psychosocial effects of orthodontic treatment during the COVID-19 pandemic		
	N	%
I feel concerned about the risk of COVID-19 transmission while I attend routine orthodontic follow-up visits		
Strongly agree	19	8.1
Agree	47	20
Neutral	44	18.7
Disagree	79	33.6
Strongly disagree	46	19.6
I am not happy to undergo orthodontic treatment during the COVID-19 pandemic		
Strongly agree	7	3
Agree	12	5.1
Neutral	14	6
Disagree	92	39.1
Strongly disagree	110	46.8
It is difficult to clean the appliance or brackets during the COVID-19 pandemic		
Strongly agree	9	3.8
Agree	24	10.2
Neutral	26	11.1
Disagree	100	42.6
Strongly disagree	76	32.3
I comply with the dietary restrictions more easily during the COVID-19 pandemic		
Strongly agree	40	17
Agree	75	31.9
Neutral	50	21.3
Disagree	48	20.4
Strongly disagree	22	9.4
I think the COVID-19 pandemic is an advantage for orthodontic treatment due to reasons such as less socialization, mask hiding the wires, and spending more time at home		
Strongly agree	90	38.3
Agree	70	29.8
Neutral	20	8.5
Disagree	32	13.6
Strongly disagree	23	9.8
Which of the advantages from the previous question outweighs you?		
Less socialization	37	15.7
Mask hiding the wires	104	44.3
Spending more time at home	64	27.2
Other (…)	30	12.8
I recommend starting orthodontic treatment more to others during the COVID-19 pandemic		
Strongly agree	66	28.1
Agree	79	33.6
Neutral	58	24.7
Disagree	20	8.5
Strongly disagree	12	5.1

N: number of participants

cleaning their appliance or brackets was not more difficult. A small percentage (8.1%) of participants were unhappy with orthodontic treatment during the pandemic, while 14% stated that the pandemic made it difficult to clean their appliance or brackets. Approximately half (48.9%) of the participants stated that they complied with the dietary restrictions more easily during the pandemic, while over two-thirds (68.1%) reported that the pandemic was advantageous for orthodontic treatment. The most commonly cited advantages were that masks hiding the wires (44.3%), they spent more time at home (27.2%), and they socialized less (15.7%). In addition, 61.7% of the participants stated that they recommended starting orthodontic treatment more to others during the COVID-19 pandemic.

The analysis of COVID-19 prevalence according to orthodontic treatment type is shown in Table 3. A history of COVID-19 infection was reported by 27.2% of the participants, while the other 72.8% had not been infected. There was no difference between the groups in terms of COVID-19 frequency and treatment types (P=0.406). The physical assessment and evaluation of intraoral findings in orthodontic patients who had COVID-19 are shown in Figure 1. Among the intraoral findings of patients who experienced COVID-19 infection, the highest score was for loss of taste (5.9±4.6), followed by metallic taste, intraoral wounds/aphthae, tooth sensitivity, tooth clenching/grinding, jaw joint pain, and tongue numbness.

Type of treatment (fixed orthodontic treatment, clear aligners, removable appliances) was not associated with statistically significant differences in responses to any of the questionnaire items (P>0.05) (Table 4).

Table 3. COVID-19 prevalence according to orthodontic treatment type

	Treatment type			Total	P*
	Fixed orthodontic treatment N(%)	Clear Aligner N(%)	Removable appliance N(%)		
COVID (+)	58(27)	3(23.1)	2(33.3)	64(27.2)	0.406
COVID (-)	157(73)	10(76.9)	4(66.7)	171(72.8)	

* Chi-square test, Statistical significance was set at P<0.05. N: number of participants

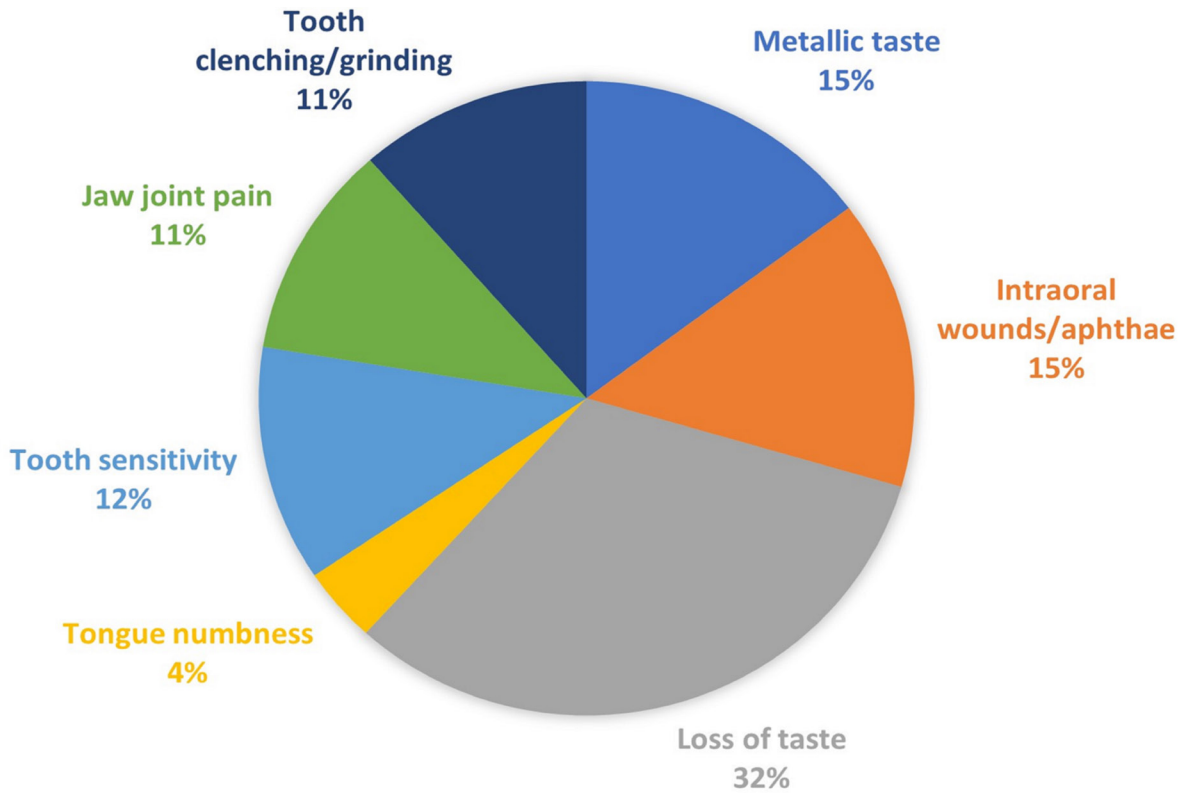

Figure 1. Intraoral findings in individuals who had COVID-19 during orthodontic treatment

Table 4. Evaluation of the questions according to treatment types

	Treatment type			p*
	Fixed orthodontic treatment N(%)	Clear Aligner N(%)	Removable appliance N(%)	
I feel concerned about the risk of COVID-19 transmission while I attend routine orthodontic follow-up visits				
Strongly agree	14(6.5)	3(23.1)	2(33.3)	
Agree	45(20.9)	1(7.7)	1(16.7)	
Neutral	42(19.5)	1(7.7)	1(16.7)	0.141
Disagree	73(34)	4(30.8)	2(33.3)	
Strongly disagree	41(19.1)	4(30.8)	-	
I am not happy to undergo orthodontic treatment during the COVID-19 pandemic				
Strongly agree	7(3.3)	0	0	
Agree	12(5.6)	0	0	
Neutral	12(5.6)	1(7.7)	1(16.7)	0.849
Disagree	81(37.7)	8(61.5)	2(33.3)	
Strongly disagree	103(47.9)	4(30.8)	3(50)	
It is difficult to clean the appliance or brackets during the COVID-19 pandemic				
Strongly agree	9(4.2)	-	-	
Agree	22(10.2)	2(15.4)	-	
Neutral	23(10.7)	1(7.7)	2(33.3)	0.877
Disagree	91(42.3)	5(38.5)	3(50)	
Strongly disagree	70(32.6)	5(38.5)	1(16.7)	
I comply with the dietary restrictions more easily during the COVID-19 pandemic				
Strongly agree	38(17.7)	1(7.7)	1(16.7)	
Agree	66(30.7)	5(38.5)	4(66.7)	
Neutral	49(22.8)	1(7.7)	-	0.388
Disagree	41(19.1)	5(38.5)	1(16.7)	
Strongly disagree	21(9.8)	1(7.7)	-	
I think the COVID-19 pandemic is an advantage for orthodontic treatment due to reasons such as less socialization, mask hiding the wires, and spending more time at home				
Strongly agree	86(40)	2(15.4)	2(33.3)	
Agree	60(27.9)	7(53.8)	3(50)	
Neutral	18(8.4)	1(7.7)	-	0.128
Disagree	29(13.5)	2(15.4)	1(16.7)	
Strongly disagree	22(10.2)	1(7.7)	-	
Which of the advantages from the previous question outweighs you?				
Less socialization	36(16.7)	-	1(16.7)	
Mask hiding the wires	94(43.7)	7(53.8)	3(50)	0.270
Spending more time at home	60(27.9)	3(23.1)	1(16.7)	
Other (…)	25(11.6)	3(23.1)	1(16.7)	
I recommend starting orthodontic treatment more to others during the COVID-19 pandemic				
Strongly agree	60(2.5)	4(2.5)	2(2.5)	
Agree	71(2.5)	5(2.5)	3(2.5)	
Neutral	54(2.5)	2(2.5)	1(2.5)	0.879
Disagree	18(2.5)	2(2.5)	-	
Strongly disagree	12(2.5)	-	-	

* Chi-square test, Statistical significance was set at P<0.05. N: number of participants

DISCUSSION

The COVID-19 pandemic had a global impact, with more than 600 million cases and over 6.4 million deaths worldwide by September 2022 (2). In dentistry, as in all other health sectors, the pandemic has had economic, psychosocial, and physical consequences for both patients and physicians. Although dentistry involves an extremely high risk of exposure, there were no universal guidelines on how to manage SARS-CoV-2 (11,12). The pandemic also necessitated measures with additional costs, such as redesigning dental clinics, adopting dental treatment approaches with minimal aerosols, increasing tele-dentistry practices, and increasing ventilation, hygiene, and personal protective measures (13). Although adverse effects such as the closure of dental clinics and treatment interruptions occurred early in the pandemic, the process became more controllable later (14). Unlike in other branches of dentistry, orthodontic treatments are longer term, lasting an average of one and a half to two years. Therefore, it is one of the areas of dentistry in which the chronic effects of the pandemic are most apparent. While the physical and psychosocial expectations of orthodontic patients vary during this period, it is important to determine the impact of the pandemic on patients. The aim of this descriptive and cross-sectional survey study was to evaluate the psychosocial and physical effects of the pandemic on patients receiving orthodontic treatment. The data from this study will be useful in terms of patient-oriented evaluation of dentistry and orthodontic treatment practices during pandemics.

A total of 235 patients participated in the study, of whom 51.1% reported starting orthodontic treatment after March 2020, when COVID-19 first appeared in Turkey, and 48.9% reported starting before the pandemic. Although the larger number of participants compared to similar studies enabled a more robust analysis of the data, in future research it would be beneficial to include larger samples and create homogeneous study groups (14,15). Our results suggest that the impact of the pandemic on social life was limited for a sizeable proportion of the study participants, considering that 46.4% stated that their work or school life were continuing normally. Of course, this may be due to the fact that the survey was conducted in 2022 and not in 2020 and 2021, when the effects of the pandemic were at their height in Turkey.

The effects of the COVID-19 pandemic on the financial, psychosocial, and social lives of orthodontists and orthodontic patients have been attributed to increased anxiety and global economic problems (16). In the second part of our cross-sectional survey, we asked seven questions evaluating the psychosocial impact of orthodontic treatment on patients during COVID-19. When the responses were evaluated, 53.2% of the participants stated that they did not feel nervous about the risk of COVID-19 transmission when coming to routine orthodontics follow-up visits, while 28.1% stated that they experienced trepidation. The relatively low level of apprehension may be related to the fact that cases of COVID-19 are now more manageable, the pathogenesis has been better analyzed, population-based vaccination rates are high, individual and social preventive measures are well understood, and dental clinics have also increased preventive measures in these areas. We believe different results may have been obtained had the survey been conducted earlier in the pandemic (in 2020-2021), when levels of social anxiety and uncertainties were at their peak. In contrast, 85.9% of the participants stated that they were happy to undergo orthodontic treatment during this period, 68.1% considered the pandemic to be advantageous for orthodontic treatment for reasons such as reduced socialization, being able to hide wires behind masks, and being at home more, and 61.7% said they recommended starting orthodontic treatment to others more during this period. Only 8.1% of the patients expressed unhappiness with undergoing orthodontic treatment during the pandemic, while 14% of the participants stated that cleaning their appliance or brackets was more difficult during this period. Among the reasons for the pandemic being advantageous, 'masks hiding the wires' was the most commonly cited, at 44.3%. The change in aesthetic appearance is one of the main complaints from patients undergoing fixed orthodontic treatment with metal brackets. With the continuous use of masks in social environments during the pandemic, orthodontic wires were effectively hidden, helping to eliminate this concern for orthodontic patients. Considering the overall psychosocial effects of the pandemic on individuals receiving orthodontic treatment, it seems that undergoing orthodontic treatment during the COVID-19 pandemic was viewed favorably. In a similar study, it was reported that the pandemic generally had a negative psychosocial impact on patients because most follow-up appointments were postponed during the COVID-19 pandemic, resulting in increased concerns about prolongation of the treatment period (6). However, as mentioned above, the stage of the pandemic in which the assessment is made will influence these findings because of changes in pandemic-related restrictions in medical services over time.

Two-thirds of the participants (n=176, 74.9%) stated that they had improved oral hygiene habits during the pandemic, and nearly half (n=115, 48.9%) reported that they adhered more easily to the list of prohibited foods. In a similar study, 60.7% of the participants reported no change in brushing habits, while 14.1% reported improved hygiene habits (6). This difference is likely related to the different age groups analyzed, as that study included patients aged 12-18 years, while the patients in our study were over 18 years old. Furthermore, the announcements and reminders to increase personal hygiene during the pandemic presented in all mass media may have contributed to the improvement in these habits (17).

A history of COVID-19 infection was reported by 27.2% (n=64) of the participants in our study, while 72.8% (n=171) said they had never been infected. There was no difference in the prevalence of COVID-19 between patients

receiving different types of orthodontic treatment. Kaur et al. (16) stated that clear aligners alone posed the least risk for SARS-CoV-2 transmission compared to fixed labial/lingual orthodontic treatment appliances, but they were not a very widespread treatment alternative (16). Orthodontic treatment with clear aligners is believed to reduce the risk of transmission compared to fixed appliances because it requires the patient to spend less time spent in the clinical environment, involves lower aerosol exposure (especially during the debonding procedure), has longer follow-up intervals, and does not cause bracket/wire-related complications (16). Although there was no difference between different treatment groups in terms of the frequency of COVID-19, further studies designed to include more participants and homogeneous study groups are needed. The most common intraoral symptom in patients with COVID-19 was loss of taste, followed in descending order by metallic taste, intraoral wounds/aphthae, tooth sensitivity, tooth clenching/grinding, jaw joint pain, and tongue numbness. Altered taste sensation, known as dysgeusia, was the first recognized oral symptom of COVID-19 (18). In a recent review, oral lesions described in COVID-19 patients included findings such as ulcers, erosion, vesicles, fissured tongue, papules, halitosis, hemorrhagic scabs, petechiae, erythema, and spontaneous bleeding, and oral lesions were reported to be more common and severe in older patients and those with clinically severe COVID-19 (18). Poor oral hygiene, certain opportunistic infections, immune suppression, and stress have been reported to be the main predisposing factors to oral symptoms in COVID-19 patients (18,19).

Based on the responses to questions about orthodontic treatment types, most participants (91.5%) were undergoing fixed orthodontic treatment. The proportions of participants being treated with clear aligners and removable appliances were 5.5% and 3%, respectively. Our rationale for grouping the patients according to treatment type was the possibility that patients receiving different treatments may experience different psychosocial effects during the pandemic. Compared to fixed orthodontic appliances, clear aligners have advantages such as shorter examination time, shorter bonding and debonding phases, longer follow-up intervals, greater feasibility of tele-orthodontics, reliable treatment planning with digital scans, better plaque control and consequent reduction in white spot lesions, and less root resorption (16,20-25). For these reasons, treatment with clear aligners may be more preferable during the pandemic than fixed appliances. However, the drawbacks of clear aligners also warrant mention, such as their limited utility in complex malocclusions, the need for additional aligners at the end stage, the need to use attachments or intermaxillary elastics, the high cost, and adherence problems (26). However, our results indicated no difference in the psychosocial effects of the COVID-19 pandemic according to orthodontic treatment type (P>0.05).

A limitation of this study was the heterogeneous number of patients in the treatment groups. It should be kept in mind that these results may vary in the evaluation of larger and homogeneous treatment groups. Further clinical and survey studies are needed to determine the ideal choice of orthodontic treatment during current and potential future pandemics.

CONCLUSION

Compared to the start of the COVID-19 pandemic, when its impact was most pronounced, patients receiving orthodontic treatment later in the pandemic seemed to experience no serious negative psychosocial effects. While a small proportion of patients receiving ongoing orthodontic treatment still feel uneasy about the risk of transmission during routine follow-up visits, the majority of participants stated they were happy to undergo orthodontic treatment during the pandemic and recommended their friends and family also receive orthodontic treatment during this period. Although we observed no differences between orthodontic treatment types in terms of the effects of the pandemic, further studies with more participants and homogeneous treatment group sizes are needed to obtain more reliable results.

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Research Article

Determination of the Most Appropriate Ultrasound Device in Healthcare Institutions with the Critic-GRA Hybrid Method

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Abstract

Aim: Medical devices used in health institutions are quite costly and many criteria such as the selection process, efficiency and ease of use of these devices should be taken into account. Careful selection of these devices is in the class of difficult problems as it involves the evaluation of various criteria. This study is to determine the selection process of the same type of medical devices and the most appropriate device of the relevant health institution, especially when alternatives are available.

Material and Methods: The solution of the problem is modeled by using the Critic and Gray Relational Analysis (GRA) methods in an integrated structure. The basis of the study is the applicability of Multi criteria decision making (MCDM) methods. The criteria and alternatives of the created decision making model were determined by using the opinions of physicians working in the field and the literature. A case study was conducted on a decision problem of determining the most suitable ultrasound device for a healthcare institution in Düzce.

Results: According to the analysis results obtained, it was determined that the most suitable device was A3 (GE) and the most inappropriate ultrasound device was A4 (MN). In addition, the most effective criterion was K1 (Price), while the least effect was K5 (Durability).

Conclusion: It has been determined that the findings obtained are consistent with the literature. In addition, the results of the study were shared with the relevant physicians and managers.

Keywords: MCDM methods, critic method, gray relational analysis method, medical devices, health sector

INTRODUCTION

In the last century, the global economy, shaped by innovations and advances in technology, has shown remarkable growth in the medical device industry, resulting in high competition between companies and manufacturers. Different brands, different quality levels and prices of the products make it difficult for the relevant health institutions to purchase a suitable product. When multiple alternatives are available, it becomes very complex to determine the most suitable alternative, as there are many criteria to consider to make the most appropriate choice. The complexity of this type of decision problem comes from conflicting and conflicting goals. After the decision taken, the necessity of a systematic analysis that guarantees minimizing regret becomes evident. Therefore, Multi criteria decision making (MCDM) methods have emerged to support the decisions taken and increase the reliability of the chosen solution (1).

In the application of MCDM methods, which alternative should not be easily selected as a priority, especially when

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comparing the alternatives according to the criteria. This indicates that the decision problem contains a difficult solution. That means the criteria are contradicting and conflicting. Otherwise, the relevant decision problem can be solved at a glance without the need for any analysis.

In the healthcare industry, systems that take into account minimum cost have always been of great interest in terms of research and development. This interest can be attributed to the high spending of this industry and the lack of savings performance compared to other leading industries such as retail and manufacturing (2) focused on health expenditures and the reasons why doctors prefer medical equipment (3). Multi-purpose decision making methods for the products preferred by doctors based on value modeling principles were used and the hierarchical structure of the created model was applied on MCDM methods.

One of the decision problems faced by health sector enterprises is the determination of optimum medical devices. The decision maker, individually or as a group, has to decide which device to purchase. The availability of different models of equipment with the same function offered by manufacturers makes it difficult for decision makers to choose the most suitable device. This problem arises when many criteria need to be considered in a decision making process and there are elements of conflict between the criteria. The emergence of this problem is important for two reasons; first, choosing products with a structured method can reduce costs. Second, the right decision can increase the rate of good treatment of patients depending on the determination of the most appropriate device. For this reason, it is essential for health sector businesses to make correct and appropriate decisions, otherwise the cost of regret after the decisions taken is very heavy.

MCDM methods help healthcare organizations determine the best benefit in the device purchasing process. These methods do not limit the cost of a device to just the purchase price; it also takes into account factors such as device energy consumption, maintenance requirements and lifetime. Thus, healthcare organizations can manage their budgets correctly and save money in the long run by choosing the optimum devices.

Another important reason for health institutions to use MCDM methods to provide optimum devices is to increase quality. High-quality devices ensure accurate diagnoses and effective treatments. This ensures that the treatment processes of patients are more successful and efficient. At the same time, devices with up-to-date and advanced technology increase the working efficiency of healthcare personnel and reduce errors.

Therefore, in the study, the selection of the most suitable medical device among many alternatives was accepted as a decision problem and its solution was handled with MCDM methods. In solving this problem, it is aimed to choose the most suitable ultrasound device alternative among many similar options. In this study, both Critic and Gray Relational Analysis (GRA) methods were used in a hybrid structure.

In the following sections of the study; literature review, methodology of the study, findings and evaluation of the results are included.

Literature Review

In the process of examining the domestic and foreign literature, studies on methods such as MCDM methods and their hybrid applications in different health fields, especially in the selection of medical devices, were presented. In addition, these studies were categorized according to their subjects and the nature of the decision making method.

Glaize and friends provide a practical perspective on how Multi criteria decision making methods are applied in different health institutions (4). They proposed a model of how MCDM methods are applied in different health areas, including medical device selection (5), and presented a new MCDM method model for the most appropriate medical device selection under uncertainty conditions. Frazao et al. determined the most suitable Magnetic Resonance Imaging (MR) system for regional hospitals in the Czech Republic (6). Comparing different MCDM methods such as AHP, TOPSIS, PROMETHEE II and Simple Additive Weighting (SAW) methods, they proposed the most appropriate MCDM model for medical equipment selection.

MCDM methods in uncertainty environments, for example (7), have presented a new approach to evaluate the smart medical device selection process under uncertainty conditions. The intuitionistic fuzzy Choquet integral (IFCI) approach was used in their work to address uncertainty and ambiguity. Carnero and Gomez proposed the fuzzy MCDM approach to evaluate a single medical device supplier in their study (8). Tadic et al. evaluate a new approach including Neutrosophic TOPSIS method to optimize the selection process of smart medical devices in a fuzzy decision environment (9). Basset et al. stated the dominance of AHP and other methods of fuzzy logic in the literature in their studies (10).

They used the AHP approach to select important medical equipment in resource-constrained environments (11). Ivlev et al. used both MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique) and FAHP (Fuzzy AHP) methods separately in their studies for the optimal selection of medical gas supply devices (12). Both AHP and fuzzy VIKOR (VIekriterijumsko Kompromisno Rangiranje) methods have been used by (13) to select the most suitable protein isolation device in a scientific research laboratory. Emec et al. used fuzzy VIKOR-based fuzzy MCDM method in the problem of evaluating available alternatives for medical waste disposal in their study (14).

A hybrid fuzzy MCDM approach (15) consisting of fuzzy AHP method and fuzzy TOPSIS method was used to

select the most suitable medical device manufacturer. A Multi criteria decision making approach (16) based on fuzzy AHP and fuzzy TOPSIS has been used in a fuzzy Multi criteria decision making environment to improve the supplier selection process in the healthcare industry.

Hybrid MCDM methods have been applied to select the most appropriate medical device in different decision environments. Goh et al. proposed an effective and efficient MCDM model that includes three different methods of AHP, Multi-Feature Range Evaluation (MARE) and ELECTRE III to solve healthcare equipment selection problems (17). Hodgett proposed a model that integrates TOPSIS (intuitionistic fuzzy set) approaches to select the most appropriate real-time location system technology in a hospital-based Multi criteria structure (18). Budak et al. developed a hybrid model combining Analytical Hierarchy Process (AHP) and TOPSIS methods for the most appropriate medical equipment selection (19). Willeme and Dumont developed the HMCDM (Hybrid MCDM) method, which mixes AHP, TOPSIS, ELECTRE, GRA and SAW methods to select the most suitable supplier in the healthcare industry (20).

No study has been found in the literature, which has contradicting and conflicting criteria, analyzed with the Critic and GRA methods, for the determination of the most appropriate medical device in the health sector. For this reason, in this study, it is aimed to present a hybrid model by using the Critic and GRA methods together on the most appropriate medical device selection for the relevant health institutions. In the research, the Critic method was used to find the criteria weights, and the most suitable alternative was determined in line with the weighted criteria with the GRA method.

MATERIAL AND METHOD

Thanks to the technological medical devices produced in recent years, diagnosis has become easier in the medical world, so the life expectancy of people has become longer (21). Since the excessive increase in health expenditures complicates health problems, scientific methods, especially MCDM methods, are needed in solving the decision problems encountered.

The main purpose of this study is the problem of determining the most appropriate medical device in health institutions, which is considered as a decision making problem. The modeling of the problem, the determination of the criteria and alternatives were created entirely by the opinions of active physicians in the sector and by examining the literature. The weights of the criteria were determined by the Critic method and the priority order of the alternatives was determined by the GRA method. Analyzes were carried out in accordance with the hierarchical solution model of the study and the solution stages of the relevant MCDM methods. The aggregated results of the analysis performed are explained in detail in the interpretation of the findings.

While determining the criteria used to identify the most suitable ultrasound device, similar studies in the literature were primarily used. Then, the opinions of doctors and technical staff working in the sector were taken. In addition, the performance values within the framework of the criteria of each alternative were obtained from the official authorities of the companies selling the devices.

Moreover, the reasons for choosing the Critic method in determining the weights of the criteria in the study are explained in detail below;

a. Its calculations include simple steps,
b. Decision makers can take action without having to make a judgment about the criteria,

c. Taking into account the trend that exists on other criteria such as standard deviation and correlation,

d. It is considered more objective than other weighting methods in the literature.

The MCDM methods used in the study and the process steps are explained in detail in the titles that follow respectively.

Critic Method

The Critic Method emerged in the first study by Diakoulaki et al. in 1995. This study aimed to evaluate the financial performance data of eight pharmaceutical companies. In the analysis phase, the Critic Method, which can be used in cases where there is no definite information about the decision makers, and which allows objective weighting to the criteria, was used.

The "Critic Method" or "Critic Approach", which is among the Multi criteria decision making methods, is a method that enables the evaluation and weighting of more than one criterion in the decision making process.

The Critic Method is an effective method used in complex decision making processes. The determination and weighting of the criteria may vary depending on the preferences and goals of the decision maker. In addition, different results can be obtained by using the evaluations of different experts or objective data.

The solution steps of the Critic Method can be listed as follows (21);

1. Normalizing the decision matrix of the decision problem: Normalizing the data in the decision matrix is done to ensure that they can be evaluated on the same scale.
2. Determining the degree of relationship between the criteria: According to the decision matrix, the degree of relationship between the criteria is determined. This refers to the importance levels of the criteria with each other.
3. Expressing the criterion weights depending on the relation degrees: The criterion weights are calculated by using the determined relation degrees. These weights are used to determine the order of importance of criteria in the decision making process.

Gray Relational Analysis (GRA) Method

The general purpose of Multi criteria decision making methods is to determine the most suitable one among the alternatives based on different criteria. Recently, GRA has become a frequently used approach. The basis of this approach was developed by Julong Deng in the early 1980s. The GRA method is based on the Gray number theory. This method, in MCDM problems, allows for the elimination of numerical uncertainties easily and makes it possible to make an evaluation based on the basic data set (22).

GRA method stands out as an approach used in MCDM problems. In this method, decision making process is performed based on Gray number theory. In GRA method, performance data is converted into Gray numbers and analyzed. Gray numbers have three components to express a particular value: upper class, middle class and lower class. These components are used to express performance values according to the level of uncertainty.

The method evaluates the relations of the alternatives with each other and determines the priority order of these relations. Thus, weights and evaluations are obtained that will be used in the decision making process to determine the most suitable alternatives.

Gray number theory-based (GRA) method can be easily used when certainty cannot be established in decision problems and there is not enough information about alternatives (23).

The GRA Method consists of six stages and these stages can be listed as follows (24);

1. Building the reference matrix based on the basic data set: In the first step, the reference matrix is created based on the basic data set. The reference matrix contains values that reflect the performance of alternatives in terms of criteria.

2. Normalizing the base data matrix: The values in the data matrix are normalized, that is, they are standardized so that they can be evaluated on the same scale.

3. Creating the Absolute Value Matrix: Absolute value matrix is created by using the normalized basic data matrix. This matrix is used to determine the relationships between criteria.

4. Determination of Gray Relational Coefficient Matrix: Based on the absolute value matrix, the gray relational coefficient matrix is determined. This matrix expresses the relationship of the alternatives with each other and the level of importance according to the criteria.

5. Determination of the weighted average values of the alternatives: The weighted average values of the alternatives are determined by using the gray relational coefficient matrix. These values are used to determine the order of importance of the alternatives.

6. Expression of gray associative degrees: In the last step, gray associative degrees are expressed. These degrees are the values that explain the relationship of the alternatives with each other and the order of importance according to the criteria.

Application: Determination of the Most Appropriate Ultrasound Device with MCDM Methods

The decision problem analyzed within the study is aimed at determining the most appropriate medical device in health institutions. The goal is to identify the device that outweighs all alternatives within the framework of the determined criteria. In this analysis process, the solution steps of the relevant MCDM methods were fully adhered to. The study was carried out in a health institution operating in Düzce and criteria and alternatives were created in line with the opinions of five physicians in the relevant health institution. According to the data obtained as a result of the physicians' evaluation of the criteria in order of importance, the first eight criteria were accepted for the analysis.

Four alternative ultrasound devices were evaluated in this study. The names of these devices are expressed with short codes on the basis of data confidentiality. The codes of these devices are AL, SA, GE and MN. In addition, in the later parts of the study, the Criteria are expressed with only their codes as K1, K2... in order to fit the tables on the pages. For example, K1 is the "Price" criterion.

Determining the Weights of the Criteria with the Critic Method

In order to apply the analysis stages of the Critic method, the basic data matrix must first be expressed. The basic data matrix is expressed in Table 1.

Table 2 shows the normalized version of the correlation matrix.

Table 1. Basic data matrix

	K1: Price ($) Min	K2: Viewing Quality (out of 10 points) Max.	K 3: Size (Size) m3 Min.	K 4: Ease of Use (out of 10 points) Max.	K5: Durability (out of 10 points) Max.	K 6: Number of Probes Max.	K 7: Warranty Period Max.	K 8: Service Time Max.
A1	35000	5	0.9	6	6	3	2	1
A2	40000	7	1.2	8	7	5	3	2
A3	44000	8	1.3	7	8	4	4	4
A4	37000	6	1.1	5	5	3	2	1

Tablo 2. Normalized correlation matrix

	K1	K2	K3	K4	K5	K6	K7	K8
K1	0.0000	1.9891	0.0530	1.5934	1.8572	1.6224	1.9780	1.9631
K2	1.9891	0.0000	1.9827	0.4000	0.2000	0.3258	0.0561	0.0871
K3	0.0530	1.9827	0.0000	1.5292	1.6803	1.6625	1.8664	1.8281
K4	1.5934	0.4000	1.5292	0.0000	0.2000	0.0561	0.3258	0.4523
K5	1.8572	0.2000	1.6803	0.2000	0.0000	0.3258	0.0561	0.0871
K6	1.6224	0.3258	1.6625	0.0561	0.3258	0.0000	0.3636	0.5076
K7	1.9780	0.0561	1.8664	0.3258	0.0561	0.3636	0.0000	0.0153
K8	1.9631	0.0871	1.8281	0.4523	0.0871	0.5076	0.0153	0.0000

The matrix containing the Cj and standard deviation values used while calculating the final weights of the criteria in the last step of the Critic method is clearly expressed in Table 3. Standard deviation values were calculated for each criterion one by one by considering all alternatives. When calculating the final Cj values, the standard deviation value for each criterion is multiplied by the row total value and divided by the total Cj value. These obtained values are also an expression of the weight of each criterion.

As it is clearly stated in Table 3; K1: The price criterion has a value of 0.216 and has priority in the first degree. The second priority is K3: Size criterion with a value of 0.203. The most important factor in obtaining the results in this way is the economic conditions of the market and the importance of functional use for physicians.

Table 3. Final weights of criteria

	STD Deviation Value	Row Totals	STD* Row Totals	Cj/Total Cj	Weights
K1	0.4351	11.0561	4.8104	0.2162	**0.2162**
K2	0.4303	5.0408	2.1692	0.0975	**0.0975**
K3	0.4270	10.6022	4.5267	0.2034	**0.2034**
K4	0.4303	4.5568	1.9609	0.0881	**0.0881**
K5	0.4303	4.4066	1.8963	0.0852	**0.0852**
K6	0.4787	4.8639	2.3284	0.1046	**0.1046**
K7	0.4787	4.6614	2.2315	0.1003	**0.1003**
K8	0.4714	4.9406	2.3290	0.1047	**0.1047**

Determining the Priority of the Most Appropriate Ultrasound Device Alternatives for the GRA Method

In order to apply the GRA method, reference values based on the basic data matrix must first be found. For this reason, Table 4 contains the reference matrix expressing the reference values.

After calculating the Reference Matrix, the basic data matrix was normalized. The obtained values are clearly expressed in Table 5.

After the data are normalized, the absolute value matrix should be created in accordance with the stages of the GRA method. Accordingly, after the absolute value matrix of the data was created, the gray relational coefficient matrix was formed. While calculating the data for this stage, ς=0.5 was accepted as the gray relational coefficient value, which is frequently used in the literature. The results obtained are clearly expressed in Table 6.

After finding the gray relational coefficient matrix values, the gray relational degrees ($\Gamma 0i$) of each alternative were calculated. According to the data obtained, the priority order of each alternative has been determined. Gray relational degrees are shown in Table 7.

At the last stage of the GRA method, the alternatives are ranked according to their priorities, taking into account the gray relational degrees of each alternative. In fact, in order to evaluate the results in detail, the weights of the criteria were calculated separately depending on whether they were equal or not. This final ranking is expressed in Table 8.

Table 4. Reference matrix

	K1	K2	K3	K4	K5	K6	K7	K8
Reference values	**35000**	**8**	**0.9**	**8**	**8**	**5**	**4**	**4**
A1	35000	5	0.9	6	6	3	2	1
A2	40000	7	1.2	8	7	5	3	2
A3	44000	8	1.3	7	8	4	4	4
A4	37000	6	1.1	5	5	3	2	1

Table 5. Normalized matrix

	K1	K2	K3	K4	K5	K6	K7	K8
A1	1.0000	0.0000	1.0000	0.3333	0.3333	0.0000	0.0000	0.0000
A2	0.4444	0.6667	0.2500	1.0000	0.6667	1.0000	0.5000	0.3333
A3	0.0000	1.0000	0.0000	0.6667	1.0000	0.5000	1.0000	1.0000
A4	0.7778	0.3333	0.5000	0.0000	0.0000	0.0000	0.0000	0.0000

Table 6. Gray relational coefficient matrix

	K1	K2	K3	K4	K5	K6	K7	K8
A1	1.0000	0.3333	1.0000	0.4286	0.4286	0.3333	0.3333	0.3333
A2	0.4737	0.6000	0.4000	1.0000	0.6000	1.0000	0.5000	0.4286
A3	0.3333	1.0000	0.3333	0.6000	1.0000	0.5000	1.0000	1.0000
A4	0.6923	0.4286	0.5000	0.3333	0.3333	0.3333	0.3333	0.3333
Δmax	1.000							
Δmin	0.000							
ς	0.5							

Table 7. Gray relational grades of alternatives

	K1	K2	K3	K4	K5	K6	K7	K8	Γ0i
A1	1.0000	0.3333	1.0000	0.4286	0.4286	0.3333	0.3333	0.3333	**0.5238**
A2	0.4737	0.6000	0.4000	1.0000	0.6000	1.0000	0.5000	0.4286	**0.6253**
A3	0.3333	1.0000	0.3333	0.6000	1.0000	0.5000	1.0000	1.0000	**0.7208**
A4	0.6923	0.4286	0.5000	0.3333	0.3333	0.3333	0.3333	0.3333	**0.4109**

Table 8. Final ranking of alternatives

	If the Criteria Have Different Weights	If the criteria are of equal weight	Final Ranking
1.	A3	A3	**A3**
2.	A1	A2	**A1 or A2**
3.	A2	A1	**A1 or A2**
4.	A4	A4	**A4**

RESULTS

Health sector businesses may always be faced with the problem of choosing the most appropriate medical device with different contradicting and conflicting criteria, but making a decision based on personal experience alone does not guarantee that the optimum selection is made. According to the clear results summarized in Table 9, it was seen that Alternative A3 outperformed other alternatives when evaluated within the framework of the criteria. The ordering of the alternatives was done by completely adhering to the solution steps in both methods. This result increases the reliability of the analyzes when choosing the best alternative and determining the worst choice for the decision maker and the relevant businesses.

According to the ranking obtained as a result, it is thought that it was determined as a result of seeing the A3

alternative as superior to the others, taking into account the criteria determined by the common opinion of the physicians. The use of the Critic method in determining the weights of the criteria has increased the reliability of the calculations in terms of the objectivity of the results. The data obtained as a result of the analyzes were shared with the relevant physicians and health institution managers. In addition, the consistency of the results obtained was confirmed by the relevant physicians. We consider this as validation of the model.

When the results obtained by both methods are examined, it is seen that the most suitable alternative is A3. The combination of the two methods yields more reliable results for hybrid structures than others. According to the data obtained, the rankings obtained by the hybrid method confirm their validity when compared with other studies in the literature. The results of the analyzes were examined in depth with the relevant physicians. Recommendations were made to those concerned that it would be possible to determine the most appropriate medical device through analyzes performed with hybrid MCDM methods.

DISCUSSION

In the study, the application of MCDM methods over the ultrasound devices to be selected for a decision problem for determining the most appropriate medical device in health institutions is shown. Physicians who are experts in their field; They were involved in the process of creating the model, determining the criteria and identifying alternatives. By using two MCDM methods in a hybrid structure, four alternatives were prioritized according to eight criteria.

As a result of these analyzes, physicians or organizations that want to supply medical devices were helped to make objective, correct and on-site decisions with MCDM methods. When the physicians participating in the study were asked how they obtained the medical devices they currently use, they said, "I do not know how and by what method the relevant management has taken it." It is an answer that leads to wrong in terms of the management of health institutions. Because of the supply of devices to be used by physicians, physicians must be included in the process and their opinions must be taken into account.

This study has two main aims; firstly, to be able to place the usability of existing MCDM methods in the health sector literature, and secondly, to guide future studies on this subject. However, some limitations were encountered while carrying out this study. These;

- The case of obtaining data from a health institution related to the subject in Düzce and therefore the limited number of the sample,
- Difficulties experienced in involving physicians in all aspects of the process in terms of work intensity,
- The medical device companies that make up the alternatives do not want to publicly declare their names in terms of data confidentiality,
- Limited number of alternatives,
- Inadequacy of software that can analyze Critic and GRA methods,
- The reluctance of health institutions to prefer scientific methods in this regard.

CONCLUSION

When the findings of the study are examined; First, the weights of the criteria were calculated. Accordingly, the most effective criterion was "Price" with a value of 0.216, followed by "Size" with a value of 0.203. In addition, A3 ranked first with a value of 0.1582 in the priority order of the alternatives calculated by the GRA method. In the last place is A4 with a value of 0.1135. These results are in line with similar studies in the literature (5,8).

The main contributions of this study to the literature can be summarized as follows;

- To propose a MCDM model that combines Critic and GRA methods in a hybrid structure for the problem of determining the most appropriate medical device with contradicting and conflicting criteria,
- To demonstrate the usability of MCDM methods in the selection process of medical devices to physicians and related researchers working in this field,
- Physicians' working with more suitable devices will speed up the treatment time and therefore reduce the patient density that causes confusion in health institutions.

MCDM methods also significantly affect the safety of patients. Healthcare organizations can keep patients' safety at the highest level by providing accurate and reliable devices. For example, the correct operation of surgical robotic systems used for sensitive surgeries is critical to ensuring the safety of patients. Devices selected with MCDM methods reduce the likelihood of technical problems and malfunctions, which contributes to patient safety.

In future studies, the inclusion of physicians as well as personnel who understand the technical structure of the devices, especially in the determination and comparison of the criteria, will provide more detailed and accurate results. It would be appropriate to use more up-to-date, hybrid, artificial intelligence-themed and fuzzy logic approaches in the analysis of the MCDM model. In addition, AHP, Entropy and Smart methods can be used in the process of weighting the criteria in future studies on similar subjects.

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Research Article

The Relationship Between Phase Angle Obtained from the Maximum Reactance and Fasting Glucose, Hemoglobin A1c in Type 2 Diabetes Mellitus

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Abstract

Aim: The phase angle obtained from the maximum reactance (PA max) is a better potential indicator than the phase angles obtained from multiple frequencies. Our aim in this study is to investigate the correlation of PA max with fasting glucose and hemoglobin A1c in Type-2 Diabetes Mellitus (T2 DM).

Material and Methods: The study was conducted prospectively, two groups were formed as T2 DM (n=75) and healthy controls (n=32) and their demographic variables were examined. Right hand, left hand, right leg, left leg, hand leg and leg leg segment measurements were taken with electrical impedance method and phase angle was obtained at maximum reactance. Correlations with fasting glucose, hemoglobin A1c and other variables were examined.

Results: Fasting glucose, glycated hemoglobin A1c, age, body mass index, body fat percentage were found to be significantly higher in the T2 DM group compared with the healthy group. However, RH PA max, RL PA max, LL PA max, H_L PA max, and L_L PA max values were found to be significantly lower than in the healthy group. In T2 DM group, hemoglobin A1c was found significantly negative correlated with PA max in all segments, while fasting glucose is negatively correlated with all segments except LH Pamax.

Conclusion: PA max is significantly reduced by the impaired glycemic index in T2 DM and is a potential marker reflecting metabolic status.

Keywords: Phase angle, diabetes mellitus, fasting glucose, hemoglobin A1c

INTRODUCTION

Type-2 Diabetes Mellitus (T2 DM) is a chronic metabolic disease characterized with hyperglycemia associated with decreased insulin secretion or effect. The International Diabetes Federation drew attention to the fact that approximately 571 million adults (20-79 years old) were diagnosed with diabetes in 2021, of which 95% were T2 DM (1,2). The prevalence of T2 DM in Turkey has increased significantly with each passing day, reaching 13.7% (3). Serious micro and macrovascular complications may develop if hyperglycemia cannot be controlled (4). There is a need to investigate the negative effects of the uncontrolled glycemic index at the metabolic and cellular level.

Recently researchers started to use bioimpedance analysis (BIA) to examine the metabolic status of T2 DM. BIA is a non-invasive, inexpensive, and easy-to-apply method that measures body compositions and cellular health levels based on the electrophysiological characteristics of the human organism (5). It provides data on muscle and fat mass, total protein and mineral ratios, intracellular and extracellular fluid amount and hydration status (6). Along with these, phase angle (PhA) is a commonly used BIA parameter in clinical studies. It gives useful information

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about cellular health and shows the electrical activity and functioning of cell membranes. PhA is closely related to the metabolism of the human body (7). It can vary according to the age, sex, ethnicity, physical activity, and health status of an individual.It is mainly between 3-15 degrees (8,9). High levels of PhA indicate increased reactance and low resistance, which reflects healthy or intact cell mass. Low levels are associated with decreased energy storage and a decline in the selective permeability of cell receptors at the cellular level (10).

PhA is used as a diagnostic and prognosis indicator in diabetes mellitus, sepsis, malignancies, cirrhosis, and renal diseases (11-14). Significant relationships were found between the use of oral hypoglycemic agents and low phase angle in elderly diabetic male patients (15). In hemodialysis patients, PhA is found to be lower in diabetic nephropathy patients compared to non-diabetic hemodialysis patients, and PhA is also found to be an independent marker for heart failure (16). It is also associated with diabetes mellitus complications, progression, and disease duration (17).

Recently, the phase angle obtained from maximum reactance (PA max) has become more objective in clinical studies. Because PA max is the best indicator of the body's electrical resistance and reactance. It is easily obtained from BIA instruments and it is calculated by the arc-tangent formula of the ratio of reactance (Rc) to resistance.It has the potential to replace multi-frequency analysis variables (11).

PhA and PA max is directly related to the cell membrane. However, PA max is independent of the PhA obtained from multi frequencies and better reflects metabolic status and glycemic regulation. There are limited studies investigating the relationship between impaired glycemic index and PA max in T2 DM patients. Our aim in this study is to examine the relationship between fasting glucose and hemoglobin A1C (HbA1C) and PA max.

MATERIAL AND METHOD

This single-center, prospective study was approved by the Kırsehir Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee (Date: 07.06.2022, Decision No: 2022-11/112). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.Informed consent forms were obtained from all patients.Our study included 107 participants, 75 had T2 DM and 32 were healthy controls. The study was conducted between August and October 2022. Venous blood samples from the forearm of all participants were obtained in the morning after at least 8-10 hours of fasting. The blood collected in non-anticoagulant gel tubes was centrifugedat 2000 g for 10 minutes after coagulation for 30 minutes. Studies were performed on an autoanalyzer (AU 5840; Beckman Coulter, California., USA) using routine laboratory methods. Fasting glucose levels were examined. Glycated hemoglobin (HbA1c) level was studied from blood samples taken into K2EDTA tubes. HbA1c was measured using high-performance liquid chromatography (HPLC) (Premier Hb9210; Trinity Biotech, Co.Wicklow, Ireland). Variables were compared between groups.

Bioimpedance analysis

The study was performed using a Tanita MC-780MA device in both groups after 8-10 hours of fasting (Tanita Europe BV Hoogoorddreef 56e 1101 BE, Amsterdam, The Netherlands). The height, sex, and age of the participants were entered into the analyzer. Participants were asked to stand on the analyzer with bare feet in such a way that the electrodes on the scale were in contact with the soles of the feet. At the same time, they were asked to hold the handpieces with their bare hands such that the electrodes on the handpieces were touching the palms of their hands, and to wait in an upright position, motionless and steady until the results appeared on the screen. Age, sex, body weight (kg), body mass index (BMI), muscle and fat percentage of the groups were examined. Maximum reactance PA max was obtained from six different segments: right hand (RH), left hand (LH), right leg (RL), left leg (LL), hand-leg (H_L), and leg-leg (LL). used as a variable.

The PAmax variables obtained from each segment were compared between the groups. In addition, the correlation of PAmax values with fasting glucose, HbA1C, age, BMI, muscle (%) and fat ratios (%) were examined.

Exclusion Criteria

The presence of malignancy, bone marrow or primary diseases, anemia, pregnancy, acute or chronic infection, smokers, conditions causing acute metabolic disorder, cardiac arrhythmia, and pacemakers were excluded from the study.

Statictical Analysis

Statistical analyzes of the study were performed using Statistical Package for Social Sciences for Windows (IBM SPSS version 28.0, Armonk, NY, USA) software. The normality assumption of continuous variables was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests. Homogeneity of variances was done by the Levene homogeneity test. Descriptive statistics of the variables are given as Arithmetic Mean±Standard Deviation. In the study, group comparisons were made using the Independentet t test. Relationships between variables were examined by Pearson correlation analysis. The sample size of the study was calculated by using Priori power analysis. Tail (s)=Two, Effect size d=0.6, α=0.05, Power (1-β err prob)=0.85, Allocation ratio N2/N1=1 taken while calculating the sample size. Priori power analysis while calculating the sample size of the study was performed with the G*Power 3.1.9.7 (Franz Foul, Unversitat Kiel, Germany) program.

RESULTS

The distribution of genders by groups is homogeneous (p>.05). Descriptive statistics of the groups and group comparisons are given in Table 1. Age, BMI and body fat (%) ratios of T2 DM are significantly higher than the healthy group (p<.001). However, T2 DM group's H_L PA max (p=.002), RL PA max (p<.001), LL PA max (p<.001), RH PA max (p=.015), L_L PA max (p<.001) values were lower than the healthy group. These values are statistically significant. In addition, the body muscle (%) ratios of healthy individuals are higher than Type 2 DM (p<.001). HbA1C and fasting glucose values were higher in T2 DM group (p<.001).

Correlations between PA max and other variables in the T2 DM group are given in Table 2. According to these results, there is a negative significant correlation between the age of the patients and H_L PA max, RL PA max, LL PA max, RH PA max, LH PA max and L_L PA max. There is no statistically significant relationship between BMI and segmental PA max (p>.05). There is a positive correlation between muscle (%) values and H_L PA max, RL PA max, LL PA max, RH PA max, LH PA max, L_L PA max. Fat (%) ratios were negatively correlated with H_L PA max, RL PA max, LL PA max, RH PA max, LH PA max and L_L PA max, H_L PA max, RL PA max, LL PA max, RH PA max, LH PA max and L_L PA max were negatively correlated with HbA1c .There was a negative correlation between fasting glucose and H_L PA max, RL PA max, LL PA max, RH PA max, L_L PA max.The relationship between LH PA max and fasting glucose was not statistically significant (p>0.05).

Table 1. Demographic, biochemical and PA max variables of the groups

Variables/Groups	Healthy n=32(29.9%)	T2 DM n=75(70.1%)	p
Gender, Male, n(%)	15(46.9%)	28(37.3%)	0.357#
Age	29.96±10.38	57.52±10.34	<0.001*
BMI	23.51±3.96	30.50±5.22	<0.001*
Fasting Glucose	97.03±8.32	183.16±67.82	<0.001*
HbA1C	5.41±0.29	8.54±2.02	<0.001*
Muscle (%)	75.08±7.05	65.43±7.65	<0.001*
Fat (%)	20.93±7.40	31.10±8.04	<0.001*
H_L PA max	6.23±0.78	5.70±0.77	0.002*
RL PA max	5.97±0.88	5.04±0.92	<0.001*
LL PA max	5.87±0.84	4.92±0.85	<0.001*
RH PA max	6.84±0.84	6.38±0.87	0.015*
LH PA max	6.65±0.76	6.36±0.72	0.070*
L_L PA max	6.04±0.82	5.06±0.85	<0.001*

*: independent t test, #: chi-square test
DM: diabetes mellitus, BMI: body mass index, HbA1C: glycated hemoglobin, PA max: phase angle at the maximum reactance value
H_L: hand_leg, RL: right leg, LL: left leg, RH: right hand, LH: left hand, L_L: leg_leg

Table 2. Correlation findings between segmental PA maxs and other variables in Type-2 DM

Variables	Fasting Glucose	HbA1C	Age	BMI	Muscle(%)	Fat(%)
H_L PAMAX	-0.274**	-0.330**	-0.356**	-0.006 NS.	0.320**	-0.318**
RL- PAMAX	-0.368**	-0.433**	-0.477**	-0.133 NS.	0.358**	-0.356**
LL- PAMAX	-0.385**	-0.469**	-0.515**	-0.141 NS.	0.384**	-0.383**
RH- PAMAX	-0.346**	-0.363**	-0.316**	-0.029 NS.	0.321**	-0.320**
LH- PAMAX	-0.188NS.	-0.230*	-0.221*	0.094 NS.	0.236*	-0.233*
L_L- PAMAX	-0.398**	-0.485**	-0.532**	-0.164 NS.	0.404**	-0.402**

*: correlation is significant at the 0.05 level, **: correlation is significant at the 0.01 level, N.S.: non-significant correlation
DM: diabetes mellitus, BMI: body mass index, HbA1C: glycated hemoglobin, PA max: phase angle at the maximum reactance value
H_L: hand_leg, RL: right leg, LL: left leg, RH: right hand, LH: left hand, L_L: leg_leg

DISCUSSION

Studies have been made between PhA and impaired glycemic index in diabetes, but it has been limited to PA max. However, PA max is the best indicator of cell receptor integrity and health. It is a parameter independent of various frequencies adopted by BIA devices (18). In our study, PA max levels were found to be significantly lower in the T2DM group compared to the healthy group (Table 1), PA max tended to decrease as fasting glucose level and HbA1C levels increased (Table 2). According to these results, we can say that an impaired glycemic index negatively affects cell receptor integrity and cellular health level.

In a study including patients with T1 DM, T2 DM, and control subjects, Buscemi et al. showed that the total body PhA obtained at 50 kHz was lower in the diabetes group (19). Buffa et al. received the phase angle from a single frequency using the standard positions of the outer and inner electrodes on the right hand and foot. They showed the presence of a lower phase angle in diabetic patients compared to healthy controls, and reported that this is a diagnostic and prognostic marker (20). In a study conducted by Jun et al, PAmax measured in the RA, LA, RL, and LL were found to be significantly lower in patients with T2 DM regardless of sex compared with the control group (11).

In our study, HbA1C decreased significantly in all segments in T2 DM group, and fasting glucose significantly decreased PA max in all segments except LH (Table 2). Ditmar et al. reported that phase angle is an indicator of catabolism in T2 DM and is negatively correlated with HbA1C (17). In their study including 321 patients with T2 DM, Choi et al. reported that phase angle measured at 50 kHz had an independent relationship with fasting glucose and HbA1C (21).

Age factor negatively affected PAmax in all segments as in HbA1c (Table 2). Buscemi et al. found a significant and independent relationship between age and PhA in a study that included patients with T1 DM and T2 DM (19). Jun et al. also found that the phase angle decreasesd as the age of patients with diabet increased and the duration of the disease increased (22).

In addition, it was revealed that while muscle percentage had a positive effect on PA max in T2 DM, fat percentage had a negative effect (Table 1). Other studies reported an increase in fat ratio and a decrease in muscle mass due to hyperglycemia (23). PA max tended to increase when muscle mass increased or fat mass decreased. Studies have found that PhA is positively correlated with muscle content and negatively correlated with fat ratios (24,25).

Studies with PhA in diabetes have generally been carried out at certain frequencies and in a limited number of segments (17,19-21). In our study, however, PA max was obtained independently of frequencies and was significantly lower in all segments except LH compared to the healthy group. This result may show that PA max reflects the metabolic status better in Type-2 DM and may be an important marker in diagnosis and prognosis. In addition, we are aware that fasting glucose and HbA1C as well as age and fat percentage negatively affect PAmax. Age is a non-changeable risk factor. However, by regulating blood glucose and reducing fat percentages, PA max levels can be increased and cellular health levels can be improved. We suggest investigating the factors affecting PAmax and the use of PAmax in the examination of metabolic status, diagnosis, and prognosis in type-2 DM.

CONCLUSION

PA max is a potential marker that can be easily obtained from BIA devices independently of multiple frequencies and reflects the metabolic status in T2 DM. Impaired glycemic index, age, and body fat percentage significantly reduce PA max. It can be used as a diagnostic and prognostic marker in clinical practice.

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

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Research Article

Ankle Bone Anatomy in Turkish Population: A Radiological Study

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Abstract

Aim: While numerous geographic locations have been examined in the literature regarding the morphological characteristics of ankle bones, no studies have been conducted specifically in Turkey. Our study aims to assess the morphological features of ankle bones in individuals residing in Turkey, utilizing ankle computed tomography (CT) images obtained from patients.

Material and Methods: In our single-centre study, the data between 2018 and 2022 were scanned. The criteria for inclusion in the study were determined as being a citizen of the Republic of Turkey, being over the age of 18, and being under the age of 65.

Results: 200 patients (100 men, 100 women) and 200 ankle CT images were selected by stratified sampling using the computer-assisted randomisation method. APA, APG, MalW, MDA, MDV, MTiTh, SRTa, SRTi, TaAL, TaW, TiAL, Th, and TiW values were measured on computed tomography images.

Conclusions: The morphological structure of the ankle bone varies from society to society and according to gender. These factors should be considered in implant design (especially in prosthetic design) and the application of these implants. Our study will guide the design of ankle implants (especially prostheses) for communities living in Turkey.

Keywords: Ankle; morphology; total ankle prosthesis; ankle morphometry

INTRODUCTION

A comprehensive understanding of the ankle's anatomy and biomechanical structure is crucial when performing surgical interventions on the ankle (1-3). This information is golden, especially in cases where appropriate restoration of the ankle joint line is required (4). Some include surgery for intra-articular extension ankle fractures after high-energy trauma, total ankle arthroplasty, or ankle deformity surgery.

It is important to provide anatomical and biomechanical correlation, especially in ankle arthroplasty. In such surgeries, the correct design and application of the implant are based on knowing the normal anatomy of the ankle (5,6). While there are many geographic locations in the literature regarding the morphological features of the ankle bones, there are no studies conducted in Türkiye.

Our study aims to determine the ankle bone morphological features of individuals living in Türkiye through the ankle computed tomography (CT) images of the patients.

MATERIAL AND METHOD

The ethics committee of Dicle University approved our study (1642). Since it was a retrospective study, informed consent was not obtained. In our single-centre study, the data between 2018 and 2022 were scanned. The criteria for inclusion in the study were determined as being a citizen of the Republic of Türkiye, being over the age of 18, and being under the age of 65. Exclusion criteria were CT images that did not include all 3 sequences and were of poor quality, previous foot or ankle surgery, previous osteomyelitis, tumour, congenital deformity, or presence of conditions that may disrupt normal foot-ankle anatomy, Kellgren and Lawrence score (7) of >3 were excluded from the analysis. Two orthopaedic specialists made measurements.

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Measurement Parameters

The measurements were obtained from the computed tomography images through the radiology information management system program. The origin of the coordinate system was taken to be at the geometric centre of the talus. The anteroposterior (A/P) axis was the line joining the Achilles tendon's calcaneal insertion and the second metatarsal head, parallel to the baseplate. The mediolateral (M/L) axis was then defined as the line perpendicular to the A/P and S/I axes. The anteroposterior inclination angle of the tibial mortise (APA), anteroposterior gap (APG), malleolar width (MalW), the distance of level of MTiTh from the anterior limit of the mortise (MDA), the distance of level of MTiTh from the vertex of the mortise (MDV), maximal tibial thickness(MTiTh), the sagittal radius of the trochlea tali arc (SRTa), the sagittal radius of the tibial mortise (SRTi), trochlea tali length (TaAL), talar width (TaW), tibial arc length (TiAL)), talar tenon height (Th) and tibial width (TiW) were measured. The parameters were measured as previously described in the literature (8). The measurements of the parameters are shown in Figure 1.

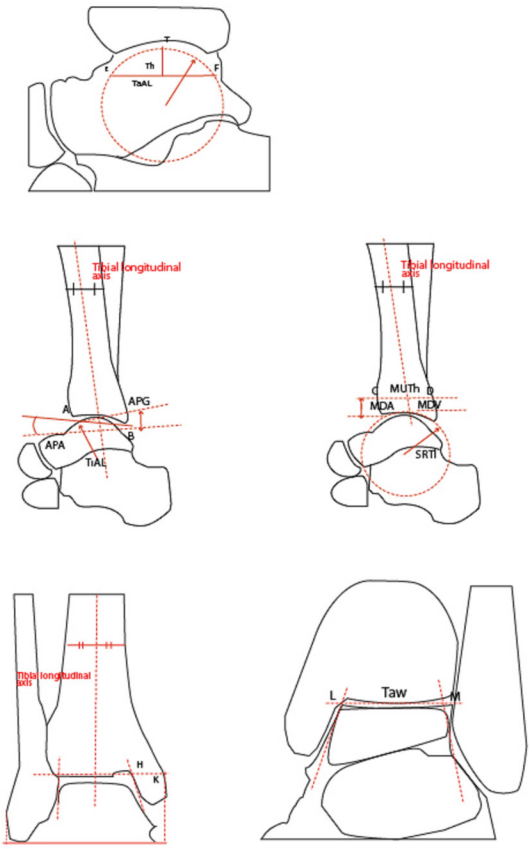

Figure 1. Morphologic measurements

To establish interobserver and intraobserver reliability, some assessments have been made. All measurements were made two times, with an interval of 2 weeks, by the clinician who made the measurement. In addition, all measurements were made again by an independent orthopaedic specialist to evaluate interobserver reliability. The intra-class coefficient (ICC) assessed interobserver and intraobserver reliability. The ICC is a value between 0 and 1, where values below 0.5 indicate poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and any value above 0.9 indicates excellent reliability (9).

Statistical analyses were performed using the Statistical Package of the Social Sciences (IBM SPSS 28.0.1.0; Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables. The Student's T-test and one-way Student's T-test were used to compare the parameters. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Between 2018-2023, 342 ankle CT images were obtained. Among the 297 ankle CT images that met the criteria, 200 patients (100 men, 100 women) and 200 ankle CT images were selected by stratified sampling using the computer-assisted randomisation method (www.randomizer.org). The mean age of the patients was 44.05±11.77. One hundred twenty-one images belong to the right ankle, and 79 belong to the left ankle. One hundred patients were male, and 100 patients were female. The mean values of APA, APG, MalW, MDA, MDV, MTiTh, SRTa, SRTi, TaAL, TaW, TiAL, Th, and TiW by gender are given in Table 1. There were significant differences between genders in all parameters except APA, APG, MDA, and MDV. In Tables 2 and 3, measurement values and comparisons made according to populations are given. Interobserver reliability was 0.91, and intra-observer reliability was 0.93.

Table 1. Mean values of ankle bone morphological parameters by gender

Gender	Male (n=100)		Female (n=100)		Total (n=200)		
	Mean	SD	Mean	SD	Mean	SD	P Value
APA(deg)	8.04	3.36	7.74	3.65	7.90	3.51	.536
APG(mm)	4.11	1.46	4.31	1.65	4.21	1.56	.374
MalW(mm)	70.39	3.18	69.41	3.49	69.91	3.37	**.039**
MDA(mm)	12.69	2.33	12.29	2.71	12.49	2.53	.264
MDV(mm)	8.23	3.50	8.14	3.65	8.19	3.57	.841
MTiTh(mm)	42.51	3.49	41.39	3.72	41.95	3.64	**.029**
SRTa(mm)	23.39	2.48	22.56	2.62	22.98	2.58	**.022**
SRTi(mm)	27.27	3.20	26.21	3.38	26.74	3.33	**.024**
TaAL(mm)	40.51	2.87	39.54	3.26	40.03	3.11	**.026**
TaW(mm)	30.44	3.30	29.53	2.81	29.99	3.10	**.036**
TiAL(mm)	30.71	3.10	29.77	3.11	30.24	3.14	**.032**
Th(mm)	11.76	1.65	11.34	1.32	11.56	1.51	**.047**
TiW(mm)	32.89	3.35	31.88	3.32	32.39	3.37	**.032**

Table 2. Comparison of ankle bone morphological parameters according to different regions

	French (10)	American (11)	Italian (12)	Korean (8)	Taiwan (13)	Northeast China (13)	Türkiye
APA(deg)	8.3±1.4	-	5±3.4	8.2±3.2	7.4±5.7	9.1±2.1	7.90±3.51
APG(mm)	-	-	2.7±1.8	4.2±1.7	3.6±2.8	4.8±1.0	4.21±1.56
MalW(mm)	-	-	69	67.6	63.1±3.4	66.6±3.9	69.91±3.37
MDA(mm)	-	-	11.5±3.5	12.4±2.7	11.4±4.0	9.3±1.3	12.49±2.53
MDV(mm)	-	-	8.7±3.5	10±10	4.0±2.2	6.2±1.3	8.19±3.57
MTiTh(mm)	-	-	41.4±3.9	39.4±3.6	42.0±5.1	40.8±2.6	41.95±3.64
SRTa(mm)	-	20.7±2.6	23.4±3.1	21.5±2.6	-	-	22.98±2.58
SRTi(mm)	-	-	27.8±4.4	23.3±2.8	-	-	26.74±3.33
TaAL(mm)	38.5±2.2	-	41.7±4.4	35.3±3.6	32.3±4.1	33.4±2.8	40.03±3.11
TaW(mm)	31.4±2.5	27.9±3	30.4±3.3	30.5±3	20.9±3.0	28.5±2.1	29.99±3.10
TiAL(mm)	30.8±3.0	-	31.4±3.5	29.2±2.9	28.4±2.9	29.4±1.6	30.24±3.14
Th(mm)	12.1±1.5	-	-	10.5±1.1	11.9±1.8	10.6±1.4	11.56±1.51
TiW(mm)	34.5±2.3	-	31.9±3.5	31.3±3.1	33.3 ± 2.5	33.4±2.2	32.39±3.37

Table 3. Comparison of Türkiye's and different regions' data with one-way Student T-test

	French (10)	American (11)	Italian (12)	Korean (8)	Taiwan (13)	Northeast China (13)
APA(deg)	0.104	-	**<0.001**	0.221	0.047	**<0.001**
APG(mm)	-	-	**<0.001**	0.933	**<0.001**	**<0.001**
MalW(mm)	-	-	**<0.001**	**<0.001**	**<0.001**	**<0.001**
MDA(mm)	-	-	**<0.001**	0.605	**<0.001**	**<0.001**
MDV(mm)	-	-	0.044	**<0.001**	**<0.001**	**<0.001**
MTiTh(mm)	-	-	**0.032**	**<0.001**	0.861	**<0.001**
SRTa(mm)	-	**<0.001**	**0.021**	**<0.001**	-	-
SRTi(mm)	-	-	**<0.001**	**<0.001**	-	-
TaAL(mm)	**<0.001**	-	**<0.001**	**<0.001**	**<0.001**	**<0.001**
TaW(mm)	**<0.001**	**<0.001**	0.063	**0.021**	**<0.001**	**<0.001**
TiAL(mm)	0.463	-	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Th(mm)	**<0.001**	-	-	**<0.001**	**<0.001**	**<0.001**
TiW(mm)	**<0.001**	-	**0.042**	**<0.001**	**<0.001**	**<0.001**

Data in the table are p values, the significance level was set at 0.05

DISCUSSION

The morphological structure of the ankle may vary from society to society. Knowing these changes is essential in choosing individual or community-specific implants (especially ankle arthroplasty) in ankle surgery. Our study found that the ankle morphometric structure of Turkish society differed from the other societies described in the literature.

In radiological studies to determine the morphometric features of any anatomical structure, the X-ray is an advantageous method to give cheap, simple, and fast results. However, besides this advantage, there are also some disadvantages. Cross-sectional image limitations, contrast limitations, the image overlap are a few of them (14). In addition, the angle of the tube during shooting and the lack of shooting at the appropriate dose also affect the image quality. On the other hand, computed tomography (CT) provides a higher resolution, thin section, and 3D image when necessary. In similar studies in the literature,

measurements were made with the help of direct radiography or computerised tomography (8,9,12,13). In the study of Hongyu et al., CT images gave more accurate results than X-ray images (13). Stagni et al. reported that there were differences in CT and X-ray measurements, but they were not significant in most parameters, and this was due to the small number of samples (15). For the reasons mentioned above, it was deemed appropriate to make measurements on computed tomography in our study. To minimise the margin of error, measurements were made 2 times on different dates by 2 different clinicians. Interobserver and intra-observer reliability were found to be excellent.

When we look at the morphological measurements of the ankle, we see that the measurements differ from society to society in studies conducted in France, Italy, Korea, Taiwan and Northeast China (13). These differences can help the surgeon to make a more accurate decision in ankle surgery operations. Although there is no geographical distinction in orthopaedics in the design, production and development phase of implants, differences can be important, especially in ankle prostheses, according to the geographical region. To prevent the negative effects of these anatomical variations on surgery, custom-made implant production has become widespread. However, it is used in selected cases because personalised production is costly and time-consuming. Hongyu et al. concluded that total ankle prostheses designed for Caucasians are unsuitable for the northeast Chinese population (13). In our study, it was found that APA, APG, MalW, MDA, MDV, MTiTh, SRTa, SRTi, TaAL, TaW, TiAL, Th, and TiW values differ in the Turkish population compared to other populations (Table 2, 3).

These parameters, measured in our study and differed in Turkish society, have various clinical significance. Ensuring optimal physiological and biomechanical harmony is important in orthopaedic surgery, especially in joint and prosthetic surgery. A larger APA in total ankle replacement surgery indicates that the distal tibial segment should be larger. Because this bone cut is made at an angle of 90 degrees to the anterior of the distal tibia. Also, the possibility of fractures in the medial and lateral malleolus is higher (16). In the study of Stagni et al. (15) stated that knowing the MDV, MDA, APG, and APA values is essential in determining the optimal level and inclination of the bone cut. In addition, these data are precious in the design of the prosthesis and instrumentation used in the operation because the preservation of the bone stock as much as possible depends on the appropriate design of the prosthesis.

The present study determined statistically significant differences in the parameters related to the size of the male and female groups. It is concluded that gender can also significantly affect the design of orthopaedic implants. In our study, it was determined that the ankle sizes of men were larger than women. It is a detail that needs attention in implant design, ankle surgery and especially in total ankle arthroplasty.

There are certain limitations of our study. Evaluating the ankle joint with bone tissue alone will not give accurate results. There are many factors affecting ankle instability (17). It is necessary to consider them as a whole. In addition, lower extremity alignment, muscle strength and other soft tissue factors are also crucial for the normal function of the ankle. In this respect, biomechanical studies are needed to test the reflection of the differences in the anatomical structure of the ankle on the clinical picture. Although our hypothesis claims these differences are clinically important in implant selection and prosthesis design, studies are needed to compare long-term functional, radiological and surgical outcomes in large patient groups. Another limitation of our study is that it is retrospective.

CONCLUSION

As a result, the morphological structure of the ankle bone varies from society to society and according to gender. These factors should be considered in implant design (especially in prosthetic design) and the application of these implants. Our study will guide the design of ankle implants for communities living in Türkiye. These data will be guiding especially for ankle prostheses to be produced in Türkiye.

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Ethical approval: *The ethics committee of Dicle University approved our study (1642,14.03.2022).*

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Research Article

Examining the Impact of Maternally Administered Bisphenol-A on Rat Kidney Development

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Abstract

Aim: Bisphenol-A (BPA) is an estrogenic chemical used today in the production of epoxy resin and as an additive in other non-polymer plastics. Due to the widespread use of BPA today, human exposure is inevitable. This exposure causes harmful effects on various body systems. The aim of this study is to investigate the effects on the development of the kidneys of the offspring of mother rats exposed to BPA during pregnancy and lactation, as a result of the offspring being exposed to BPA through the placenta and milk.
Material and Methods: In this study, 13 adult Wistar albino female rats were divided into 3 groups. In Group 1 (Control group), rats were only administered 1 ml/kg/day corn oil intraperitoneally. Group 2 (25 mg BPA group) rats were administered 25 mg/kg/day BPA; Group 3 (50 mg group) rats were administered 50 mg/kg/day BPA intraperitoneally for 5 weeks. At the end of the experiment, the intracardiac blood and kidney tissues of the offspring rats were taken and examined for urea, total protein, creatinine, TAS, TOS, MDA values.
Results: At the end of the study, it was determined that BPA increased serum urea, creatinine and total protein levels, induced the formation of reactive oxygen species causing oxidative damage in kidney tissue, and caused serious structural damages
Conclusion: Only mother rats exposed to BPA. BPA transferred to pups via placenta and milk, causing structural damage: narrowing in Bowman's space of renal corpuscle, dilatation in proximal/distal tubules and collecting ducts, occasional cell loss, vacuolization in tubule epithelia.

Keywords: Bisphenol-A, urea, protein, creatinine, oxidative stress

INTRODUCTION

The kidney is a vital organ in the human body. Its primary functions include the excretion of metabolites and harmful substances, maintaining water balance, preserving electrolyte and acid-base balance, regulating blood pressure, promoting red blood cell production, and encouraging Vitamin D activation to ensure internal stability. Any structural or functional abnormalities in the kidney are defined as chronic kidney disease (CKD). Numerous chemical and environmental factors we encounter in daily life can trigger chronic kidney disease by affecting various systems, primarily the endocrine system. The main substances affecting the endocrine system include Bisphenol-A (BPA), polychlorines, biphenyls, phthalates, pesticides, and phytoestrogens. One of these endocrine disruptors, widely used today, is a synthetic compound known as BPA. BPA, an estrogenic chemical with the formula 2,2-bis(4-hydroxyphenyl) propane, is used as an additive in the production of epoxy resins and other non-polymer plastics. BPA can act as a selective estrogen receptor modulator by binding to the estrogen receptor in some tissues to trigger a response, while in other tissues, it prevents the estrogen receptor from binding, thus inhibiting a response. The widespread use of BPA in the plastic industry leads to its extensive distribution in the environment (1,2).

The harmful effects of BPA on human health arise from

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the community's continuous exposure to low doses, especially during fetal development and subsequent periods. Maternal exposure to BPA increases the risk of adverse outcomes such as liver tumors, breast cancer, birth defects, lung inflammation, Parkinson's disease, diabetes, and reproductive anomalies in offspring (2,3). It has been reported by Rezg et al. in 2014 that BPA exposure affects the physiology of the central nervous system (CNS), especially during the brain's development stage, and due to its lipophilic structure, it can easily cross the blood-placenta and blood-brain barriers, making its effect more pronounced during the lactation period (4,5). The aim of our study is to investigate the histological and biochemical effects on the early development of the kidneys of offspring indirectly exposed to BPA through placental and milk transfer as a result of maternal exposure during pregnancy and lactation periods. BPA, which has an extremely widespread production and usage area, is also defined as an endocrine disruptor.

MATERIAL AND METHOD

In this study, a total of 13 adult female Wistar Albino rats and 60 newborn rats were used. Female rats were mated with male rats during their estrus cycle to ensure pregnancy. Pregnant female rats were randomly divided into three separate groups: control (n:3), 25 mg BPA group (n:5), and 50 mg BPA group (n:5). Starting from the 6th day of pregnancy, 1 ml/kg/day of corn oil was administered intraperitoneally to the mother rats in the control group (Group 1), while 25 mg/kg/day (Group 2) and 50 mg/kg/day (Group 3) BPA were given to the mother rats in the non-control groups until the 21st day of the postnatal lactation period. A total of 10 randomly selected offspring rats from different mothers in each group were sacrificed on the 21st day (n=30) and 45th day (n=30) by intraperitoneal injection of Xylazine hydrochloride at a dose of 10 mg/kg and Ketamine hydrochloride at a dose of 90 mg/kg. The abdominal anterior wall of the anesthetized subjects was opened by incision to reach the heart from the diaphragm, and their intracardiac blood was collected. Kidney tissues were taken for pathological examination. From the serum samples, urea (OttoScientific, OttoBC157, Türkiye), total protein (OttoScientific, OttoBC154, Türkiye), creatinine (OttoScientific, OttoBC139, Türkiye), Total Antioxidant Levels (TAS) (Rel Assay, RL0017, Türkiye), Total Oxidant Levels (TOS) (Rel Assay, RL0024, Türkiye), and Malondialdehyde (MDA) values were determined using a colorimetric method with the MINDRAY-BS400 device, strictly adhering to the protocol provided by the manufacturer. The kidney tissues taken from the subjects were rinsed with 0.9% cold saline. The tissues were fixed in containers with a 10% neutral formalin solution labeled to indicate which group they belonged to. The Hematoxylin-Eosin (H&E) staining method, one of the most commonly used methods for staining sections, and the Masson-Trichrome staining method were used to show the difference in fibrous tissue formation in the experimental and control groups due to possible kidney toxicity. The tissues were examined under a microscope to determine which experimental groups had damage areas.

Histopathological findings were evaluated by measuring Bowman's space. The ratio of Bowman's capsule area to glomerular area was used in the assessment of Bowman's space. A decrease in this ratio indicates a reduction in the space, whereas an increase indicates an enlargement. One-way analysis of variance (ANOVA) was employed to assess the differences between groups. Sidak's multiple comparison test was used for post hoc analysis. A significance level of $p<0.05$ was considered for all tests. GraphPad Prism version 8.0.2 for Windows, GraphPad (Software, Boston, Massachusetts, USA) was utilized for statistical analyses.

RESULTS

Histopathological Findings

In our study, the kidney tissues of 21 and 45-day-old offspring born to mother rats administered with 25 mg and 50 mg BPA were examined at the light microscope level and the statistical analysis results given at Table 1.

Table 1 Statistical results of histopathological findings

	Mean 1	Mean 2	SE of diff,	Summary	Adjusted P Value
21th day Control vs. 21th day 25mg	72.15	82.4	1.575	****	<0.0001
21th day Control vs. 21th day 50mg	72.15	90.9	1.638	****	<0.0001
21th day 25mg vs. 21th day 50mg	82.4	90.9	1.548	****	<0.0001
45th day Control vs. 45th day 25mg	71.71	87.62	2.644	****	<0.0001
45th day Control vs. 45th day 50mg	71.71	93.19	2.919	****	<0.0001
45th day 25mg vs. 45th day 50mg	87.62	93.19	2.535	ns	0.2331
21th day Control vs. 45th day Control	72.15	71.71	2.435	ns	>0.9999
21th day 25mg vs. 45th day 25mg	82.4	87.62	1.883	ns	0.0535
21th day 50mg vs. 45th day 50mg	90.9	93.19	2.297	ns	0.9689

Histopathological findings of 21-day-old rats

Findings related to the control group (Group 1)

Upon examining the kidney tissues of the 21-day-old Control group at low magnification with a light microscope, it was observed that the renal corpuscles located in the cortex exhibited normal histological features when examined at high magnification. This included the Bowman's capsule located on the outer part, the parietal leaf epithelial cells, the Bowman's space where the filtrate is filtered and sent to the urine, and the glomerular capillary tuft structure. The proximal and distal tubules and the macula densa cells appeared normal. No deformation was observed in the structure and cells of the proximal and distal tubules located in the medulla, the thin part of the Henle's loop with flat epithelial cells, and the collecting ducts (Figure 1).

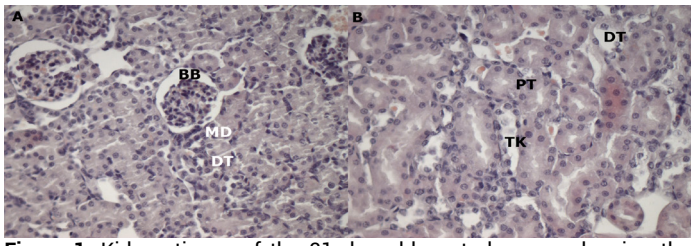

Figure 1. Kidney tissue of the 21-day-old control group, showing the structure of the renal corpuscle (G), Bowman's space (BB), macula densa cells 17, proximal (PT) and distal (DT) tubules, and collecting ducts (CD) (H&E, 40x)

Findings related to the 25 mg BPA group (Group 2)

When tissue samples taken from the kidneys of newborn rats in the group administered with 25 mg BPA on the 21st day were examined at low magnification under a light microscope, it was observed that there were numerous renal corpuscles and nephron tubules in the cortex of the kidney tissue, and collecting ducts and tubules in the medulla. Upon examination at high magnification, it was observed that in many renal corpuscles located in the cortex, narrowing occurred in the Bowman's space as a result of the expansion of capillary tufts in the glomerulus due to BPA. No serious deformation was observed in the cells and epithelia of the proximal and distal tubules located in the medulla. It was observed that the cuboidal epithelial cells of the collecting ducts transformed into squamous epithelial cells. When sections examined with Masson's trichrome staining, it was seen that there were small amounts of connective tissue areas between the renal corpuscles and tubules (Figure 2).

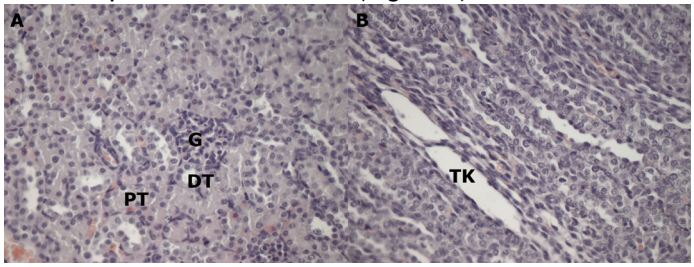

Figure 2. In the renal cortex of the 21-day-old 25 mg BPA group, the renal corpuscle (G), narrowing in the Bowman's space (*), proximal (PT) and distal tubules (DT), and dilation in the collecting duct (CD) located in the medulla are shown (H&E, 20x)

Findings related to the 50 mg BPA group (Group 3)

When tissue samples taken from the kidneys of newborn rats in the group administered with 50 mg BPA on the 21st day were examined at low magnification under a light microscope, it was observed that the general appearance of the kidney tissue had a clear distinction between the cortex and medulla; numerous renal corpuscles were located in the cortex, and collecting ducts and tubules were in the medulla. Upon examination at high magnification, it was found that there were deformations in the capillary tuft in some of the renal corpuscles located in the cortex as a result of BPA exposure. As a result of the expansions in the capillary tuft, narrowing occurred in the Bowman's space; no serious disruption was observed in the cells and epithelia of the proximal and distal tubules located in the medulla. It was observed that the cuboidal epithelial cells of the collecting ducts transformed into squamous epithelial cells, and there was tubular dilation in some. When sections examined with Masson's trichrome staining, it was seen that there were connective tissue areas between the renal corpuscles and tubules and around the blood vessels (Figure 3).

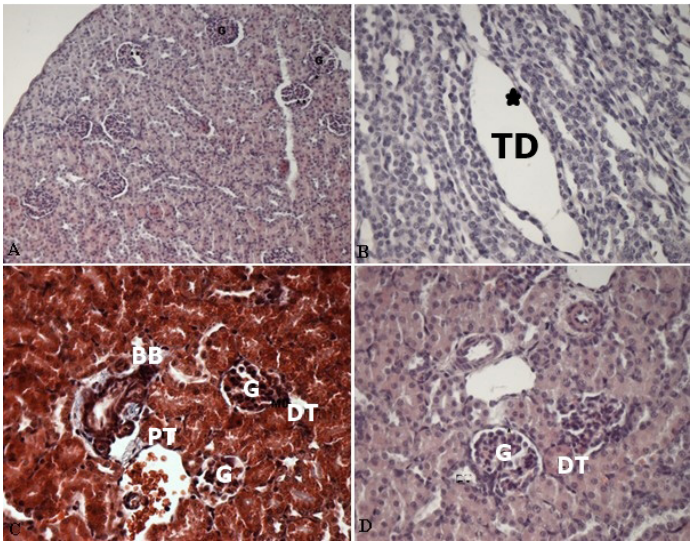

Figure 3. Kidney tissue of the 21-day-old 50 mg BPA group; A) Renal corpuscle (G) in the renal cortex, deformation in the capillary tuft (**) (H&E, 20x); B) Renal medulla; tubular dilation (TD) in the collecting duct, squamous transformation in epithelia(*) (H&E, 40x); C) Glomeruli (G), macula densa cells 17, proximal tubule (PT), distal tubule (DT) and connective tissue (BD) (MTK, 40x) in the renal cortex; D) Structures located in the renal cortex are shown (H&E, 40x)

Histopathological findings of 45-day-old rats

Findings related to the control group (Group 1)

In the 45-day-old Control group, light microscopic examinations at low magnification revealed the presence of numerous renal corpuscles and nephron tubules in the cortex, and collecting ducts and tubules in the medulla. Upon high magnification examination of the renal corpuscles located in the cortex, the Bowman's capsule located on the outer part, parietal leaf epithelial cells, the Bowman's space where the filtrate is sieved and sent to urine, the glomerular capillary tuft formed by the convergence of capillaries, and the macula densa

cells were observed to be normal. No deformation was observed in the cells and structures of the proximal, distal tubules, Henle's loop, and collecting ducts located in the medulla. No pathological findings were encountered in the collecting ducts. Sections examined with Masson's trichrome staining revealed a small amount of connective tissue around the blood vessel (Figure 4).

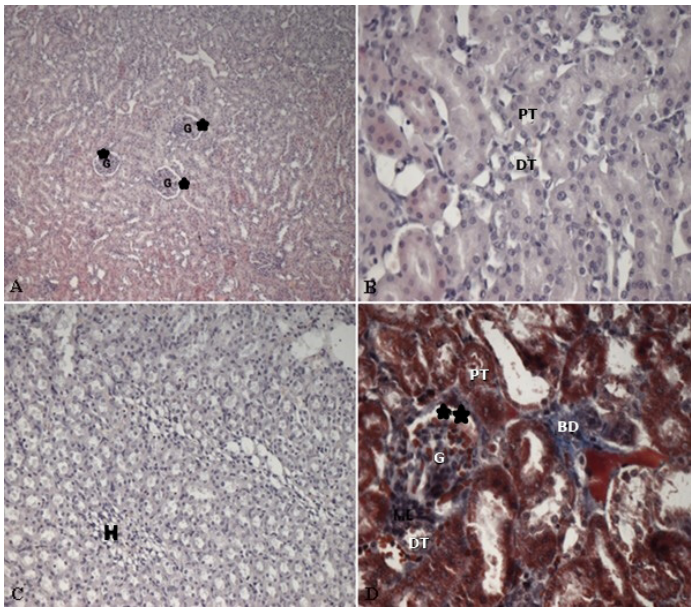

Figure 4. Kidney tissue belonging to the 45-day-old control group; A) Renal corpuscles (G) located in the renal cortex, Bowman's space (*) (H&E, 10x). B) Renal medulla; proximal tubule (PT) and distal tubule (DT) (H&E, 40x). C) Henle's loop (H) (H&E, 20x); D) Glomerule (G), Bowman's space (**), Macula densa cells 17, proximal tubule (PT), distal tubule (DT), and connective tissue (BD) in the renal cortex are shown (MTK, 40x)

Findings related to the 25 mg BPA group (Group 2)

In the high magnification examinations of tissue samples taken from the adult rat kidneys of the 45-day-old 25 mg BPA group, it was observed that due to BPA exposure, there was a narrowing in the Bowman's space in the renal corpuscles in the renal cortex, and in some, this space was completely closed; there were occasional cell sloughing in the cells and structures of the proximal and distal tubules located in the medulla. Dilatation in the collecting ducts and a decrease in epithelial cells were detected (Figure 5).

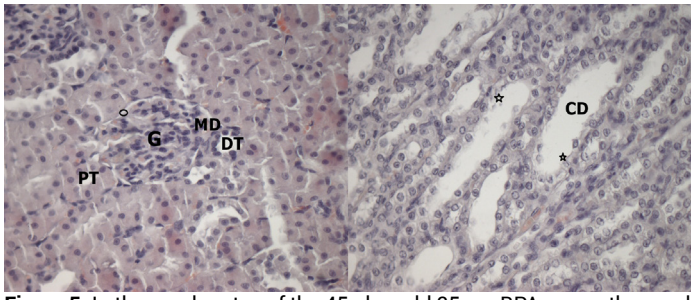

Figure 5. In the renal cortex of the 45-day-old 25 mg BPA group, the renal corpuscle (G), narrowed Bowman's space (•), Macula densa cells 17, proximal (PT) and distal tubule (DT), and dilatation in the collecting duct (CD) and decrease in epithelial cells (*) are shown (H&E, 40x)

Findings related to the 50 mg BPA group (Group 3)

In the high magnification examinations of tissue samples taken from the adult rat kidneys of the 45-day-old 50 mg BPA group, it was observed that in most of the renal corpuscles in the cortex, due to BPA-induced expansion in the capillary tuft, there was a narrowing in the Bowman's space, and in the majority, this space was completely closed. Destruction of epithelial cells in the tubules and the formation of vacuoles were also observed. Serious damages such as cell loss and deformation in the cells and epithelium of the distal, proximal tubules located in the medulla were observed; it was seen that the cuboidal epithelial cells of the collecting ducts were transformed into squamous epithelial cells in places, some epithelial cells decreased, and dilatation was observed in some collecting ducts (Figure 6).

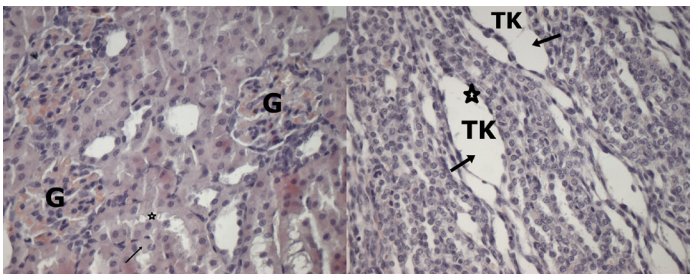

Figure 6. In the renal cortex of the 45-day-old 50 mg BPA group, renal corpuscles (G), vacuolization in proximal tubules (left picture-arrow) and cell loss (*); flattening (*) in the cells of the collecting duct (TK) in the renal medulla and tubule dilatation (arrow marks) (H&E, 40x)

Biochemical Findings

Total antioxidant level results

Upon analyzing the TAS values studied from the sera, it was found that the highest TAS value belonged to the 21-day 50 mg BPA group (4.5150 mmol/L), while the lowest TAS value belonged to the 21-day 25 mg BPA group (1.4833 mmol/L). A significant difference was detected between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between Group 2 (25 mg BPA, 21-day) and Group 3 (50 mg BPA, 21-day); and between the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 2).

Total oxidant level results

Upon analyzing the TOS values studied from the sera, it was found that the highest TOS value belonged to the 21-day 50 mg BPA group (54.5900 µmol/L), while the lowest TOS value belonged to the control group (Group 1, 21-day) (3.8163 µmol/L). A low degree of significant difference was found between the control group (Group 1, 21-day) and Group 2 (25 mg BPA, 21-day); a significant difference was found between Group 1 (Control, 21-day) and Group 3 (50 mg BPA, 21-day); between 25 mg BPA (Group 2, 21-day) and 50 mg BPA (Group 3, 21-day); and between the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 2).

Oxidative stress index results

Upon analyzing the OSI values studied from the sera, it was found that the highest OSI value belonged to the 25 mg BPA group (Group 2, 21-day) (1.224) and the 50 mg BPA group (Group 3, 21-day) (1.207), while the lowest

Oxidative Stress Index (OSI) value belonged to the control group (Group 1, 21-day) (0.1519). A significant difference was found between the control group (Group 1, 21-day) and Group 2 (25 mg BPA, 21-day); between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between the 25 mg BPA groups (Group 2, 21-day-45-day) and the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 2).

Malondialdehyde level results

Upon analyzing the MDA values studied from the sera, it was found that the highest MDA concentration value belonged to the 50 mg BPA group (Group 3, 21-day) (178.6 mmol/L), while the lowest MDA value belonged to the 25 mg BPA group (Group 2, 45-day) (5.213 mmol/L). A low level of significant difference was found between the 25 mg BPA group (Group 2, 45"-day) and the 50 mg BPA group (Group 3, 45-day); a significant difference was found between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between the 25 mg BPA group (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day); and between the 50 mg BPA groups (Group 3, 21-day-45-day) ($p<0.0001$) (Table 3).

Table 2. Comparative analysis of TAS, TOS, and OSI values across different groups

Test details	TAS		TOS		OSI	
	Summary	P Value	Summary	P Value	Summary	P Value
(21 day) Control vs. 25 mg BPA	Ns	0.3423	*	0.026	****	<0.0001
(21 day) Control vs. 50 mg BPA	****	<0.0001	****	<0.0001	****	<0.0001
(45 day) Control vs. 25 mg BPA	Ns	>0.9999	Ns	>0.9999	Ns	>0.9999
(45 day) Control vs. 50 mg BPA	Ns	>0.9999	Ns	>0.9999	Ns	0.5599
(21 day) 25 mg BPA vs. 50 mg BPA	****	<0.0001	****	<0.0001	****	<0.0001
(45 day) 25 mg BPA vs. 50 mg BPA	Ns	>0.9999	Ns	>0.9999	****	<0.0001
25 mg BPA (21 day) vs. 25 mg BPA (45 day)	Ns	0.0536	Ns	0.6426	Ns	>0.9999
50 mg BPA (21 day) vs. 50 mg BPA (45 day)	****	<0.0001	****	<0.0001	Ns	>0.9999

Table 3. Comparative analysis of MDA, TP, UREA, creatinin values across different groups

Test details	MDA		Total Protein		UREA		Creatinin	
	Summary	P Value	Summary	P Value	Summary	P Value	Summary	P Value
(21 day) Control vs. 25 mg BPA	ns	>0.9999	ns	0.1893	ns	0.1851	*	0.0389
(21 day) Control vs. 50 mg BPA	****	<0.0001	****	<0.0001	ns	0.7596	****	<0.0001
(45 day) Control vs. 25 mg BPA	ns	>0.9999	ns	>0.9999	ns	>0.9999	ns	>0.9999
(45 day) Control vs. 50 mg BPA	ns	0.2962	ns	>0.9999	ns	>0.9999	ns	0.3589
(21 day) 25 mg BPA vs. 50 mg BPA	****	<0.0001	ns	>0.9999	ns	>0.9999	****	<0.0001
(45 day) 25 mg BPA vs. 50 mg BPA	**	0.0048	****	<0.0001	**	0.0014	ns	>0.9999
25 mg BPA (21 day) vs. 25 mg BPA (45 day)	ns	>0.9999	****	<0.0001	*	0.0234	***	0.0004
50 mg BPA (21 day) vs. 50 mg BPA (45 day)	****	<0.0001	ns	>0.9999	ns	>0.9999	****	<0.0001

Total protein level results

Upon analyzing the Total Protein (TP) values studied from the sera, it was found that the highest TP concentration value belonged to the 50 mg BPA group (Group 3, 21-day) (15.41 g/dL), while the lowest TP value belonged to the control group (Group 1, 21-day) (4.412 g/dL). A significant difference was found between the control group (Group 1, 21-day) and Group 3 (50 mg BPA, 21-day); between the 50 mg BPA groups (Group 3, 21-day-45-day); and between the 25 mg BPA group (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day) ($p<0.0001$) (Table 3). The highest total protein concentration level in the 50 mg BPA group supports the notion that BPA causes proteinuria.

Urea level results

Upon analyzing the urea values studied from the sera, it was found that the highest urea concentration value belonged to the 25 mg BPA group (Group 2, 45-day) (74 mg/dL), while the lowest urea value belonged to the 25 mg BPA group (Group 2, 21-day) (56.67 mg/dL). A low level of significant difference was found between the 25 mg BPA group (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day); a low level of significant difference was found between the 25 mg BPA groups (Group 2, 21-day-45-day) ($p<0.0001$) (Table 3).

Creatinine level results

Upon analyzing the creatinine values studied from the sera, it was found that the highest creatinine level belonged

to the 50 mg BPA group (Group 3, 21-day) (3.083 mg/L), while the lowest creatinine value belonged to the 25 mg BPA group (Group 2, 21-day) (0.5767 mg/L). A low level of significant difference was found between the 25 mg BPA group (Group 2, 21-day) and the control group (Group 1, 21-day); a medium level of significant difference was found between the 25 mg BPA groups (Group 2, 21-day-45-day); a high level of significant difference was found between the control group (Group 1, 21-day) and the 50 mg BPA group (Group 3, 21-day); between the 25 mg BPA groups (Group 2, 21-day) and the 50 mg BPA group (Group 3, 21-day); and between the 50 mg BPA group (Group 3, 21-day) and the 50 mg BPA group (Group 3, 45-day) ($p<0.0001$) (Table 3).

The question with the lowest score in this study was "The lack of face-to-face interaction make learning difficult (Figure 2). This question was reverse-coded and scored. While 10 students in the female group and 13 students in the male group answered completely agree (1 point), 13 students in the female group and 11 students in the male group answered agree (2 points).

DISCUSSION

After oral intake, BPA is rapidly absorbed from the intestines into the body. In cases where glomerular filtration rate is low, BPA accumulates in the body. The accumulated BPA undergoes elimination through conjugation with glucuronic acid in the liver and is excreted from the body through urine by the kidneys (6-8).

Due to its estrogenic activity, BPA exhibits sensitivity in developing organs towards abnormal endocrine signals caused by this chemical. Therefore, BPA particularly affects developing organs during the prenatal period. Studies have shown that even at low concentrations, BPA binds to nuclear receptors and affects the physiological functions of cells and tissues. BPA is also known to interact with thyroid hormone receptors, androgen receptors, peroxisome proliferator-activated receptors, and other endocrine system receptors. It has been shown to have adverse effects on the CNS, cardiovascular system, respiratory system, excretory system, and immune system. Additionally, BPA exposure has been reported to cause changes in the endogenous cannabinoid system of the liver (ECS), decrease sperm quality and quantity indices, lead to neuroendocrine disruptions, birth defects, and diseases such as breast cancer (9).

BPA, an endocrine-disrupting chemical, interacts with estrogen receptors (ERα) by mimicking the synthesis of endogenously produced estrogens, and exhibits estrogenic effects. As a result, it disrupts endocrine functions, leading to decreased fertility and congenital malformations in the reproductive system and increased cancer risk in tissues that interact with estrogen. BPA also has toxic effects on the cardio-renal system, causes changes in the structure of cardiac and renal tissues, affects the activities of redox enzymes, and alters gene expression. It is known to induce oxidative stress and contribute to hypotension, along with various adverse effects on the CNS, cardiovascular system, respiratory system, excretory system, and immune system (6,10,11).

With the increase in industrialization today, various chemicals caused by environmental pollution adversely affect human health. These chemicals we are exposed to in daily life affect many systems, especially the endocrine system, leading to the emergence of chronic diseases. Bisphenol-A (BPA), which is industrially produced and the most common environmental pollutant, comes first. Bisphenol-A is one of the phenolic compounds known as endocrine disruptors with estrogenic activity. BPA accumulating in the body first undergoes elimination in the liver, is conjugated with glucuronic acid, and is excreted from the body by the kidneys through urine (6-8). As it is a chemical with estrogenic activity, developing organs are quite sensitive to abnormal endocrine signals caused by this chemical. Therefore, BPA has an effect especially on organs developing in the prenatal period. BPA affects the function of many vital organs, including the kidney, testis, brain, heart, liver, and pancreas, by accumulating in them (3,12).

In most of the experimental studies on BPA, evaluations have generally been made with the findings obtained on the animals to which BPA was applied (13,14). As a result of these studies, the most observed morphological findings were structural damages such as narrowing in the Bowman's space in the renal corpuscle, dilatation in the proximal, distal tubules and collecting ducts, cell loss in tubule epithelia, and vacuolization. Shin et al. have examined the spread of Bisphenol A with placental transfer to the placenta, fetus, maternal serum, and amniotic fluid. As a result of the study, they determined that the distribution of BPA to the placenta, fetus, and amniotic fluid occurred rapidly, the accumulation of BPA in the amniotic fluid was less than the other placenta, fetus, maternal serum, and the maximum concentration level was reached within 0.6 hours (36 minutes) after intraventricular (iv) injection (15).

In the study where Edres et al. investigated whether BPA causes kidney damage, they determined that after BPA application, there was an increase in serum urea, creatinine levels, formation of reactive oxygen species, degenerative changes in kidney tubules, narrowing in the Bowman's space in the renal corpuscle with hydronephrosis, significant expansions in cortical renal blood vessels and the emergence of intertubular hemorrhagic areas, and concluded that BPA causes serious damage in kidney tissues. In our study, we found that the serum urea levels increased in the BPA group compared to the control group in the analysis results of the 50 mg/kg/day BPA group rats, and as a result of the TAS, TOS, MDA tests we performed, BPA caused oxidative stress and caused damage in the kidney tissue. In addition, as a result of our histopathological examinations, we detected degeneration in the kidney tubules, especially cell loss with vacuolization in the proximal tubules, structural disorders in the renal corpuscle with narrowing in the

Bowman's space, expansions in renal blood vessels, and hemorrhagic areas between the tubules. Therefore, this study we conducted supports the hypothesis put forward by Edres et al. (14).

During the embryonic/fetal period and infancy, BPA exposure leads to developmental impairments in certain organs, including the reproductive system, due to oxidative stress (OS) and lipid peroxidation in tissues. Maternal exposure to BPA limits the fetus's ability to metabolize this chemical component, leading to significant complications. There is also evidence linking BPA exposure in adults and children to proteinuria. BPA-induced damage is associated with OS and can disrupt the oxidative balance directly or indirectly, affecting mitochondrial activity, modulation of antioxidant enzymes, and increased levels of thiobarbituric acid-reactive substances. Studies by Kovacic in mice showed that BPA administration increased the levels of thiobarbituric acid-reactive substances, which are considered markers for ROS-OS. Additionally, embryonic/fetal and infancy exposure induced tissue OS and peroxidation, resulting in developmental impairments in the brain, kidneys, and testes. In rats, BPA was found to reduce the activities of superoxide dismutase, catalase, GSH reductase, and GSH peroxidase while increasing hydrogen peroxide and lipid peroxidation levels, supporting the hypothesis proposed by Esplugas et al. (11).

Studies related to BPA are generally conducted on rats directly exposed to BPA. However, studies investigating the harmful effects of BPA on the kidneys of newborn rats indirectly exposed to BPA are limited. Therefore, in this study, we focused on the effects of BPA exposure through milk and placenta on the development of the kidneys in newborn rats. We investigated the impact of BPA administered to the mother through the placenta during the intrauterine period and through lactation on the development and structure of the newborn rat kidneys, as well as its effects on protein, creatinine, and urea levels. Pregnant rats were identified for this study. The pregnant rats were exposed to BPA during the gestational and lactation periods. After weaning, blood samples and kidney tissues were collected from some of the 21-day-old newborn rats, while the remaining rats were allowed to reach adulthood. At 45 days of age, the adult rats were sacrificed, and blood samples and kidney tissues were collected for histological examination. The analysis and examinations conducted in this study revealed that maternal exposure to BPA through milk and placenta induced oxidative stress and resulted in kidney damage. Microscopic examination of the kidney tissue showed narrowing or complete closure of Bowman's space in the renal corpuscles, loss of epithelial cells in the proximal and distal tubules, and tubular dilatation, supporting the findings of the study conducted by Kabuto et al. (16).

CONCLUSION

In this study we conducted, we compared the degrees of BPA impact on pups exposed to BPA through the mother, on the 21st day, which is the end of the exposure period, and on 45-day-old rats that survived the exposure and entered adolescence. According to the results we obtained, we determined that the damage seen on the 45th day continued even without exposure to BPA and the damage did not show recovery during this period. When we closely examined the structure and biochemical values of the kidney tissues on the 21st and 45th days, we obtained the following results:

1. BPA increased serum urea, creatinine, and total protein levels,
2. As a result of our TAS, TOS, MDA analyses, we found that BPA induced the formation of reactive oxygen species, causing oxidative damage in the kidney tissue,
3. Although only mother rats were exposed to BPA, we determined that BPA was transferred to the pup rats through the placenta and milk, causing serious structural damages such as narrowing in the Bowman's space of the renal corpuscle located in the kidneys of the pup rats, dilatation in the proximal, distal tubules and collecting ducts, and occasional cell loss, vacuolization in tubule epithelia.

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

Ethical approval: *Ethical approval of this study was obtained with the decision numbered 60758568-020/72039 of Pamukkale University Animal Experiments Ethics Committee.*

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Research Article

Evaluation of Patients Diagnosed with Generalized Anxiety Disorder in Terms of Early Maladaptive Schemas

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Abstract

Aim: It has been reported that individuals with generalized anxiety have many interpersonal problems and these problems occur through schemas such as emotional inhibition, shyness, subjugation, self-sacrifice and intervention. In light of this information, the purpose of this study was to compare individuals with generalized anxiety disorder (GAD) and healthy controls in terms of early maladaptive schemas (EMSs).

Material and Methods: This research involved 92 participants aged 18 to 55, including 48 GAD patients and 44 healthy controls. Sociodemographic data form, Young Schema Questionnaire-Short Form-3 (YSQ-S3), Generalized Anxiety Disorder 7-item scale (GAD-7), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were administered to the participants. The study was approved by the ethics committee (KÜTF KAEK NO:2023.02.16).

Results: The patients' average age was 38.19±11.29, and 83.3% of them (n=40) were women. The average age of healthy controls was significantly lower, however, neither group differed significantly in terms of education or marital status. The mean GAD-7 score of the patients was 6.26±6.81. Emotional deprivation (p=0.024), pessimism (p<0.001), approval seeking (p=0.034), self-sacrifice (p=0.004), punitiveness (p<0.001), abandonment (p<0.001), vulnerability (p=0.042) schema scores, and BAI (p<0.001) and BDI (p<0.001) scores were significantly higher in GAD group. Moreover, there was a positive correlation (p<0.05) between GAD-7 score and early maladaptive schemas (excluding failure, insufficient self-control and defectiveness).

Conclusion: Our findings show that multiple EMSs play a role in patients with GAD. In this context, EMSs should be considered in the approach to patients with GAD, as it is one of the diseases that cause the most disability and is closely related to other psychological disorders.

Keywords: Maladaptive schema, anxiety, psychiatric disorders

INTRODUCTION

Generalized anxiety disorder (GAD) is defined as a person experiencing extreme anxiety in certain activities on most of the days for at least six months and having difficulty controlling their worry. For the diagnosis of GAD, anxiety and worry must be accompanied by at least three of the symptoms such as restlessness, nervous tension, fatigue, easy anger, muscle tension, difficulty in concentration and sleep disturbance (1). The lifetime prevalence of GAD is reported to be 4.3% (2). It has been suggested that GAD is one of the most disabling disorders because of its chronic process, high prevalence, and association with other psychological disorders (3). It has been reported that the development of anxiety disorders is multifactorial, and genetic structure, parenting styles, temperament and environmental factors are effective (4). In addition, the importance of investigating early maladaptive schemas (EMS) and ways of coping with schemas are emphasized in the factors that sustain anxiety disorder (5).

EMSs are defined as lifelong repetitive memories, cognitions, and emotions that arise from neglected essential emotional needs in childhood and adolescence.

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Young identified 18 EMSs containing five schema domains. The schema domains are separation/exclusion domain, impaired autonomy domain, other-directedness domain, impaired boundaries domain, hypersensitivity and suppression domain. While EMSs initially help the child cope with problems, they become dysfunctional over time and disrupt harmony with the environment (6, 7). It has been shown in the literature that EMSs are associated with anxiety disorders; especially impaired autonomy, disconnection and rejection schema domains came to the fore (8, 9). Shariati and Ghasemian (2014) also found a significant association between EMSs and anxiety. They reported that defectiveness/shame schemas from EMSs were predictors of anxiety, and early self-sacrifice schema had an inverse correlation with anxiety (10).

Considering the high prevalence of GAD and its accompanying psychiatric conditions (eg depression, etc.), it becomes important to investigate the factors contributing to this disorder (11). However, the number of research investigating the relationship among GAD and EMSs is limited in the scientific literature. Considering this information, we intended to fill this gap in the literature and we planned this study in line with the hypothesis "There is a significant relationship between anxiety and early maladaptive schemas". This study aims to compare early maladaptive schemas between patients with generalized anxiety disorder and healthy controls.

MATERIAL AND METHOD

Study Design

The design of the study was cross-sectional and was carried out in Kırıkkale University Faculty of Medicine Psychiatry Outpatient Clinic between March 2023 and April 2023. As the only university hospital in our province, our clinic provides diagnosis and treatment services to all psychiatric diagnosis groups. Power analysis was applied to determine the number of samples to be included in our study. At the end of the G-power analysis (Means: Difference between two independent means (two groups)) made by accepting the number of participants belonging to the groups as different revealed that the total sample size of the study should consist of at least 72 participants (Critical t=1.989, effect size d=0.792, total sample size=72, actual power= 0.952). In this context, a total of 92 individuals—48 patients between the ages of 18 and 50 and 44 healthy controls diagnosed with GAD (according to DMS-5) after applying to the outpatient clinic—were included in the study. A psychiatrist who is an expert in the field evaluated patients with a diagnosis of GAD according to the DSM-5 diagnostic criteria. Those with any psychiatric or neurological disease other than the diagnosis of GAD were not included in the study. Healthy controls were selected from volunteers who applied to our outpatient clinic for any reason (license renewal, etc.) and did not have any psychiatric diagnosis. The study was approved by Kırıkkale University Faculty of Medicine Non-Invasive Research Ethics Committee with the decision number 2023.02.16 on 22.02.2023.

Sociodemographic data form, Young Schema Questionnaire-Short Form-3 (YSQ-S3), Generalized Anxiety Disorder 7-item scale (GAD-7), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were applied to the patients who gave consent to participate in the study.

Instruments

Young Schema Questionnaire-Short Form-3 (YSQ-S3): It was developed by Young et al. (2003) to identify EMSs. The Turkish adaptation of the questionnaire was made by Soygüt, Karaosmanoğlu and Çakır (2009), and 5 schema domains and 14 sub-dimensions were reached in the adaptation study. Disconnection (emotional deprivation, emotional inhibition, social isolation/insecurity, defectiveness), impaired autonomy (involvement/dependence, pessimism, abandonment, failure, vulnerability to harm), impaired limits (entitlement, insufficient self-control), other-directedness (self-sacrifice, punitiveness), and excessive standards (high standards, approval seeking) are among the five domains and dimensions mentioned. The instrument contains 90 queries, and each question is scored between 1 and 6. The increase in score shows how much the functionality of the schema domain is impaired (6,12).

Generalized Anxiety Disorder 7-item scale (GAD-7): It consists of a brief, self-reported test created by Spitzer and colleagues to evaluate generalized anxiety disorder. It's a 7-item, 4-point Likert scale that assesses how you've been feeling during the past two weeks. The GAD-7 needs approximately 1–2 minutes to administer and provides the following response options for each symptom: "not at all," "several days," "over half the days," and "nearly every day," which are scored as 0, 1, 2, or 3, respectively. In patients with a total score of 10 or higher, additional methods are required to investigate and confirm the diagnosis of GAD. When the total score threshold was set at 10, the diagnostic sensitiveness for GAD was 89% and the accuracy was 82% (13,14).

Beck Depression Inventory (BDI): Beck et al. established this scale to measure the severity of depression. The study was adapted to Turkish and cut off value of the scale was determined as 17 points. The scale consists of 21 items, and total score that can be received from the scale vary between 0 and 63. The degree of depression is indicated by the scale's high score. Hisli made a version of the scale for use in Turkish (15,16).

Beck Anxiety Inventory (BAI): The self-report scale was developed by Beck and colleagues. It consists of 21 items, each with four points that reflect levels of increasing severity of each of the symptoms. BAI evaluates the following symptoms: heat, tremor in the legs and hands, inability to relax, fear of the worst happening, dizziness, a faster heartbeat, emotional instability, feeling terrified or

frightened, nervousness, and weakness and vulnerability. The classification of the indicative scores for anxiety is: minimal (0-10), mild (11-19), moderate (20-30), and high (31-63). Ulusoy et al. developed the Turkish version of BAI (17,18).

Statistical Analysis

SPSS software, version 23.0 from SPSS Inc. USA, was used to analyze the data. For numerical parameters, means and standard deviations were calculated, whereas percentages were calculated for qualitative parameters. With the help of the Kolmogorov-Smirnov test, data patterns were clarified. When comparing continuous measures, independent sample t-tests were utilized, whereas Mann-Whitney U tests were utilized for discrete numerical variables. The qualitative factors within the study group were compared using chi-square analysis. The association between early maladaptive schemas and GAD-7 was examined using the Spearman correlation test.

RESULTS

Age of participants on average in our study was 38.19±11.29, and 83.3% (n=40) of them were women. The healthy controls' mean age was found to be substantially lower than that of the sick p<0.001, however, no significant variances in education or marital status were noticed between the groups (p>0.05) (Table 1).

Tablo 1. Demographic characteristics of the participants

Data	Patient (n=48)	Control (n=44)	p
Age, mean±SD	38.19±11.29	26.34±6.24	<0.001
Gender, n			0.019
Female/Male	40/8	27/17	
Education, n (%)			0.821
Primary	18 (37.5)	9 (20.5)	
High	14 (29.2)	30 (67.7)	
Above	16 (33.3)	5 (11.8)	
Martial status, n (%)			0.301
Single	18 (37.5)	12 (27.3)	
Maried	30 (62.5)	32 (72.7)	
Working status, n (%)			0.903
Housewife	17 (31.8)	15 (24.6)	
Worker	31 (17.6)	29 (16.4)	
Family psychiatric illness n(%)			<0.001
Yes	19 (39.6)	2 (4.5)	
No	29 (60.4)	42 (95.5)	

Mean±SD: Standard Deviation, *p<0.05, **p<0.001

The average GAD-7 score of the patients was 11.70±4.01, BAI score was 26.85±10.27, and BDI score was 13.17±7.86. Emotional deprivation (p=0.024), pessimism (p<0.001), approval seeking (p=0.034), self-sacrifice (p=0.004), punitiveness (p<0.001), abandonment (p<0.001), vulnerability (p=0.042) schema scores, and BAI (p<0.001) and BDI (p<0.001) scores were significantly higher in GAD group (Table 2).

Table 2. Comparison of the participants in terms of clinical characteristics

Variables (mean±SD/	Patient (n=48)	Control (n=44)	X^2/Z	p
YSQ-S3				
Emotional deprivation	11.13±6.09	8.61±4.16	13.70[a]	0.024
Failure	10.64±4.76	11.38±5.57	-.507[b]	0.612
Pessimism	17.69±6.84	11.70±4.65	10.13[a]	<0.001
Social isolation	16.25±7.60	18.36±6.84	-1.60[b]	0.19
Emotional inhibition	12.77±6.12	10.91±5.02	2.39[a]	0.116
Approval seeking	20.67±7.22	17.64±6.26	1.01[a]	0.034
Enmeshment	16.64±7.09	19.21±8.67	-1.28[b]	0.19
Insufficient self control	19.34±6.71	20.95±6.47	0.21[a]	0.311
Self-sacrifice	14±5.21	17.62±6.40	2.96[a]	0.004
Abondanment	12.36±5.73	8.64±4.73	-3.69[b]	<0.001
Punitiveness	16.43±5.50	21.43±7.04	5.76[a]	<0.001
Defectiveness/shame	9.70±4.64	10.04±3.97	-.60[b]	0.547
Vulnerability to harm/illness	10.25±4.13	12.77±6.01	-2.03[b]	0.042
Unrelenting standarts	8.45±3.99	8.41±3.07	0.04[a]	0.86
GAD-7	11.70±4.05	0.36±2.41	31.9[a]	<0.001
BAI	6.36±5.27	26.85±10.87	15.78[a]	<0.001
BDI	4.86±4.71	13.17±7.86	-5.31[b]	<0.001

YSQ- S3: young schema questionnaire- short form 3, GAD-7: generalized anxiety Disorder test-7, BAI: beck anxiety inventory, BDI: beck depression inventory, *p<0.05, **p<0.00

Moreover, a correlation existed between GAD-7 score and emotional deprivation (r=0.314, p=0.002), pessimism (r=0.596, p<0.001), social isolation (r=0.282, p=0.006), emotional inhibition (r=0.234, p=0.025), approval seeking (r=0.235, p=0.024), intimacy/dependence (r=0.306, p=0.003), self-sacrifice (r=0.348, p=0.001), abandonment (r=0.442, p<0.001) and punitiveness (r=0.368, p<0.001) schema scores (Table 3).

Table 3. Correlation analysis of early maladaptive schemas in patients with GAD

Variables	GAD-7	Age
YSQ-S3		
Emotional deprivation	0.314**	0.262*
Failure	0.194	-.021
Pessimism	0.596**	0.172
Social isolation	0.282**	0.030
Emotional inhibition	0.234*	-.054
Approval seeking	0.235*	-.146
Enmeshment	0.306**	0.163
İnsufficient self control	-.083	-.057
Self-sacrifice	0.348**	0.204
Abondanment	0.442**	0.158
Punitiveness	0.368**	0.052
Defectiveness/shame	0.15	0.041
Vulnerability to harm/illness	0.366**	0.077
Unrelenting standarts	0.033	0.011

SQ- S3: young schema questionnaire- short form 3, GAD-7: generalized anxiety Disorder test-7, R values are presented in the table, *p<0.05, **p<0.001

DISCUSSION

In the present research, the GAD group had significantly higher scores of impaired autonomy (pessimism, abandonment, vulnerability), disconnection (emotional deprivation), other-directedness (punitiveness, self-sacrifice) and excessive standards (seeking approval) from EMS domains were significantly higher. Moreover, there was a positive correlation between GAD-7 score and all of EMSs (except for failure, insufficient self-control, and defectiveness).

GAD is a common mental disorder that causes severe disability but is not adequately recognized and treated (11). Therefore, it is essential to comprehend the underlying causes of this disorder. Today, it is seen that EMSs are considered as an important explanatory while trying to understand the psychological basis of anxiety. EMSs are defined as "schemas related to one's relationships with oneself and others that develop during childhood or adolescence, are elaborated throughout life, and are significantly dysfunctional". The mixture of a child's genetic temperament and dysfunctional experiences with parents, siblings, and peers leads to the development of these schemas, and may predispose individuals to the development and maintenance of psychological disorders (6). EMS is also common among people experiencing GAD symptoms (19,20).

Similarly, it was determined in our study that the scores of impaired autonomy (pessimism, abandonment, vulnerability), disconnection (emotional deprivation), other-directedness (punitiveness, self-sacrifice) and excessive standards (seeking approval) from EMS domains were significantly higher in GAD group. In a meta-analysis that examined the relationships between anxiety symptoms and five schema domains, it was found that EMS and anxiety symptoms in general were significantly correlated. The results from the distinct schema domains revealed associations between disconnection/rejection, impaired autonomy/performance, and other-directedness schemas that were significantly stronger (21). In this respect, our findings are compatible with Young's theory. Accordingly, significant schema areas related with anxiety symptoms include the failure to create secure and stable connections, a lack of independence, reliance, harm, and an excessive attention on the needs of others. From this point, our findings can be explained by the fact that individuals with GAD, depending on the schema content, think that catastrophic and dangerous situations are unavoidable and cannot cope with them, and secondarily, their feelings of anxiety and worry increase (22). Considering that some of the main features of GAD are excessive anxiety about various life conditions such as health, relationships, and work, it would theoretically make sense that individuals with core EMS, where autonomy and performance are impaired, may be prone to GAD symptoms (23).

Moreover, a positive correlation existed between GAD-7 score and EMS (excluding failure, insufficient self-control and defectiveness) in our study. The number of studies evaluating the association between GAD symptoms and EMS is limited in the literature. In a study that investigated the role of EMS in predicting MDD and GAD symptoms in people getting inpatient treatment for drug abuse, GAD symptoms were positively and significantly associated with all EMS domains (24). In a study evaluating the association between permanent anxiety and EMS in a non-clinical sample group, it was reported that all schema domains were predictors of permanent anxiety (25-27). In this respect, our study result was supported by the literature. Moreover, various studies have shown that EMS is associated with GADs. In the study conducted by Welburn et al in which the association between EMS and anxiety symptoms was evaluated, 13 of 15 EMSs evaluated were significantly associated with anxiety symptoms. However, results were not presented here by primary disorder (28). In the study by Delattre et al., EMSs from a group of people with different kinds of anxiety disorders were compared to non-psychiatric subjects. The anxiety group significantly outperformed controls on each of the 13 EMS assessed. The results were interpreted to suggest that YSQ measured general permanent anxiety because there were no individual EMSs that occured specifically for anxiety disorders. However, participants with any of the three anxiety disorders (panic disorder, social phobia, or GAD) were included in the sample, and results were not broken down by illness (19). The fact that only patients

with a diagnosis of GAD were evaluated in terms of EMS in our study makes our study different in this respect. The absence of an association between GAD-7 score and failure, inadequate self-control and defectiveness schemes in our study can be explained by the fact that these schemes are associated with depression symptoms, as mentioned in the literature (29). However, longitudinal studies are needed for this.

Limitations should also be considered when interpreting our study. First, due to the cross-sectional nature of the study design, no causal inferences can be made. Longitudinal research is needed that examines the relationship identified in the current study. Second, the questionnaires/surveys were completed by the participants themselves, and SCID-5-CV (American Psychiatric Association, 2000) (Structured Clinical Interview for DSM-5—Clinical Version) was not administered to the participants. The strength of our study is that it is a pioneering study evaluating early maladaptive schemas in patients with a diagnosis of GAD.

CONCLUSION

Our findings show that multiple EMSs (emotional deprivation, pessimism, approval seeking, self-sacrifice, punitiveness, abandonment, and vulnerability) play a role in patients with GAD. Considering that individuals with generalized anxiety have many interpersonal problems and these problems occur through schemas such as emotional inhibition, shyness, subjugation, self-sacrifice, and intervention (30), the evaluation of EMS becomes important. In this respect, when our study was considered together with previous studies (21,24), GAD symptoms were found to be related to disconnection/rejection, impaired autonomy/performance, and other-directedness schema domains. However, the literature data on this subject is limited and longitudinal studies are needed.

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Ethical approval: *The study was approved by Kırıkkale University Faculty of Medicine Non-Invasive Research Ethics Committee with the decision number 2023.02.16 on 22.02.2023.*

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Research Article

Ultrastructural Changes and Inflammatory Processes of Day-Dependent Cisplatin Administration on Rat Cardiac Tissue

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Abstract

Aim: Cisplatin (CP) is used to treat a variety of cancers as a chemotherapeutic agent. This drug has also severe side effects and its use exhibits serious toxicity in a number of organs, including kidney and heart. The aim of the present study was to evaluate the ultrastructural and inflammatory changes induced by CP treatment in rat cardiac tissue in a time-dependent manner.

Material and Methods: Rats were randomly divided into three experimental groups; control (only saline), CP D2 (treated with CP 2.5 mg/kg/day for 2 days), and CP D7 (treated with CP 2.5 mg/kg/day for 7 days). Cardiac tissues were examined under an electron microscope. Inflammation markers including tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β) were analyzed by immunohistochemistry. In addition, electrocardiography was performed to measure the electrical activity.

Results: The ultrastructural analysis of the CP D7 group revealed that myofibrils were disrupted and disorganized, mitochondria degenerated, and interstitial edema developed. When compared to the control and CP D2 groups, there was a noticeable increase in the level of TNF-α and IL-1β expression in the CP D7 group according to immunohistochemistry results. Electrocardiography showed that RR interval was longer in CP D7 than CP D2 and control groups.

Conclusion: CP for 7 days damaged the ultrastructural morphology in cardiac tissue. Therefore, these findings suggest that the potential therapeutic approaches to reduce mitochondrial damage and inflammation against toxicity caused by CP may provide for clinically significant prevention when using the drug for an extended period of time.

Keywords: Cardiotoxicity, cisplatin, inflammation, mitochondrial damage, ultrastructure

INTRODUCTION

Cardiac damage caused by anticancer chemotherapeutic agents has become a major problem (1). Several types of anticancer drugs, including cisplatin (cis-diamminedichloroplatinum, CP) have exhibited high cardiovascular complications. CP has the ability to cure a variety of solid tumors, but its clinical application is constrained by its severe dose-dependent side effects on tissue (2).

Myocarditis, arrhythmias, congestive heart failure, cardiomyopathy, hypertension, and cardiac ischemia are among the documented cardiotoxic adverse effects of CP (2,3). The underlying mechanisms of CP-induced cardiac injury include mitochondrial dysfunction, inflammation, oxidative stress, apoptosis, and endoplasmic reticulum (ER) stress (3). Immune cell infiltration into damaged site and increased production of proinflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin-1

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beta (IL-1β), and interleukin-6 (IL-6) are indicators of inflammation, which is recognized as a key factor in cardiac tissue injury induced by the CP. Neutrophil and macrophages infiltration impair cardiac function by generating reactive oxygen species (ROS), which lead to tissue injury and cell death. Excessive ROS production causes inflammatory factors to be released, which exacerbates damage (4).

As they are the target of toxic drugs like CP, mitochondria-rich cardiomyocytes are extremely vulnerable to mitochondrial damage (5). CP accumulates in the mitochondrial matrix of cells, impairing mitochondrial respiration and producing excessive ROS (6). Thus, CP causes left ventricular dysfunction and functional abnormalities that disrupt ultrastructural morphology in mitochondria of cardiomyocytes (7). Furthermore, CP treatment has been linked to both nuclear and mitochondrial DNA damage in an experimental rat model (8). Mitochondrial targeted antioxidants may be a viable way to reduce cardiovascular problems (9).

There are very few experimental studies examining cardiovascular changes following acute CP treatment and the mechanisms underlying these changes. The goal of the current study was to evaluate the ultrastructural and inflammatory changes, and alterations in electrocardiography parameters after CP treatments in the myocardial tissue.

MATERIAL AND METHOD

Study Design

After receiving approval from Kahramanmaras Sutcu Imam University's local ethics council for conducting animal experiments (date: 22.11.2022, protocol number 2022/11-4), the following study was conducted. Twenty-four male Wistar albino rats were housed in a controlled environment with access to food and water at a temperature of 22±3°C and a 12-hour light and dark cycle. The Guide for the Care and Use of Laboratory Animal was followed for performing animal treatments (10). Electrocardiography (ECG) of all groups was performed under anesthesia (ketamine (75 mg/kg)-xylazine HCl (10 mg/kg) prior to CP administration for baseline values. Following electrocardiography (ECG) recordings, rats were divided randomly into 3 groups each consisted of eight rats, as listed below:

Control group (n=8): The vehicle (0.9% NaCl solution) was given intraperitoneally (ip).

CP D2 group (n=8): CP (Kocak Farma, Turkey) was injected 2.5 mg/kg/day ip for 2 days.

CP D7 group (n=8): CP was injected 2.5 mg/kg/day ip for 7 days (11).

Twenty-four hours after the last dose of the CP, ECG recordings was re-recorded. Then cardiac tissues from left ventricles of animals were rapidly removed for immunohistochemistry and electron microscopy analysis.

Electron Microscopic Examination

The ventricular tissue samples were first fixed with 2.5% glutaraldehyde in 0.1 M phosphate buffer, followed by 1% osmium tetra-oxide post-fixation, dehydration with a graded alcohol series, cleaning with propylene oxide, and embedding in epon. Ultrathin sections were prepared for transmission electron microscopy (TEM). After that, lead citrate and uranyl acetate were used to stain the sections. The ultrathin sections were examined by TEM (JEM-1011; JEOL Ltd, Tokyo, Japan).

Immunohistochemical Analysis

The rat ventricular myocardial tissues were processed using a standard protocol, fixed in 10% formalin in phosphate buffer, and then embedded in paraffin blocks. Sections were cut at 4-5 µm thickness on a rotary microtome (Leica 2125RT, Deer Park, IL, US) and then they were transferred to adhesive slides. The sections were incubated in Tris-EDTA solution (pH 9.0; ab93684, Abcam, Waltham, MA, USA) in the microwave to accomplish antigen retrieval. After that, the slides underwent phosphate-buffered saline (PBS) washing and 3% H2O2 treatment. After blocking with normal goat serum, the sections were incubated with primary antibodies for anti-TNF-α (1:100, ab6671, Abcam, Waltham, MA, USA), and anti-IL-1β (1:100, ab9787, Abcam, Waltham, MA, USA) overnight at 4 °C. The sections were then washed with PBS before being treated with anti-rabbit IgG secondary antibody (1:200, 65-6140, Thermo Scientific, Waltham, MA, USA) for 30 min at room temperature. Following a PBS wash, the slides were incubated with horseradish peroxidase (HRP; 1: 200, 43-4323, Thermo Scientific, Waltham, MA, USA) for 10 minutes. Mayer's hematoxylin was used as a counterstain for sections following treatment with diaminobenzidine (DAB; ab64238; Abcam, Waltham, MA, USA) as a chromogen. Under a Carl Zeiss Axio Imager A2 microscope, the prepared sections were examined for immunohistochemical changes and rated as strong (++++), medium (+++), weak (++), or absent (+) in all sections.

Electrocardiography

ECG of all rats was conducted to using a BIOPAC MP36 (Biopac Systems, Inc., Camino Goleta, CA, USA). The rats were stabilized by placing them on the experimental platform while under light anesthesia. ECG electrodes were inserted lead at derivation I ; V+, V− and ground were placed on the right-left extremities of rats. In electrode (Skintact, FS-RG1/10, Innsbruck, Austria) insertion, attention was paid to ensure that the area was hairless, wiped with alcohol, and gelled the electrodes. ECG was recorded for 2 min (0.05 100 Hz, AHA). The data were confirmed by AcqKnowledge software (Biopac Systems, Inc., Camino Goleta, CA, USA) and the analysis were saved at an appropriate time frame after the study. Parameters such as the PR interval (ms); RR interval, QT interval (ms), Tp (ms), and heart rate per minute were determined from the ECG traces.

Statistical Analysis

For statistical analysis, SPSS version 22 (IBM SPSS for Windows version 22; IBM Corporation, Armonk, New

York, USA) and R.3.3.2 software were used. The data was analyzed using One Way Anova and Shapiro-Wilk test to see if the variables followed a normal distribution. The differences in the variables that were not distributed normally between the groups were assessed using the Kruskal-Wallis H test, which was followed by a post hoc comparison test performed using the Dunn's test. The acquired data was presented as the median, 25% quartile, and 75% quartile. Statistically significant difference was defined as one with p<0.05.

RESULTS

Electron Microscopic Results

Electron microscopic examination of control group (Figure 1a) showed the cardiac muscle fibers with euchromatic nucleus and rows of mitochondria between the regularly arranged bundles of myofibrils. With swollen mitochondria in between, some myofibrils in the CP D2 group (Figure 1b) appeared disorganized or disrupted. Regular arrangement of the myofibrils was almost preserved. But in contrast to the CP D2 group, the CP D7 group showed disruption and disarrangement in myofibrils, interstitial edema, dilated vacuoles in sarcoplasm, mitochondrial degeneration, and intracapillary neutrophils (Figure 1c and 1d).

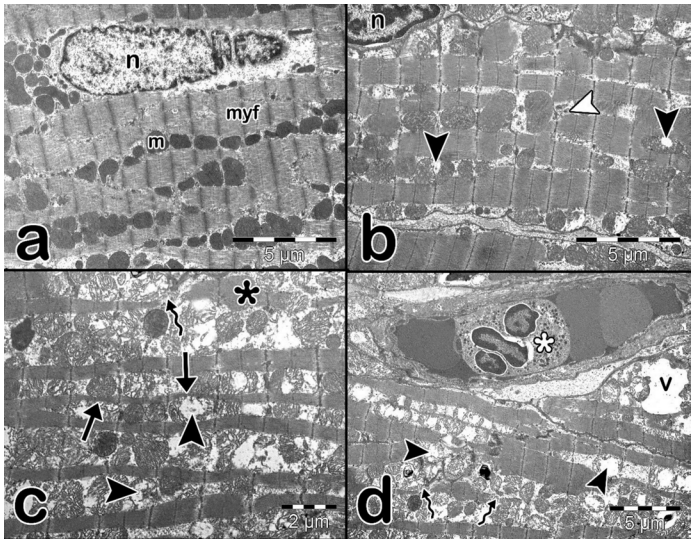

Figure 1. Electron micrographs of the myocardial muscle fibers. a (7.500×) Control group; euchromatic oval nucleus (n), rows of mitochondrion (m) and regularly arranged myofibrils (myf). b (7.500×) CP D2 group; disrupted myofibrils (white arrowhead) and swollen mitochondria (black arrowheads). c (10.000×) and d (5.000×) CP D7 group; disarrangement (asterisk), interruption (curved arrow) and local thinning (arrows) in myofibrils, dilated vacuole (v), mitochondrial degeneration (black arrowheads), and intracapillary neutrophil (white asterisk)

Immunohistochemical Results for TNF-α and IL-1β

The immunohistochemistry staining analysis revealed that the control group's muscle fibers had weak expressions of TNF-α (Figure 2a) and IL-1β (Figure 3a). When compared to the control group, the CP D2 group (Figure 2b and 3b) showed significantly higher immunoreactivity for both antibodies (p<0.001; Figure 2d and 3d). In contrast to the findings in the control and CP D2 groups, the CP D7 group displayed a strong immunoreaction for the expression of TNF-α (Figure 2c) and IL-1β (Figure 3c).

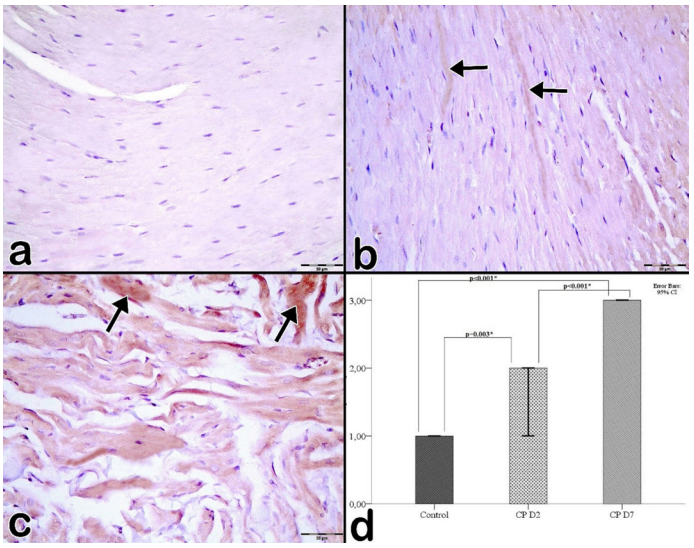

Figure 2. Representative immunohistochemical images of TNF-α in myocardium (400×). (a) Control group, (b) CP D2 group shows mild TNF-α immunreactivity (arrows). (c) CP D7 group shows intense TNF-α immunreactivity (arrows) in cardiac fibers. (d) Comparison of TNF-α immunreactivity between the studied groups. Kruskal Wallis H test; statistical significance level (α): 0.05; Post-hoc: Dunn test; *The difference between groups was statistically significant. Bar statistics: Median; Error Bars: 95%confidence interval

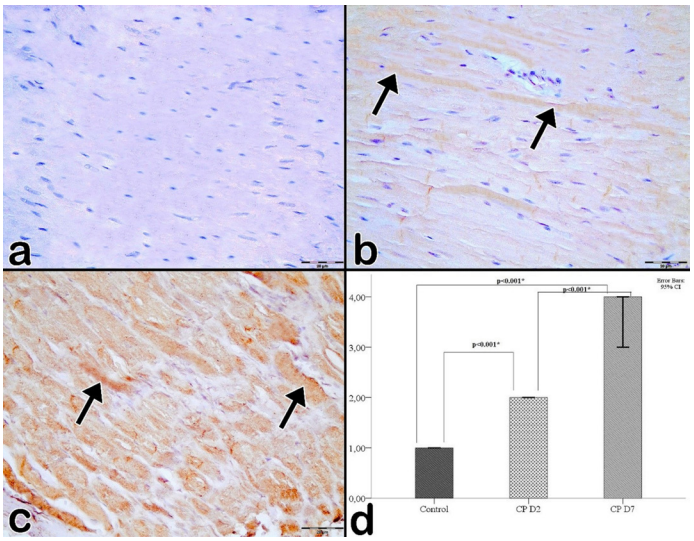

Figure 3. Representative immunohistochemical images of IL-1β in myocardium (400×). (a) Control group, (b) CP D2 group shows mild IL-1β immunreactivity (arrows). (c) CP D7 group shows intense IL-1β immunreactivity (arrows) in cardiac fibers. (d) Comparison of IL-1β immunreactivity between the studied groups. Comparison of IL-1β immunreactivity between the studied groups. Kruskal Wallis H test; statistical significance level (α): 0.05; Post-hoc: Dunn test; *The difference between groups was statistically significant. Bar statistics: Median; Error Bars: 95% confidence interval

Electrocardiography Parameters

As shown in Table 1, comparing the CP D7 group to the CP D2 and control groups, the RR interval was longer (p=0.045, p=0.032, respectively). When comparing the CP D2 group to the control group, it was non-significant (p=0.678). There were no differences between the groups for other ECG parameters such as heart beats per min, PR, QT, and Tp intervals.

Table 1. CP-induced ECG alterations

					Post-Hoc		
	Control	CP D2	CP D7	P value	Control-CP D2	Control-CP D7	CP D2-CP D7
QT[a] (ms), Mean±SD	0.0783±0.0153	0.0954±0.0555	0.1130±0.0544	0.618			
RR[b] (ms), Median (Q1-Q3)	0.0340(0.0270-0.3100)	0.1310(0.0320-0.1950)	0.3575(0.3190-0.4020)	0.045*	0.678	0.032*	0.045*
HB[a] (per min), Mean±SD	191.4833±21.8490	203.9800±60.0153	163.7333±36.4509	0.350			
PR[b] (ms), Median (Q1-Q3)	0.0430(0.0090-0.0590)	0.0600(0.0570-0.0620)	0.0655(0.0600-0.0840)	0.068			
Tp[b] (ms), Median (Q1-Q3)	0.0034(0.0024-0.0250)	0.0200(0.0180-0.0250)	0.0315(0.0230-0.0400)	0.098			

HB heart beats. [a]One Way Anova; [b]Kruskal Wallis H test; Post-hoc: Dunn test; alpha statistical significance level (α): 0.05; *The difference between the groups was significant

DISCUSSION

Alkylating chemotherapeutic agents like CP, have always been one of the potent drugs in overcoming human cancers (12). However, most platinum-based anticancer drugs cause cytotoxicity in tissues, which limits their clinical application (13). CP toxicity risk in a dose-dependent manner may require adjustments or stopping administration of the therapy (2). CP administration is thought to result in cardiotoxicity due to a number of mechanisms, including ER stress, mitochondrial dysfunction, oxidative stress, inflammation, and mitochondrial dysfunction (4,14,15).

Several studies have reported that CP treatment give rise to disorganization and interruption of myofibrils, mitochondrial swelling, increased area of cristae and matrix volume, ER dilation and membranous debris in a mice and rats (7,11). Similarly, our results pointed out that CP D7 group exhibited severe ultrastructural damage including loss of cristae and swelling in the mitochondria, interruption and disarrangement of myofibrils, interstitial edema, and vacuoles. CP D2 group, on the other hand, displayed mild degeneration, including disarray or disruption, with swollen mitochondria in-between some myofibrils. In some studies on mitochondrial damage caused by CP treatment, it was observed that its accumulation depletes ATP levels in cardiomyocytes, causing cell damage and cell death (16,17). Furthermore, ROS production induced by CP leads to mitochondrial functional impairment, membrane depolarization, mitochondrial swelling, and the release of pro-apoptotic factors into cytosol, which activates caspase-dependent apoptosis (2,17,18). The destruction of cellular components or increased ROS generation which cause oxidative damage, could be a consequence of damage we examined by TEM in cardiac tissue.

TNF-α and IL-1β are two important proinflammatory cytokines that are actively involved in the inflammatory response, as is well documented. TNF-α and IL-1β production in cardiac tissue is increased as a result of CP treatment, activating nuclear factor kappa B (NF-κB) transcription factor. Increased TNF-α production by cardiomyocytes recruits inflammatory cells that cause damage to surrounding cardiac tissue one week after CP injection in mice (4). It has been demonstrated that in C57BL/6 mice, inflammatory cell infiltration increased 72 hours after a single dose of CP administration (20 mg/kg, ip) (19). It is known that CP-induced oxidative stress activates inflammation (20-22). We found that the expression of TNF-α and IL-1β was statistically higher in the CP D7 group than in the control and CP D2 groups based on the immunohistochemical results. In addition, 2 days of CP therapy increased the expression of these proteins significantly more than the control group. By increasing the expression of two important pro-inflammatory cytokines, CP administration promoted the inflammatory reactions particularly in the CP D7 group, and brought ultrastructural damage to myocardial cells, which supports our electron microscopic findings. Furthermore, some investigations have demonstrated that CP induces the production of TNF-α and IL-1β, as well as myocardial myeloperoxidase activity in experimental studies (4,18).

The clinical data showed that supraventricular tachycardia, bradycardia and conduction abnormalities leaded by CP (23,24). Based on our results, CP administration prolonged the RR duration. The difference in PR, QT, Tp intervals and heart beats between the CP D2, CP D7 and control groups were not statistically significant.

CONCLUSION

CP for 7 days damaged the ultrastructural morphology in cardiac tissue. Therefore, these findings suggest that therapeutic approaches that reduce mitochondrial damage and inflammation caused by CP may provide the clinically significant prevention when using the drug for an extended period.

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Research Article

Ganglion Cell Layer, Inner Plexiform Layer, and Choroidal Layer Correlate Better with Disorder Severity in ADHD Patients than Retinal Nerve Fiber Layer: An Optical Coherence Tomography Study

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Abstract

Aim: To assess the thickness of the choroidal layer, inner plexiform layer (IPL), ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL) in individuals with attention-deficit/hyperactivity disorder (ADHD).

Material and Methods: In this retrospective study, we used a spectral optical coherence tomography (OCT) device. The CPRS-48 was performed to the ADHD group.

Results: Both groups consisted of 60 subjects. There were significant differences in NS segment of RNFL (right p=0.039; left p=0.035). The mean right choroidal thickness of ADHD group was significantly lower than the control group (p=0.015). The left GCL and IPL volumes of ADHD group were significantly lower than the control group (p<0.05). In ADHD group, a significant correlation was found between right choroid and opposition (r=0.278, p<0.05) and conduct (r=0.373, p<0.01) subscales of CPRS-48; between age and right choroid (r=0.248, p<0.05). In control group, a significant correlation was found between age and right NS (r=-0.370, p<0.05), right TS (r=-0.381, p<0.05), right mean RNFL (r=-0.352, p<0.05), left NS (r=-0.397, p<0.05), right choroid (r=0.422, p<0.01), left choroid (r=0.443, p<0.01), right GCL (r=0.425, p<0.01), right IPL (r=0.446, p<0.01).

Conclusion: This study demonstrated that there is an association between disorder severity, duration of disorder, choroidal layer thickness, GCL, IPL and ADHD.

Keywords: Ganglion cell layer, retinal nerve fiber layer, inner plexiform layer, attention-deficit/hyperactivity disorder, optical coherence tomography

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD), which is characterized by problems in concentration, attention, activity, and impulse control, is a common, childhood-onset persistent developmental disorder with a prevalence of approximately 5% (1). The clinical appearance of ADHD is thought to be influenced by both hereditary and environmental variables, making it an etiologically multifactorial condition. It has been established that ADHD has a solid neurological basis, although the pathophysiology of the disorder is still poorly understood (2). Researchers have regularly employed various structural, functional neuroimaging, and neuropathological techniques to pinpoint certain anomalies connected to this illness (3). Another device used to increase our understanding of ADHD is optical coherence tomography (OCT) (4).

In 2018, Herguner et al. (5) have used the OCT to investigate the changes in 45 ADHD patients (mean age 8.6±1.9 years). They reported that ADHD group had significantly lower retinal nerve fiber layer (RNFL) thickness than the controls. The number of studies

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examining the association between ADHD and OCT has gradually expanded throughout the ensuing years. According to Ulucan Atas et al. (6), the healthy control group had much thicker RNFL in the nasal region and thicker macular tissue than the ADHD group did (mean age 9.5±2.2 years). Işık ve Kaygısız (7) demonstrated that the ganglion cell layer (GCL), global RNFL thickness, and central macular thickness of both eyes were not significantly different across treatment-naive children with ADHD (mean age 9.0±2.41 years), ADHD patients using methylphenidate (MPH) treatment, and healthy subjects. Akkaya et al. (8) reported that the ADHD patients (mean age 9.4±1.9 years) had a significantly higher mean choroidal thickness than the healthy controls. Bodur et al. (9) demonstrated that the GCL thickness of the ADHD group (mean age 111.62±27.05 months) was thinner than the control group. According to the study of Ayyildiz and Ayyildiz (10), corneal thickness was significantly higher in ADHD group (mean age 142.89±24.31 months) than in controls. Also, there was no discernible variation in RNFL thickness between groups. According to Tosun et al. (11), there was no discernible change in the GCL and RNFL thickness values between the control and ADHD (mean age, 9.902.15 years) groups.

The results of the investigations in the literature differ from one another, as is evident. More studies are needed to clearly reveal the ADHD-OCT relationship. In this research, we sought to examine the choroidal thickness, IPL, GCL, and RNFL of OCT in healthy controls and ADHD patients.

MATERIAL AND METHOD

The study was approved by the Clinical Research and Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey (Date of Approval: 28.03.2019; Decision Number: 10/1).

Study Sample

In this retrospective study we compared the patients diagnosed with ADHD with a control group. The study was approved by the ethics committee.

Patients with ADHD who were diagnosed according to the DSM-5 (12) criteria were included. Patients who had organic pathologies were excluded. Mental retardation was excluded with the WISC-R (13). A spectral-OCT device was used.

Conners' Parent Rating Scale-48

Conners' Parent Rating Scale-48 (CPRS-48) consists of 48 items and four subscales ("opposition", "attention-deficit", "hyperactivity", "conduct") (14,15). The Turkish validity and reliability study of scale was performed by Dereboy et al. (16) Four-grade Likert type scale questions are answered by parents.

Statistical Analyses

SPSS 22.0 was used in statistical analyses. Two variables with normally distributed distribution were compared using an independent samples t-test, and two variables with non-normally distributed distribution were compared using the Mann-Whitney U test. In the ADHD group, a Pearson correlation analysis was done (p<0.05).

RESULTS

Both groups consisted of 60 people. There were 39 males (65.00%) and 21 females (35.00%) in patient group, 36 males (60.00%) and 24 females (40.00%) in the control group. The mean age was 9.61±2.38 in the patient group and 10.27±3.72 in the control group (p=0.322).

The data for RNFL and its sublayers were indicated in Table 1.

Table 1. The retinal nerve fiber layer thickness and sublayers

Parameters	ADHD (n=60) (Mean±SD)	Control (n=60) (Mean±SD)	p value
Right			
NS	112.61±20.57	124.35±35.26	**0.039***
N	75.57±14.46	78.15±21.09	0.473
NI	116.07±25.08	117.35±27.78	0.814
TI	137.25±20.76	146.50±20.83	**0.032***
T	72.05±9.81	74.00±9.57	0.330
TS	141.28±17.82	141.85±18.48	0.880
Mean	100.30±8.98	104.40±11.09	0.056
Left			
NS	119.96±21.39	142.10±68.02	**0.035***
N	69.23±12.72	83.10±39.54	**0.038***
NI	116.84±23.69	118.05±26.84	0.819
TI	141.20±17.64	140.30±29.01	0.842
T	71.69±10.31	73.00±14.61	0.915
TS	136.69±16.84	136.65±16.92	0.433
Mean	99.96±9.11	106.25±18.29	**0.042***

*p<0.05
Note: Unit is µm. ADHD: attention-deficit/hyperactivity disorder, SD: standard deviation, NS: naso-superior, NI: naso-inferior, N: nasal, TS: temporo-superior, TI: temporo-inferior, T: temporal

The data for choroidal thickness were indicated in Table 2. The data for GCL and IPL volumes were indicated in Table 2.

Table 2. Choroidal thickness, GCL, and IPL volumes of ADHD and control groups

Parameters	ADHD (n=60) (Mean±SD)	Control (n=60) (Mean±SD)	p values
Right Choroid	319.24±55.63	354.66±72.70	**0.015***
Left Choroid	328.39±57.93	346.03±66.37	0.339
Right GCL	1.13±0.08	1.16±0.08	0.084
Left GCL	1.10±0.09	1.15±0.07	**0.007***
Right IPL	0.91±0.06	0.94±0.07	0.065
Left IPL	0.89±0.07	0.94±0.06	**0.003***

*p<0.05
Note: Unit is µm. ADHD: attention-deficit/hyperactivity disorder, GCL: ganglion cell layer, IPL: inner plexiform Layer, SD: standard deviation

The results of correlation analysis of ADHD and control groups were given in Table 3 and Table 4.

Table 3. Correlation analysis of ADHD group in terms of CPRS-48 subscore

	Attention-Deficit	Hyperactivity	Opposition	Conduct
Right				
NS	0.099	-0.160	-0.057	-0.042
N	-0.035	-0.081	0.015	-0.067
NI	0.093	-0.231	-0.215	-0.107
TI	-0.137	0.009	-0.003	-0.122
T	-0.051	0.125	0.151	0.094
TS	-0.045	0.081	0.008	-0.044
Mean	-0.004	-0.114	-0.051	-0.104
Choroid	-0.015	0.082	**0.278***	**0.373****
GCL	-0.056	-0.123	0.010	0.099
IPL	-0.081	-0.166	-0.069	0.017
Left				
NS	0.001	-0.091	-0.085	-0.068
N	-0.071	-0.028	0.041	-0.035
NI	0.085	-0.215	-0.177	-0.069
TI	-0.048	-0.087	-0.079	-0.111
T	-0.056	-0.051	-0.018	-0.079
TS	-0.012	-0.020	-0.005	-0.108
Mean	-0.030	-0.137	-0.095	-0.129
Choroid	0.026	0.030	0.207	0.233
GCL	-0.061	0.008	0.052	0.147
IPL	-0.110	0.006	0.005	0.092

*p<0.05, **p<0.01
ADHD: attention-deficit/hyperactivity disorder, CPRS-48: conners' parent rating scale, NS: naso-superior, NI: naso-inferior, N: nasal TS: temporo-superior; TI: temporo-inferior; T: temporal; GCL: ganglion cell layer, IPL: inner plexiform layer

Table 4. Correlation analysis of ADHD and control groups in terms of age

	ADHD	Control
Right		
NS	.101	**-.370***
N	-.144	-.035
NI	-.027	-.204
TI	.125	-.114
T	-.008	-.073
TS	.113	**-.381***
Mean	.021	**-.352***
Choroid	.248*	**.422****
GCL	.194	**-.425****
IPL	.192	**-.446****
Left		
NS	.197	**-.397***
N	-.032	-.311
NI	-.176	-.132
TI	.178	.211
T	.021	.231
TS	.077	-.007
Mean	.050	-.289
Choroid	.132	**.443****
GCL	.166	-.147
IPL	.168	-.237

*p<0.05, **p<0.01
ADHD: Attention-Deficit/Hyperactivity Disorder; CPRS-48: Conners' Parent Rating Scale; NS: Naso-Superior; NI: Naso-Inferior; N: Nasal; TS: Temporo-Superior; TI: Temporo-Inferior; T: Temporal; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer

DISCUSSION

The RNFL was connected to our study's first significant finding. We have found significant thinning in nasal quadrant of RNFL between the ADHD group and healthy subjects. This finding related to RNFL was consistent with the studies of Herguner et al. (5) and Ulucan Atas et al. (6). The literature reported a delay in maturation in ADHD patients (Figure 1) (17). Considering the age of our patient group, it is acceptable that some RNFL parameters were significantly thinner than the control group (18). There are also studies that do not support our findings. Işık ve Kaygısız (7), Ayyildiz and Ayyildiz (10), Tosun et al. (11) found no significant RNFL differences between patient and control groups.

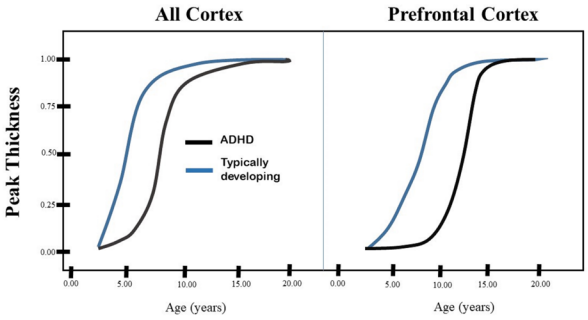

Figure 1. Development of cortex

Secondly, a significant thinning was found in patient group compared to the healthy subjects in terms of IPL and GCL volumes. Similar to our study, Bodur et al. (9) demonstrated that the GCL thickness of the ADHD patients was thinner than the control group. On the other hand, Işık ve Kaygısız (7), Tosun et al. (11) reported no alteration in GCL value. In our study, GCL and IPL parameters were found to be different in the left eye between the patient and control groups. Numerous studies have used spectral domain OCT to identify intra- and interocular differences in the OCT parameters in children. These studies were conducted to establish a standard reference range in different populations, age groups, and genders and have reached different values of OCT parameters. The researchers stated that the retinal asymmetry may be physiological up to some values, but in some cases this asymmetry may be pathological, and even this asymmetry may be used in the early diagnosis of some diseases (19, 20). Whether retinal asymmetry in our study is a limitation or is an important finding is the subject of further studies. Again, several studies reported anatomical and functional hemispheric asymmetries in ADHD brains (21, 22). Hale et al. (23) demonstrated increased right hemisphere (RH) activation in ADHD. However, some investigations found similarities between patients with RH damage and those with ADHD in the area of hemispheric processing (24). Neuroimaging studies provide additional support for the idea that RH dysfunction is one of the fundamental abnormalities in ADHD. Using MRI images, Almeida Montes et al. (25) found changes in the RH's cortical thickness (CT) exclusively between people with ADHD and controls. The degree of ADHD symptoms in this study was linked with the CT differences. In our investigation, it

was shown that the right eye's GCL and IPL had greatly diminished, whereas the left eye had not seen this change. These contradictory findings highlight the need for more research on this topic.

The basic assumption in ADHD is on maturation delay (17). Two meta analyses revealed that, the basal ganglia structural differences between individuals with ADHD and controls tended to disappear as people get older (26, 27). In animals, the majority of retinal neurons develop before birth, and the neurogenesis of RCGs—the retina's output neurons—is mostly governed by intrinsic factors (28). However, numerous additional investigations have also demonstrated that RGCs significantly refine their synaptic connections and dendritic morphology over the postnatal period. RGC dendrites in the IPL become significantly more narrowly stratified with subsequent maturation. These findings unequivocally show that targeted dendritic elimination and ramification, and ongoing dendritic development were all necessary for RGCs to develop their lamina-restricted dendritic pattern (29). In ADHD, these pre- and/or postnatal maturation changes of retina may have abnormalities (24). When the correlation of age and GCL, IPL volumes were examined, no significant correlation was found. This situation may be a finding that can support the hypothesis that delay in maturation decreases with time. However, there is a need for studies aiming at clarifying the potential normalization effects of age, disease severity, and medication.

Our third conspicuous finding was related to the choroidal layer thickness. One of the human body's most highly vascularized tissues is the choroid. Therefore, choroid tissue is indirectly proportional to cell number and is influenced by any inflammatory or autoimmune disorders that alter blood flow (4). Dopamine is also recognized to be involved in retinal function, but it is unclear how dopamine impacts the retina (30). The literature claims that dopamine enhances retinal vascular width and decreases flicker-induced alterations to the retinal vessels (31). Dopamine significantly improves the perfusion of the retina in people (32). We have shown that the left eye's choroidal layer thickness is noticeably thinner in the ADHD group. As opposed to that, Akkaya et al. (8) reported that the ADHD patients had a significantly higher mean choroidal thickness than the healthy controls. The disparity between the results of our study and the literature needs to be investigated further.

CONCLUSION

In conclusion, our findings are consistent with delay in maturation in ADHD and its neurodevelopmental feature. It is possible that the differences between studies in the literature are related to methods and limitations.

Limitations

The cross-sectional design of this study is its main limitation. Equal study subjects for men and women are required.

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

Ethical approval: *The study was approved by the Clinical Research and Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey (Date of Approval: 28.03.2019; Decision Number: 10/1).*

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MEDICAL RECORDS-International Medical Journal

Research Article

The Relationship between Spondylolisthesis and Modic Changes: An MRI Study

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Abstract

Aim: We aimed to investigate the relationship between the presence of spondylolisthesis and Modic changes (MCs) by using lumbar magnetic resonance imaging (MRI).

Methods: The study included 139 adult patients aged 18-65 years with lumbar spondylolisthesis detected on lumbar MRI. Demographic characteristics such as age, gender, and levels and grades of spondylolisthesis, and presence of lumbar MCs/types were recorded. The findings were compared between two groups including grade 1 and grade 2 spondylolisthesis.

Results: Grade 1 and 2 spondylolisthesis groups were similar for age (p=0.787), sex (p=0.076), listhesis' level (p=0.268) and direction (p=0.280). The presences of pars spondylolysis, disc space narrowing, and MCs were significantly higher in patients with grade 2 spondylolisthesis than those with grade 1 (94.4% vs 64.1%), (97.2% vs 83.5%), and (100% vs 83.5%), respectively (all p<0.05). Grade 2 spondylolisthesis patients had significantly higher proportion of type 2 MCs than patients with grade 1 (88.9% vs 63.1%) (p<0.05).

Conclusion: MCs are associated lumbar spondylolisthesis. The presence of spondylolisthesis may be a predisposing factor for MCs occurred in the lumbar spine. Prospective studies on the topic should be examined in more detail.

Keywords: Modic lesions, spondylolisthesis, modic changes, lumbar

INTRODUCTION

Spondylolisthesis is described as the translocation of a superior vertebral body with respect to the one subjacent (1). Lumbar spondylolisthesis is a cause of low back pain and classified into subtypes such as isthmic (spondylolitic) and degenerative. Isthmic spondylolisthesis includes pars interarticularis defect and mostly affects L5-S1 level (2). Degenerative spondylolisthesis is seen in persons over 50 and commonly affects the L4-L5 level (3). The standard grading of spondylolisthesis is based on the persentage of the translocation, and called Meyerding grading system (1). Diagnostic tools are history taking, physical exam, and radiologic evaluations by using x-ray, computerized tomography (CT), and magnetic resonance imaging (MRI) (1,2). Therapeutic approaches encompases conservative (rest, bracing, physical therapy, and analgesic drugs and applications) and surgical management (decompression, stabilization, and fusion) in resistant or advanced cases (1).

Modic changes (MCs) are bone marrow and vertebral endplate lesions visible on spinal MRI. Lumbar MCs are associated with low back pain and correlated with degenerative processes of the affected spinal segment (4,5). The classification of MCs is based on the T1 and T2 weighted images (WI) of MRI sequences, and also the histopathological meanings (5). Although the exact etiopathogenesis underlying MCs is not fully understood, segmental instability, increased mechanical loading, and degenerative immune reaction following infections in the spine are suggested mechanisms (6-9). There is no

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consensus on the best effective treatment option for MCs, but it has been found that nonoperative therapy is useful for low back pain patients with MCs (10,11).

There are some similarities between spondylolisthesis and MCs occured at the lumbar spine. For example, both the conditions are associated with low back pain and alleviated with lumbar therapies (2,11). Furthermore, both spondylolisthesis and MCs are associated with segmental instability and degenerative process in the lumbar spine (5,7). Therefore, we hypothesized that MCs may be involved to spondylolisthesis, and an increased grade of spondylolisthesis may be related to the presence of MCs in the lumbar spine. In this study, to address the presence/absence of MCs in patients with lumbar spondylolisthesis, and also to reveal the relationship between the features of the two conditions such as grade of spondylolisthesis and types of MCs were aimed. Thanks to this, if the mentioned associations can be demonstrated, the conditions' pathophysiological processes may be better understand, and thus, more appropriate protective and curative approaches may be applied more easily.

MATERIAL AND METHOD

In this study, lumbar MRI records taken on machines with 1.5T or 3T magnet power at Şanlıurfa Harran University Hospital between October 2021 and October 2022 were examined retrospectively. The MRI findings of patients with lumbar spondylolisthesis were evaluated by the same radiologist for the presence/absence of MCs, pars interarticularis defects, and intervertebral disc height at the spondylolisthesis segment. Before start the study, which was conducted in accordance with the Helsinki Declaration, approval was received from the Ethics Committee of Harran University (dated 31.11.2022 and HRU/22-21-11 number).

The Meyerding system was used for the grading of spondylolisthesis. Accordingly, grade I is 0% to 25%, grade II is 25% to 50%, grade III is 50% to 75%, grade IV is 75% to 100%, and grade V is >100% of slip (1,12).

The classification of MCs was made based on the changes in the endplate signal intensity (SI) on the T1 and T2 WI. Accordingly, type 0: no changes in the endplate SI; type I: SI is hypo on T1WI and hyper on T2WI; type II: SI is hyper on T1WI and iso or hyper on T2WI; type III: SI is hypo on both T1WI and T2WI in the endplate (5,13).

Of the 200 patients with lumbar spondylolisthesis, those between the ages of 18 and 65 years were included in this study. Those with a history of spinal surgery, fractures, tumors, infections or inflammatory rheumatological diseases, and one case with grade 4 spondylolisthesis, and also one with MCs type 3 were excluded from the study to provide homogeneity. After applying the exclusion criteria, demographic characteristics such as age and gender, the findings of MRI related to spondylolisthesis and MCs were examined and recorded in 139 patients (Figure 1).

Flow of study progress.

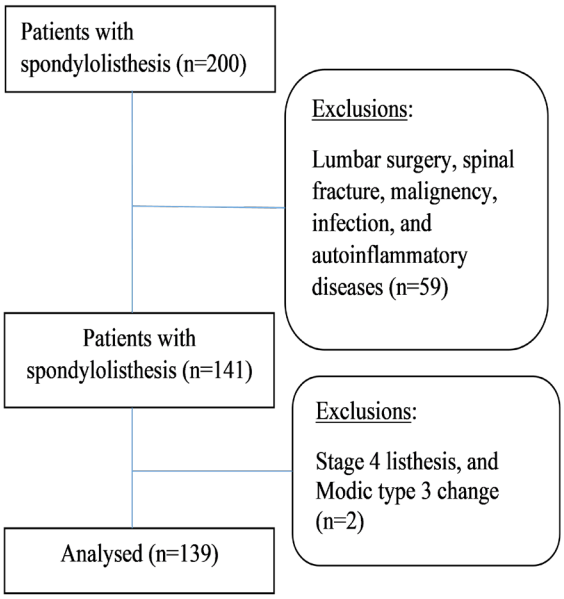

Figure 1. Flow of study progress

Statistical Analysis

Statistical analysis were performed using SPSS 20.0 for Windows (Armonk, NY: IBM Corp.). Since continuous variables had normal distribution according to the results of Kolmogorov-Smirnov test, the Student's t test was used in the statistical comparisons of age scores between the groups. Continuous data were given as mean±SD (min.-max.). Categorical variables were assessed by the Chi-Square test or Fisher's Exact test. In addition, compare column proportions with Bonferroni method by z test was used when needed. Categorical variables were given as number (percentage). Statistically significance level was considered as $p<0.05$.

RESULTS

Figure 1 schematizes the flow of progress of the study. A total of 200 patients with lumbar spondylolisthesis were assessed for eligibility. Out of the 141 patients who have eligibility criteria, 139 included in this study (n=139; 103 females, 36 males; mean age 49.83±10.14 years; range 22 to 65 years). Group 1 consisted of 103 patients with grade 1 spondylolisthesis (n=103; 72 females, 31 males; mean age 49.69±10.12 years; range 22 to 65 years). Group 2 consisted of 36 patients with grade 2 spondylolisthesis (n=36; 31 females, 5 males; mean age 50.22±10.35 years; range 24 to 65 years).

Table 1 shows the characteristics and MRI findings considering all patients.

Table 1. Characteristics and MRI findings of patients with lumbar spondylolisthesis (n=139)

	Data
Age (years)	49.83±10.14
Gender	
Female	103 (74.1)
Male	36 (25.9)
Spondylolisthesis grade	
Grade 1	103 (74.1)
Grade 2	36 (25.9)
Spondylolisthesis level	
L3-L4	13 (9.4)
L4-L5	49 (35.3)
L5-S1	77 (55.4)
Spondylolisthesis direction	
Anterior	118 (84.9)
Posterior	21 (15.1)
Pars interarticularis defect	
Yes	100 (71.9)
No	39 (28.1)
Disc space narrowing	
Yes	121 (87.1)
No	18 (12.9)
Modic change type	
Type 0	25 (18.0)
Type 1	17 (12.2)
Type 2	97 (69.8)

Data are given as mean±standard deviation or total number (%)

Table 2 shows comparisons of patients' characteristics and MRI findings considering lumbar spondylolisthesis grades. The two groups were similar for age (p=0.787), sex (p=0.076), spondylolisthesis level (p=0.268), and spondylolisthesis direction (p=0.280). The two groups were significantly different each other for the presence/absence of pars interarticularis defect (p<0.001), disc space narrowing (p=0.042), MCs (p<0.001), and for the type of MCs (p=0.003) (Table 2).

In terms of the presence of pars interarticularis defect (spondylolysis), disc space narrowing, and MCs, patients with grade 2 spondylolisthesis had significantly higher proportions than patients with grade 1 spondylolisthesis (94.4% vs 64.1%), (97.2% vs 83.5%), and (100% vs 83.5%), respectively. In terms of the type of MCs, patients with grade 2 spondylolisthesis had significantly higher proportion of type 2 of MCs than patients with grade 1 spondylolisthesis (88.9% vs 63.1%) (Table 2).

Table 2. Comparisons of patients' characteristics and MRI findings considering lumbar spondylolisthesis grades

	Spondylolisthesis grade 1 (n=103)	Spondylolisthesis grade 2 (n=36)	p
Age (years)	49.7±10.1	50.2±10.3	0.787*
Gender			0.076§
Female	72 (69.9)	31 (86.1)	
Male	31 (30.1)	5 (13.9)	
Spondylolisthesis level			0.268†
L3-L4	11 (10.7)	2 (5.6)	
L4-L5	39 (37.9)	10 (27.8)	
L5-S1	53 (51.5)	24 (66.7)	
Spondylolisthesis direction			0.280§
Anterior	85 (82.5)	33 (91.7)	
Posterior	18 (17.5)	3 (8.3)	
Pars interarticularis defect			**<0.001§**
Presence	66 (64.1)[a]	34 (94.4)[b]	
Absence	37 (35.9)[a]	2 (10.1)[b]	
Disc space narrowing			**0.042§**
Presence	86 (83.5)[a]	35 (97.2)[b]	
Absence	17 (16.5)[a]	1 (2.8)[b]	
Modic change			**<0.001§**
Presence	78 (75.7)[a]	36 (100)[b]	
Absence	25 (24.3)[a]	0 (2.8)[b]	
Modic change type			**0.003†**
Type 0	25 (24.3)[a]	0 (0)[b]	
Type 1	13 (12.6)[a]	4 (11.1)[a]	
Type 2	65 (63.1)[a]	32 (88.9)[b]	

Data are given as mean±standard deviation or total number (%); *: Student's t test; §: Fisher's Exact test; †: Chi-Square test; a, b: Compare column proportions with Bonferroni method by z test

DISCUSSION

In the present study, the findings of MCs were assessed considering lumbar spondylolisthesis grades. As result, the frequency of MCs was higher in patients with grade 2 spondylolisthesis than those with grade 1, but only type 2 MCs had higher frequency. Thus, these results suggest that increased lumbar spondylolisthesis may be involved in occured MCs, and spondylolisthesis may occurs a predisposition for development of MCs, especially for type 2 MCs.

In the previous studies, it has been shown that both spondylolisthesis and MCs occured at the lumbar spine are associated with segmental instability and sagittal imbalance (7,13). In addition, these two conditions are also associated with degenerative process in the lumbar spine

(5,7,13). Therefore, considering these common features of spondylolisthesis and MCs, it can be said that the present study is based on a sensible and scientific basis.

This study demonstrated higher proportions of spondylolysis, disc space narrowing, and MCs in patients with grade 2 spondylolisthesis compared to those with grade 1. These are not surprising results. Because spondylolysis, disc space narrowing, and MCs are degeneration-related conditions can resulted from impaired biomechanics, increased loading, and damaged anatomical structures (14-16), which are expected in the presence of spondylolisthesis. Therefore, it is logical that these conditions may be increased in patients with higher degree of spondylolisthesis than those with lesser.

According to the results of this study, patients with grade 2 spondylolisthesis had higher proportion of type 2 MCs than those with grade 1. However, grade 1 and grade 2 spondylolisthesis groups were similar to each other for the proportion of type 1 MCs. It is known that type 1 and type 2 MCs have interconvertible properties, and type 2 MCs has more stable structure (9,17). Therefore, the increased type 2 MCs seen in patients with grade 2 spondylolisthesis may be due to a conversion of type 1 and the stability of type 2 MCs. Also, type 2 MCs are more associated with overloading (18) which is possible in the presence of spondylolisthesis.

The main limitation of this study was the relatively small sample size. Since it was a retrospective study, we could not access information including the reasons for MRI, trauma histories, etiology of spondylolisthesis, duration of complaints, and body mass index. Because of certain age group in the study, the results cannot generalised to other age group. Due to no a previous study addressed MCs in patients with spondylolisthesis, a comparison with literature and an indepth discussion could not be done.

CONCLUSION

In conclusion, there is a relationship between spondylolisthesis and MCs. The presence of spondylolisthesis may be a predisposing factor for MCs occurred in the lumbar spine. In the future, with prospective studies involving multicenter and high number of MRI examinations, this issue should be examined in more detail.

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Ethical approval: Approval was received from the Ethics Committee of Harran University (dated 31.11.2022 and HRU/22-21-11 number).

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Research Article

lncRNA MALAT1, MEG3, and PANDAR Levels may be Potential Diagnostic Biomarkers in Multiple Myeloma

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Abstract

Aim: Long non-coding RNAs (lncRNAs) play a significant role in the development of various diseases, including cancer, and have been investigated as potential diagnostic and prognostic markers. The specific mechanisms underlying their involvement in the progression and development of multiple myeloma (MM), as well as their potential as diagnostic markers, remain to be fully elucidated. This study aimed to elucidate the involvement of lncRNAs in the pathogenesis of MM, explore their relationship with clinical parameters, and assess their potential as biomarkers for MM diagnosis.

Material and Methods: Patients above 18 years of age, diagnosed with MM and not yet receiving treatment, were included in the study. The expression levels of three lncRNAs (MALAT1, PANDAR, MEG3) regulated by the p53 gene were determined in a study involving 19 patients diagnosed with MM and 20 healthy volunteers. The expression levels were determined using RT-PCR.

Results: The levels of plasma lncRNAs were observed to be significantly down-regulated ($p<0.05$) in the patient group. No significant difference was observed between disease stages and the expression levels of the lncRNAs. There was a negative correlation between lncRNA expression levels and albumin levels ($p=0.019$; $p=0.048$; $p=0.033$, respectively), while no significant associations were found with other clinicopathological characteristics. ROC analysis demonstrated that the plasma expression levels of lncRNAs had diagnostic value in predicting MM (AUC=0.729, $p=0.015$; AUC=0.742, $p=0.010$; AUC=0.703, $p=0.031$, respectively).

Conclusion: In conclusion, MALAT1, PANDAR and MEG3 may serve as novel biomarkers for MM patients. Furthermore, these lncRNAs may be potential drug targets in MM.

Keywords: lncRNA, multiple myeloma, MALAT1, MEG3, PANDAR

INTRODUCTION

Multiple myeloma (MM) is a type of blood cancer where abnormal plasma cells in the bone marrow multiply uncontrollably (1). The pathogenesis of MM involves complex genetic and epigenetic processes (2). Advances in genetic and molecular research have shed light on the connection between the clinical manifestations of MM patients and the underlying biological properties of myeloma cells, enabling personalized treatment approaches (3).

The findings of the Human Genome Project have revealed that a minimum of 90% of the human genome undergoes active transcription into RNA molecules, whereas the contribution of RNA in encoding proteins is less than 2% (3). Non-coding RNAs (ncRNA) have been found to be unregulated in cancerous tissues and contribute to oncogenic or tumor-suppressive processes (4). Furthermore, lncRNAs are recognized for their ability to epigenetically modulate gene expression and participate in diverse biological functions (3). Additionally, their dysregulation has been implicated in numerous cancer types. Extensive research indicates their association with disease diagnosis, prognosis, tumor initiation, and metastasis (5).

MALAT1, located on chromosome 11q13.1, exhibits

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heightened expression in tumor tissues and is implicated in the processes of tumor invasion and metastasis (6). This lncRNA, approximately 800 nucleotides in length, demonstrates conservation among mammals (7). Existing literature highlights that reduced MALAT1 expression leads to the activation of p53 (8). However, MALAT1 has been observed to be indispensable for G1/S cell cycle progression and mitotic advancement (9, 10). MALAT1 expression has been identified in bone marrow, B lymphocytes, and lymphoid tissue (11).

PANDAR, located at chromosome 6p21.2, produces a non-coding RNA, which is thought to regulate the DNA damage response. This gene is induced by p53 and modulates its activity by interacting with a transcription factor. The deregulation of this gene has been associated with cancer progression (12-14). Emerging research indicates that PANDAR exerts oncogenic effects in the context of tumorigenesis, and its expression is dysregulated in numerous tumor tissues (15-20).

MEG3 is located on 14q9 and is defined as a tumor suppressor gene in various malignant tumors (21). MEG3 is expressed in many tissues and is known to regulate the p53 gene expression and induce p53-dependent transcription (22). It has been demonstrated in the literature that the expression of MEG3 is significantly downregulated in the brain, bladder, cervix, colon, bone marrow, lung, liver, and prostate cancer cells (23-25).

The current study focuses on the role and diagnostic power of cell-free lncRNAs in the bloodstream in the pathogenesis of MM. When we analyzed the expression levels in different cells and tissues in databases to select the most appropriate lncRNA molecules involved in the MM pathogenesis, we planned to analyze the expression of 3 lncRNAs in MM patients according to their tumor suppressor (MEG3) and oncogenic (MALAT1, PANDAR) functions that regulate the p53 gene and p53 targets (9,22).

The aim of this study was to determine the expression levels of lncRNAs that are regulated by the p53 gene in the plasma of patients diagnosed with multiple myeloma (MM). Additionally, the study aimed to explore the association between these expression levels and clinical parameters. Furthermore, the diagnostic potential of these lncRNAs was assessed by comparing the MM patients with a control group.

MATERIAL AND METHOD

Selection of Samples and Clinical Data

This study received local ethics committee approval (dated 27.05.2019 with decision number 77420). All patients provided written informed consent. Nineteen patients with untreated MM (mean age 69±8.8 years, 10 males, 9 females) and 20 controls (mean age 43.9±3.7 years, 12 males, 8 females) were included in the study. Patients older than 18 years of age who were diagnosed with MM and who had not yet received any treatment were included in the study. The study excluded patients with diseases other than multiple myeloma (MM). The control group consisted of individuals without chronic illnesses or medication usage. The patients' medical histories were obtained and recorded. Cases were evaluated in terms of cytogenetic evaluation with parameters such as age, gender, complete blood count, sedimentation rate, CRP, leukocytes, ferritin, iron, IgG, IgA, IgM, globulin, albumin, total protein, creatinine, and calcium. In addition, patients were classified by stage and subclassification according to the Durie-Salmon classification. 4 ml of venous blood from the patients was drawn into EDTA tubes.

cDNA Synthesis

RNA extraction from plasma cells of the patients was conducted following the protocol recommended by the manufacturer (Gene All Biotechnology, Korea). Briefly, homogenization was performed by adding 1mL of RiboEx reagent to a 200 µl plasma sample. The homogenate was centrifuged at 10,000 g for 13 minutes. The resulting supernatant was carefully transferred into a tube, and 200 µl of chloroform was added. After incubating at room temperature for 2 minutes, the mixture was subjected to centrifugation at 9000 g for 14 minutes. The supernatant was transferred to a clean tube and centrifuged with the addition of RB1 buffer, SW1 buffer, and RNW buffer respectively, and the collection tube was changed.

Subsequently, 50 µL of RNase-free water was gently added to the column, and the mixture was maintained at room temperature for 1 minute. mRNA samples were obtained by centrifuging at 10,000xg for 1 minute. The quantification of isolated total RNAs was performed using a Thermo Fisher NanoDropTM spectrophotometer instrument. Total RNA isolated from plasma samples was used for cDNA synthesis using the Hyper ScriptTM First-Strand Synthesis Kit. The obtained cDNA samples were stored at -80 °C until RT-PCR was conducted.

Quantification of lncRNAs

Real-time amplification of lncRNAs was performed using the Step One Plus RT-PCR Detection System (ThermoFisher Scientific, USA) according to the manufacturer's recommended protocol. The expression levels of lncRNAs were examined using the SYBR Green method with the Actin Beta gene (ACTB) serving as the internal control (housekeeping gene). The cycle threshold (CT) values of the target primers (Table 1) were determined, and the reference gene ACTB was used for normalization. The fold change in expression for each lncRNA was calculated using the 2-ΔΔCt equation.

Table 1. The primer sequences of the detected lncRNA		
Gene	Primer sequence	GenBank accession number
MALAT1	F 5′-CGCCATTTTAGCAACGCAGA	NR_144567.1
	R 5′- CCCAAGGACTCTGGGAAACC	NR_144567.1
PANDAR	F 5′- GCTTGTTCCAGAGCCAGGAT	NR_109836.1
	R 5′- CATCCTCAATGCCACCACCT	NR_109836.1
MEG3	F 5′- CCCTAGCGCAGACGGC	NR_046467.1
	R 5′- GAAGACAAGGAGGTGGACGG	NR_046467.1
ACTB	F 5′- CATGTACGTTGCTATCCAGGC	NM_001101
	R 5′- CTCCTTAATGTCACGCACGAT	NM_001101

Statistical Analysis

Independent samples t-test was used for normally distributed data, while the Mann-Whitney U test was utilized for non-normally distributed data. The chi-square test was employed to compare categorical variables. Pearson correlation analysis was conducted to determine the relationship between continuous variables. Additionally, ROC analysis was performed to calculate the AUC, specificity, and sensitivity values.

RESULTS

Patient Characteristics

The characteristics of the study groups are presented in Table 2. Hemoglobin, leukocyte, neutrophil, lymphocyte, thrombocyte, total protein, creatinine, calcium, LDH, and albumin levels were studied from the serum samples of the patient and control groups. IgG, IgA, IgM, cytogenetic, and FISH analyses were also performed in the patient group. Ten (52.6%) of the multiple myeloma patients included in the study were male, 9 (47.4%) of them were female; whereas 12 (60%) patients in the control group were male, 8 (40%) of them were female. hemoglobin (SD, 11.1±2.7), leukocyte (SD, 5±1.6), and albumin levels (SD, 8.7±1.8) of the MM group were significantly lower (Table 2). Total protein (SD, 8.7±1.8) was significantly higher in the MM group (Table 2).

Table 2. Demographic and clinical data of groups			
	Multiple miyeloma (n=19)	Control (n=20)	p*
Male/female, n	10/9	12/8	0.444
Age (years)	69±8.8	43.9±3.7	0.000
Haemoglobin	11.1±2.7	14.2±1.3	0.000
Leukocyte	5±1.6	7.5±1.8	0.000
Neutrophil	55.8±12.4	59.4±9.4	0.314
Lymphocyte	32.7±12.2	27.6±11.6	0.191
Platelet	192.5±104.7	270.2±65.4	0.08
Calcium	9.5±1.1	9.4±0.5	0.934
Total protein	8.7±1.8	7.2±0.7	0.03
Albumin	3.4±0.6	4.3±0.5	0.000
Creatinine	0.9±0.3	0.8±0.3	0.328
LDH	211.6±83.5	239.8±140.3	0.453
IgA	1090.6±2059.9	-	
IgM	39.4±45.1	-	
IgG	1701±1479.1	-	
Cytogenetics		-	
Normal (46,XX/XY)	13 (68.4%)		
No metaphase	6 (31.6%)		
FISH			
Del17p	0 (0%)		
Del13q	4 (21.1%)		
Monozomy	4 (21.1%)		
Trizomy	1 (5.3%)		
t(4;14)	2 (10.5%)		
t(11;14)	1 (5.3%)		

Data are expressed as mean±SD. *p<0.05 was considered to be significant. LDH: lactatedehydrogenase, IgA: immunoglobulin A, IgM: immunoglobulin M, IgG: immunoglobulin G, FISH: flouresan in situ hybridization

There was no difference in neutrophil (SD, 55.8±12.4), lymphocyte (SD, 32.7±12.2), platelet (SD, 192.5±104.7), calcium (SD, 9.5±1.1), creatinine (SD, 0.9±0.3), lactate dehydrogenase (LDH) (SD, 211.6±83.5) levels between the groups (Table 2). In cytogenetic analysis, 13 (68.4%) of the patients had a normal karyotype, whereas metaphase could not be obtained from 6 (31.6%) of them. In FISH analysis, although no 17p deletion was found in the patients, it was found that 4 of them (21.1%) had del13q, 4 of them (21.1%) had monosomy (monosomy 13, monosomy 14, monosomy 7), 1 of them (5.3%) had trisomy 8, 2 of them (10.5%) had t (4; 14), 1 of them (5.3%) had t (11; 14) (Table 2).

Plasma lncRNA Expression Levels

The relative expression levels of cell-free lncRNA PANDAR, MALAT1, and MEG3 in the plasma from patients with multiple myeloma were 2.28±2.06, 1.49±1.55, and 0.19±1.76, respectively, and were significantly downregulated in the MM group (p=0.006; p=0.006; p=0.009, respectively). In the MM group, the changes compared with the control group were 0.23, 0.14, and 0.28, respectively. The relative expression levels of lncRNA of the groups are shown in Figure 1, and the scatter plot of these expression values is shown in Figure 2.

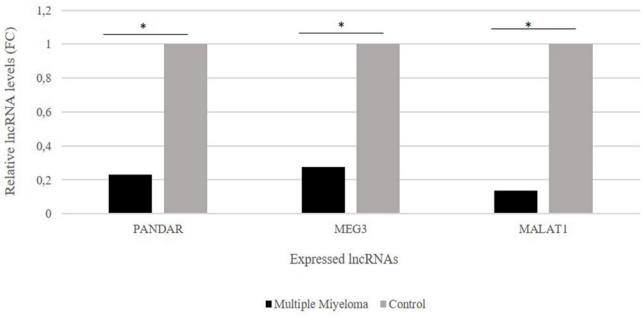

Figure 1. Relative lncRNA expression of MM according to healthy controls. *p<0.01, statistically significant. FC; fold change. The relative expression value of the control group was accepted as 1. Expression levels of specific lncRNAs PANDAR, MEG3, MALAT1 (FC=0.23, p=.006; FC=0.28, p=.009; FC=0.14, p=.006, respectively) in 19 MM patients, and 20 HC were analyzed using parametric Independent Samples Test. Data are presented as a median of normalized lncRNA expression in log2(2−ΔΔCT)

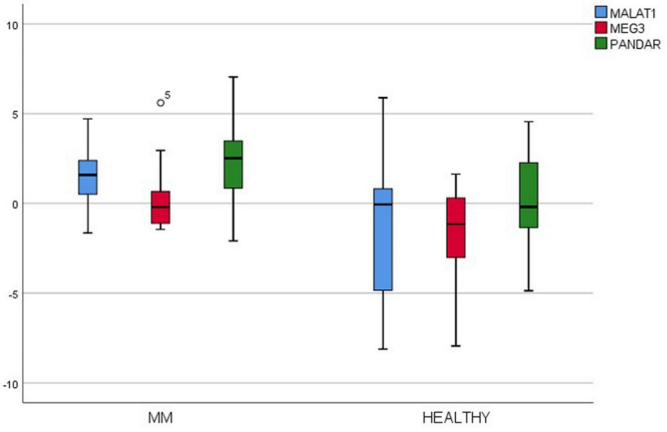

Figure 2. Distribution of the lncRNA expression levels in the disease groups

Expression Levels and Clinicopathological Characteristics

The correlation between clinicopathological parameters such as hemoglobin, leukocyte, neutrophil, lymphocyte, thrombocyte, calcium, total protein, albumin, creatinine, LDH, IgA, IgM, IgG levels, and Durie-Salmon staging was investigated to determine the clinical relationship of lncRNA expressions in MM. While there was a negative correlation between serum albumin levels and plasma lncRNAs of MALAT1, MEG3, and PANDAR in MM patients (r=-0.373, p=0.019; r=-0.342, p=0.033; r =-0.318, p=0.048; respectively), no significant correlation was found for the other clinicopathological parameters (p>0.05). According to the Durie-Salmon staging system; 6 (31.58%) patients were classified as stage 1A and 13 (68.42%) as stage 2A. No significant difference (p>0.05) was found in the expression levels of lncRNAs when compared across different stages of the disease.

ROC Analysis

ROC curves were plotted to evaluate the potential diagnostic power of plasma MALAT1, PANDAR, and MEG3 in MM patients (Figure 3). For MALAT1, the area under the curve (AUC) was 0.729 (95% CI, 0.560-0.898, p=0.015). For PANDAR, the AUC was 0.742 (95% CI, 0.582-0.902, p=0.010). For MEG3, the AUC was 0.703 (95% CI, 0.536-0.869, p=0.031).

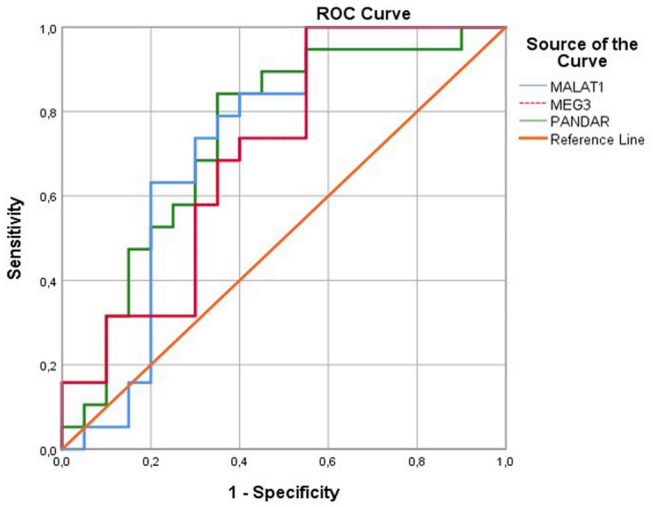

Figure 3. Receiver operating characteristic (ROC) curves based on RT-qPCR data. ROC; receiver operating characteristic. Sensitivity, specificity (both with 95% CI), AUC, and cutoff values of normalized lncRNA expression in log2(2−ΔΔCT) for MM obtained by ROC analysis

DISCUSSION

Multiple myeloma is considered to be multifactorial, and both genetic and epigenetic changes have been reported in its pathogenesis. Recent studies have shown that altered lncRNA levels in MM can lead to abnormal expression of genes related to oncogenesis (3). LncRNAs play a crucial role in tumor biology and possess the potential to serve as diagnostic biomarkers for specific types of cancers (26).

In this study, we investigated the expression levels of 3 candidate lncRNAs from plasma samples of patients with MM. To the best of our knowledge, this study is the first

to reveal the expression levels of MALAT1, PANDAR and MEG3 in the plasma of MM patients. Our findings revealed down-regulation of all lncRNAs evaluated in the patient group. This finding suggests that MALAT1, PANDAR, and MEG3 may play a role in the pathogenesis of MM.

Studies have shown that lncRNAs can regulate the p53 gene or p53 targets and are overexpressed in various human cancers (8). In a study conducted in AML patients, it was revealed that MALAT1 was upregulated and caused poor prognosis by affecting proliferation and apoptosis pathways (27). It was also associated with poor prognosis and carcinogenesis in non-small cell lung cancer (28). In another study, MALAT1 was shown to be upregulated in mononuclear cells of treated MM patients (2). Işın et al. (29) demonstrated increased MALAT1 expression in CLL patients and suggested that this increase was compatible with cell proliferation. In our study, we observed a significant downregulation of MALAT1 expression in MM patients (FC=0.14; p=0.006). We hypothesize that this downregulation of MALAT1, which is involved in the splicing mechanism and mitotic progression of the cell cycle, may lead to abnormal splicing formation and cell proliferation.

Recent studies have provided evidence of deregulation and oncogenic effects of PANDAR in various tumor tissues (15-20). Peng et al. (19) and Li et al. (16) reported upregulation of PANDAR in their respective study groups, which correlated with poor prognosis. Another study suggested that PANDAR predicts poor prognosis in non-small cell lung cancer and influences apoptosis through Bcl-2 (15). In contrast, Zhan et al. (21) found significant upregulation of PANDAR in bladder cancer tissues. Yang et al. (30) demonstrated upregulation of PANDAR in patients with acute myeloid leukemia (AML) and its association with poor prognosis. These studies collectively indicate the prognostic value of PANDAR in cancer patients. In our study, we observed downregulation of lncRNA PANDAR in the patient group, which is consistent with the findings of Han et al. (15) (FC=0.23; p=0.006). We believe that the expression and function of PANDAR, which is a type of lncRNA, may vary in different cell types and different diseases, depending on the various interaction mechanisms and the elements involved in these mechanisms.

MEG3 has been shown to induce p53-dependent transcription by regulating the expression of the tumor suppressor gene p53. Down-regulated lncRNA levels are common in various types of cancer and are recognized as a cancer biomarker and therapeutic target (22). In the literature, Sun et al. (31) demonstrated that upregulation of MEG3 inhibits the proliferation and metastasis of endometrial cancer cells. Yao et al. (32) reported downregulation of MEG3 in acute myeloid leukemia cell lines. Consistent with the existing literature, our study revealed a significant downregulation of MEG3 in the patient group (FC=0.28; p=0.009). The downregulation of MEG3 suggests its potential contribution to tumor cell proliferation by influencing the binding of the tumor suppressor gene p53 to its target.

In recent years, there has been a growing interest among researchers in exploring novel tumor biomarkers and investigating the molecular mechanisms that are associated with tumor screening, diagnosis, prognosis, and the assessment of treatment effectiveness (33). To date, many studies have been conducted on how lncRNAs can be prognostic biomarkers in cancer. Kong et al. (34) reported that MEG3 may be a prognostic biomarker (AUC=0.73, p=0.0003) for lung metastasis in early-stage colorectal cancer. Wan et al. (35) showed that MEG3 has a diagnostic value in predicting cervical cancer (AUC=0.858, p=0.03). Jiang et al. (36) showed that the expression of MEG3 in acute promyelocytic leukemia (APL) has an important diagnostic value (AUC=0.840, p<0.0001) in the diagnosis of APL. Li et al. (37) reported that the expression of MALAT1 can predict the poor prognosis of cervical cancer (AUC=0.788, p<0.05). Another study showed that MALAT1 can function as an oncogene in gastric cancer and serve as a marker for distant metastasis (38). Yang et al. (39) reported that the expression of PANDAR can be used as a biomarker (AUC=0.800, p<0.001) in the diagnosis of acute myeloid leukemia. Yang et al. (39) also suggested that the expression of PANDAR may be a diagnostic biomarker (AUC=0.767, p<0.05) for predicting gastric cancer. In our study, the sensitivity of MALAT1, PANDAR, and MEG3 in plasma was 95%, while the specificity was 70%, which demonstrated that these lncRNAs have high sensitivity and specificity. Our results suggest that these lncRNAs may be a potential diagnostic target in MM patients.

The findings from our study indicate that the relative expression of the studied lncRNAs could potentially serve as a valuable adjunctive test in the diagnosis of MM. However, there are some limitations in generalizing our results in this study. These limitations include a small sample size, assessment of a small number of lncRNAs, sample collection from a single institution, underreporting of personal data, and studying only plasma samples.

CONCLUSION

In conclusion, our study demonstrates that the expression levels of the cell-free lncRNAs investigated were significantly downregulated in the plasma samples of patients with MM. Our results suggest that MALAT1, PANDAR, and MEG3 may play a role in MM pathogenesis and could be potential diagnostic targets in MM patients. While these findings provide valuable insights for future research, additional molecular studies are required to elucidate the potential involvement of these lncRNAs in disease prognosis and their potential contribution to targeted therapeutic approaches. In addition, long-term follow-up and further examination are required to evaluate the predictability of these plasma lncRNAs.

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

Ethical approval: *The study protocol complies with the Helsinki Declaration principles and was approved by the Süleyman Demirel University Clinical Research Ethics Committee (dated 27.05.2019 and with 77420 decision number).*

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MEDICAL RECORDS-International Medical Journal

Research Article

Retrospective Analysis of Our Experience with Percutaneous Tracheostomy in Our Intensive Care Unit

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Abstract

Aim: Percutaneous tracheostomy (PT) application has advantages such as being able to be applied at the bedside in a short time and less bleeding. It is frequently preferred in intensive care units with indications such as prolonged artificial respiration requirement, facilitating weaning, and providing emergency airway. It is an alternative method to surgical tracheostomy. In this study, we aimed to retrospectively evaluate the percutaneous tracheostomy cases we performed in the Intensive Care Unit (ICU) in the last three years.

Material and Methods: Patients who underwent percutaneous tracheostomy in the 3rd Level our Hospital between January 2018 and December 2022 were examined. Demographic data of the patients, diagnosis of hospitalization, Acute Physiology and Chronic Health Evaluation II Score (APACHE II score), hospitalization time, intubation time, time from intubation to tracheostomy, early and late complications of tracheostomy were retrospectively analyzed.

Results: Ninety-seven patients were analyzed. The mean age of the patients was 77.6±10.9 (range, 41-100) years and the female-male ratio was 40/57. The most common hospitalization diagnosis was neurological reasons (54.6%). The patients were intubated for 20.3±7.9 (range, 7-48) days and the total length of stay in the ICU 65.3±30.3 (range, 17-175) days. The number of patients who developed complications related to the PT procedure was 17 (12.9%).

Conclusion: Percutaneous tracheotomy, which is performed in the ICU with indications such as the need for prolonged mechanical ventilation, facilitating weaning, and providing an emergency airway, is a simple, minimally invasive procedure with a low complication rate.

Keywords: Intensive care, tracheotomy, complication

INTRODUCTION

Percutaneous tracheostomy (PT) is an interventional method that is frequently used in the treatment of upper airway obstructions and in intensive care patients who have undergone endotracheal intubation, which is thought to require long-term mechanical ventilation (MV) (1,2). The purpose of PT in intensive care unit (ICU) patients; protect the airway, prevent intubation-related complications, reduce laryngeal injury, facilitate nursing care and clearance of airway secretions, reduce dead space volume, facilitate patient transport from the intensive care unit to general services, increase patient comfort, assist and enable speech, improve airway resistance, counted as reducing the need for sedation, providing safer and faster weaning, shortening the length of stay in the ICU, and facilitating oral feeding (3,4).

PT has been shown to be a viable method due to its key advantages including easy bedside application, low complication rates, and short application time. Moreover, PT is frequently used in ICU patients requiring elective tracheostomy (5). As PT is an invasive procedure, it may lead to both intraoperatif and postoperative complications. Tracheostomy can be performed with surgical and percutaneous methods. Percutaneous tracheostomy techniques are frequently preferred in intensive care patients because they can be applied at the bedside in a short time (6,7).

Although percutaneous tracheotomy has complications such as pneumothorax, emphysema and bleeding, it has advantages such as being simple, having a very low

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complication rate, not requiring operating room conditions, and being a method that can be applied at the bedside in a short time (8,9).

In this study, we aimed to retrospectively evaluate the percutaneous tracheostomy cases we performed in the ICU in the last three years.

MATERIAL AND METHOD

After obtaining the ethics committee approval from the ethics committee of Karabük University (2023/1244), the patients who underwent PT between January 2018 and December 2022 in our hospital's intensive care units were evaluated retrospectively. Informed consent was not obtained as it was a retrospective study. Cases over the age of 18 who underwent PT between the dates we determined were included in the study. Surgical tracheostomy was performed in 21 patients. However, these patients were excluded from the study.

A total of 97 cases, 40 female and 57 male, who underwent percutaneous tracheostomy with the Griggs method, were retrospectively analyzed. Patients without bleeding disorders (platelet count greater than 50,000 (mm3)-1, activated partial thromboplastin time and prothombin time less than 1.5 times the control value) were included. The procedure was applied to patients with normal trachea and neck structure (no previous neck surgery, goiter, soft tissue infection in the patient's neck). All tracheostomies were performed under elective conditions by an experienced specialist or an anesthesia assistant who has completed at least 2 years in the presence of a specialist. After intravenous administration of fentanyl 1 µg kg-1, propofol 3 mg kg-1 and rocuronium 0.1 mg kg-1 before the procedure, positive pressure mechanical ventilation (MV) with 100% oxygen was applied to the patients. After the patient was placed in a flat supine position, the head was extended with under-shoulder support. After the endotracheal tube cuff was lowered by the assistant standing on the head of the patient, the tube was pulled under the vocal cords, and the tube cuff was inflated again. Was dressed sterile for the procedure. The neck area was covered with perforated green after wiping with antiseptic solution. The first and second or second and third intervals of the tracheal cartilage were palpated and local anesthesia was administered with 2% lidocaine (2-3 ml) to the area to be treated. After local anesthesia, a vertical incision (8-10 mm) was made in the skin area with the help of a scalpel. With the help of an injector with a 14G needle at the withdrawn end of 3 ml of saline, aspiration was made from the determined area and the tracheal lumen was entered. When air was aspirated into the syringe, the syringe was separated from the needle and the guide wire passed through was placed in the lumen of the trachea. The area was enlarged with the help of an 8F dilator passed over the guide wire. After removing the dilator and expanding the skin, subcutaneous and trachea with the help of forceps, a 7.5, 8 or 8.5 tracheotomy tube was inserted into the trachea. The guide wire was pulled. The patient was connected to the ventilator after in-tube aspiration was performed by inflating the tracheotomy tube cuff. After cleaning around the tracheotomy tube, sterile sponge was wrapped. After listening to the respiratory sounds, the patients had a chest X-ray in their bed.

Gender, age, diagnosis at the time of hospitalization, APACHE II scores, total length of stay (days), and discharge status (healthy/tracheotomy/death) of the cases were recorded. The number of days intubated, the anesthetic agents (All patients were given intravenous fentanyl 1 µg kg-1, propofol 3 mg kg-1 and rocuronium 0.1 mg kg-1 before the procedure; local anesthesia was administered with 2% lidocaine (2-3 ml) to the area to be treated) used during the procedure, and the complications that developed during and after the procedure were recorded.

Bleeding; minor bleeding (bleeding that can be stopped by wrapping sponge around the stoma in a short time) was classified as moderate bleeding (continuation of bleeding from the trachea with stoma/aspiration despite compresses) and bleeding from the appendix (bleeding that is intervened in the operating room).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency and ratio values were used. SPSS 28.0 program was used in the analysis.

RESULTS

There are three separate tertiary ICUs in our hospital. The number of patient beds varies between 24-28. Due to technical reasons, the number of beds decreased in some periods and some of the patient beds were reserved for the follow-up of patients infected with Covid-19 in certain periods due to the Covid-19 pandemic. Between January 2018 and December 2022, PT was performed to 104 patients. Seven cases whose data could not be accessed were excluded from the study.

Demographic data, diagnoses, early complications, late complications and discharge status of the cases are shown in Table 1. The mean age of the cases included in the study was 77.6±10.9 (41-100) years. 58.8% of these cases are male. The most common hospitalization reasons of the cases were due to neurological reasons (54.6%). Respiratory disease rate (28.9%), post-CPR rate (9.3%), cardiac disease rate (7.2%) were found. The duration of intubating the cases was 20.3±7.9 (7-48) days. The duration of follow-up in the intensive care unit was 65.3±30.3 (17-175) days.

All PT procedures were performed by specialist physicians. Forceps dilatation (Griggs) method was applied in all of them. 11.3% of our patients developed early complications and 2.1% developed late complications. Among the early complications, bleeding was the most common with 5.2%. One of our cases died due to paratracheal localization. Tracheoesophageal fistula and tracheal stenosis were seen in 1% of our cases as late complications.

The discharge status of our cases is also shown in Table 1. Intensive care treatments were completed in 30.9% of the cases. 10.3% of the cases were transferred to their homes and 20.6% of them were transferred to the services. 62.9% of our cases died.

Table 1. Demographic data, diagnosis, complications, discharge status

		Min-Max	Median	Mean±ss	n-%
Age		41.0-100.0	79.0	77.6±10.9	
Sex	**Female**			40	41.2%
	Male			57	58.8%
Diagnosis	**Neurological disease**			53	54.6%
	Respiratory disease			28	28.9%
	Post CPR			9	9.3%
	Cardiac disease			7	7.2%
Apache II score		6.0-47.0	21.0	22.1±7.5	
Early complication	**None**			86	88.7%
	Yes			11	11.3%
	Bleeding			5	5.2%
	Paratracheal placement			2	2.1%
	Subcutaneous emphysema			2	2.1%
	Death			1	1.0%
	Pneumothorax			1	1.0%
Late complications	**None**			95	97.9%
	Yes			2	2.1%
	Trachea-oesophageal fistula			1	1.0%
	Tracheal stenosis			1	1.0%
Intensive care hospitalization period		17.0-175.0	60.0	65.3±30.3	
Endotracheal intubation days		7.0-48.0	21.0	20.3±7.9	
Discharge status	**Death**			61	62.9%
	Clinic			20	20.6%
	Home			10	10.3%
	Currently in ICU			6	6.2%

DISCUSSION

In order to simplify long-term airway management, tracheostomy is often needed in critically ill patients in the intensive care unit due to the need for long-term MV. Although this concept remains unchanged, its current timing is still a matter of debate. Continued research is needed as it depends primarily on physician's prediction of the need for long-term MV rather than evidence-based practice (10). The advantages of PT are that it can be done with a small skin incision, less damage to tissues, less risk of bleeding, reduction in tissue deformity, and less infection at the application site. In addition, the advantages of PT can be considered to be reduced transport risks and costs, shorter opening time, and reduced complication rates, since it can be performed at the bedside and therefore does not require an operating room. For these reasons, PT is preferred more than surgical tracheostomy (11-15). Surgical tracheostomy was performed in 21 of 183 patients hospitalized in our ICU in the last 4 years, and PT was performed in 97.

Considering the diagnosis of hospitalization, it is seen that the most common cause is neurological. This is followed by respiratory causes (16,17). Similar results were obtained in our study.

In the study by Antonelli et al., the expected mortality rate according to the SAPS II score of the patients was approximately 34%. In the study by Destegul et al., the expected mortality rate according to the APACHE II score was approximately 95% (7,18). In another study, this rate was found to be %73 (19). In our study, the mean expected mortality rate was %38 according to the APACHE II score.

Since there are no proven guidelines, the appropriate timing to perform tracheostomy in the ICU in critically ill patients followed in MV varies according to the medical conditions of the patients, the foresight of the intensive care physician, and communication with the families of the patients (20). General view is that mechanical ventilation can be opened between 2-10 days (21). In some studies conducted in Turkey, the number of intubated days until tracheostomy is opened varies between a minimum of 8.20±5.44 days and a maximum of 19.51±10.23 days (13,16,17). In our study, the number of days to intubate was found to be 20.3±7.9 (7-48). This period is long. In fact, although the physicians in our intensive care unit decided to have a tracheostomy in accordance with the average, the main reason is that the families give their consent late in order to open a tracheostomy, which is obligatory. We observe that this situation is more evident especially in elderly patients. In another study, they reached the same results as ours (22).

Bleeding not requiring transfusion or surgery, subcutaneous emphysema, paratracheal insertion of the cannula, injury to the posterior tracheal wall, short-term hypoxia, and stoma infection are the most common complications in percutaneous techniques. In the percutaneous tracheotomy series of 827 cases, perioperative mortality was 0.6%, perioperative complication rate was 6%, and early postoperative complication rate was 5% (23). In our study, we had early complications in 11 patients and late complications in 2 patients.

There are studies reporting different results regarding bleeding from PT complications (8). Studies show that minor bleeding due to PT procedure is 1.5-5.2% and major bleeding is 0.75-2.6% (16,17,24). It has been reported that minor bleedings are seen in prolonged procedures and can be controlled with compression, ligation is required in major bleedings, and it has been shown that blood loss in the form of leakage from the stoma is 50-100 ml (8).

The main early complication of PT is bleeding in the anterior tracheal wall. It can be controlled by pressure or sewing. Major bleeding occurs in less than 5% of cases and is typically venous. Catastrophic bleeding is rarely seen and in most cases it is seen in the late period due to tracheo-innominate artery fistula. Tracheo-innominate artery fistula is a rare but life-threatening complication encountered during PT placement. The frequency rate is 0.3%. Fatal aortic arch laceration was reported as an early complication of PT in one case (25,26). These complications should be identified in the early period; emergency neck exploration and appropriate surgical intervention should be performed.

Opening the PT above the cricothyroid membrane increases the likelihood of tracheal stenosis, while opening it below the 4th tracheal ring increases bleeding complications (27). In a study, the rate of tracheal stenosis was reported as 5.7% (17). In our study, this rate was only 1%.

The incidence of mortality associated with PT procedure varies between 0-8% in the literature (28,29). In our study, mortality was detected in 1 patient. We have developed hypoxia after pneumothorax due to the paratracheal location of the tracheostomy and lost the patient. Some authors recommend routine use of fiberoptic bronchoscopy to prevent paratracheal placement (30).

In the study of Karasu et al., 25.7% of the cases were discharged. 48.5% of them died (22). In our study, intensive care treatments were completed in 30.9% of our cases. 10.3% of the cases were transferred to their homes and 20.6% of them were transferred to the services. 62.9% of our cases died.

CONCLUSION

It was observed that PT is a simple procedure that can be performed at the bedside and has low complication rates.

Study Limitations

The main limitation of our study is that the people who performed the procedure were not the same, it was not known how many times these people performed the procedure, and the study was a retrospective study.

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Research Article

Social Determinants of Hip Fractures in Elderly Patients–A Case-Control Study

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Abstract

Aim: Hip fractures are common orthopedic traumas and are known as a problem in terms of public health, particularly among the elderly. Preventing fractures and determining risk factors are critical in reducing morbidity, mortality, and social and economic burden. The purpose of this study was to examine the social determinants affecting hip fractures.

Material and Methods: This case-control study was conducted with a case group of 108 (36.1%) patients and a control group of 191 (63.9%). Hip fracture status was selected as the dependent variable in the study. The independent variables were marital status, place of residence, single-story or multi-story residence, use of stairs, use of assistive devices, cohabitants, working status, chronic disease status, education status, fixed income status, health insurance, family history of hip fractures, fractures in the last five years, getting help in daily work, smoking, fear of falling, and perception of general health status.

Results: Marital status, cohabitants, chronic disease status, having a fixed income, having health insurance, fear of falling, and perception of general health differed to a significant extent between the case and control groups. Nonetheless, no statistically significant difference was found between the groups regarding their places of residence, living in whether single-story or multi-story residences, the use of stairs, assistive device usage, active employment status, education status, family history of hip fractures, fractures in the last five years, getting help in daily work, and smoking.

Conclusion: Social factors affect the risk of hip fracture. Clinicians should be alert to the importance of this issue and raise the awareness of elderly patients.

Keywords: Hip fractures; orthopedics; risk factors; social determinants; elderly patients

INTRODUCTION

Hip fractures, a global public health problem, are generally seen in the elderly and have gained more importance with the increasing average age expectation of society with the advancing medical developments. Hip fractures include neck, trochanteric, and subtrochanteric regions proximal to the femur. While it is predicted to affect approximately 18% of women and 6% of men, the number of hip fractures, which was 1.66 million in 1990, is expected to reach 6.26 million in 2050 (1,2). Ninety percent of hip fractures cases in the geriatric population occur after a simple fall (3). The incidence of these fractures, often a consequence of low-energy trauma, increases with age. It constitutes approximately 20% of the workload in orthopedic traumas (4). Studies on risk factors have shown that factors such as racial differences, gender, decrease in bone mass and related fracture history, low activity, family history of hip fracture, smoking, and corticosteroid use increase the risk (5,6). In addition, patients may have substantial comorbidities and impaired cognitive functions (7). Hip fractures are usually treated surgically to return to daily life early and experience minimal complications, except for patients with poor general condition who cannot handle anesthesia. Nevertheless, hip fractures cause severe morbidity and mortality (8). Post-surgical mortality increases even more among patients with comorbidities. It was shown that the mortality after fracture rises to 20-

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24%; 40% of the patients cannot walk unaided, 60% need help, and 33% are entirely dependent (9). Patients who have experienced hip fractures have a doubled likelihood of mortality within one year following the development of these fractures development compared to age-matched control groups (10).

Treatments developed in recent years to prevent osteoporosis and treat age-related diseases, reduced body mass index, healthier elderly populations, improved functional ability, and various fall prevention measures have contributed to reducing the incidence of age-related hip fractures (11). Despite this, medical, psychosocial, and mechanical complications cause hospitalization, treatment process prolongation, and rehabilitation delay. The long treatment, care, and rehabilitation process puts a severe economic burden on the patients' families and the countries' health systems. Due to all these effects, studies are carried out on hip fracture prevention, treatment, postoperative care, and rehabilitation processes. In the present study, that researchers aimed to identify the risk factors associated with hip fractures among patients who are older than 65 years old. Since studies on the social determinants of hip fractures are limited, this study is expected to make a contribution to the relevant literature.

MATERIAL AND METHOD

This case-control study was carried out at Kafkas University Faculty of Medicine Hospital Hospital Orthopedics and Traumatology Clinic. The case group consisted of patients over 65 with a history of hip fractures. Those with no history of hip fracture at a similar age were selected for the control group. The control group was formed for each case at a ratio of 1:2. The sample of this study excluded individuals younger than 65 years old, those staying in a nursing home, and those who refused to participate. One hundred and ninety-one (63.9%) people in the control group and 108 (36.1%) in the case group were reached. The study was performed using a data collection form created by screening the literature. The form was administered in person to the patients in both groups.

The study's independent variables are marital status, place of residence, single-story or multi-story residence, use of ladders, use of assistive devices, cohabitants, active working status, presence of chronic disease, education, fixed income, health insurance, first-degree hip fracture history, any fracture in the last five years, assistance in daily work, smoking, fear of falling, and perception of general health status. The ethics of the study were obtained from the Ethics Committee of the Faculty of Medicine of Kafkas University with the protocol number 80576354-050-99/244 on 23/11/2021. Both verbal and written (informed consent) consent was obtained from the study participants. The study was conducted per the Declaration of Helsinki.

Data were analyzed using the SPSS version 21.0 program (IBM Corp. Armonk, NY, USA). Descriptive statistics were evaluated as frequency and percentage values, and the categorical variables were analyzed using the Chi-squared test. Numeric variables were tested for normality assumptions using the Kolmogorov-Smirnov test. Median, largest, and smallest values, and 1st and 3rd quartiles and variables were evaluated. The Mann Whitney U test was applied to analyze the significance of differences between two groups of numeric variables. The statistical significance value was taken as 0.05.

RESULTS

In the study, there were 108 (36.1%) people in the case group and 191 (63.9%) in the control group (Table 1). The median age, 1st and 3rd quartile values, and the largest and smallest values in the case and control group patients were determined as 76 (71-81.50) (min 66-max 92) and 75 (71-81) (min 66-max 95). When the median ages of the patients in the two groups were examined, they had no statistically significant difference (p=0.568). In addition, when the two groups were analyzed in terms of their gender distributions, no statistically significant difference was revealed (p=0.315). Therefore, case and control groups were matched in age and gender.

While the rate of widowed and unmarried was 41.7% in the case group, it was 24.1% in this control group. A statistically significant difference was identified between the marital status distributions of the case and control groups (p=0.002). When the place of residence, type of house, use of stairs, and use of assistive devices were examined, no significant variation was observed between the participants in the two groups (p=0.162; p=0.938; p=0.480; p=0.372, respectively). While the rate of those living alone in the case group was 8.3%, it was 4.7% in the control group. In the examination of the patients in the two groups regarding the people they lived with, a significant difference was found (p =0.002). While the presence of chronic disease was 63.9% in the case group, it was 46.1% in the control group, and this difference was found significant (p=0.003). While the rate of those with fixed income was 79.6% in the case group, this rate was 88.0% in the control group, and this difference was significant (p=0.047). While the rate of those with health insurance in the case group was 79.6%, it was 88.5% in the control group; this result revealed a statistically significant difference between the groups (p=0.038). While the rate of those with a fear of falling was 50.0% in the case group, this rate was 34.0 in the control group, and this difference was statistically significant (p=0.007). When people were asked how they found their general health status, the rate of those who expressed themselves as bad in the case group was 33.3%, while this rate was 19.9 in the control group. According to the analysis outcomes, this difference was statistically significant (p=0.003). No significant difference was determined between the two groups when the participants were examined regarding active employment status, education status, presence of a hip fracture near the first degree, fracture in the last five years, getting help in daily work, and smoking.

DISCUSSION

Risk factors of hip fractures, which become more critical with increasing aging, are also being investigated in all

aspects. Among these, social, cultural, and economic determinants are essential. In addition, the relationship between patient-specific factors such as comorbidity, familial conditions, and smoking with hip fractures has recently increased its importance. In our study, significant differences were found between the case group and the control group in terms of some determinants. Marital status, cohabitation, chronic disease status, having a stable income, having health insurance, fear of falling and general health perception were significantly different between the case and control groups.

Men and women are complementary to each other. Especially in old age, supporting each other physically, mentally, and socially is essential. Therefore, marital status is vital in terms of health. Previous studies have shown the relationship between marital status as a social determinant and hip fracture risk. In this study, the marital status category of widowed and single women was significantly more frequently found in the case group. In a study conducted in Sweden, the risk of hip fracture was lower in married women (12). A similar study reported that marital status was related to the risk of hip fracture, and hip fracture was less common in married people (13). Marital status may also affect the mean age of hip fracture (14). Considering the cultural norms in the region where the study was conducted, people generally live with their spouses and children. Therefore, the number of patients living alone in the study was small. However, the rate of living alone in the case group was significantly greater than the rate identified in the control group. A previous study demonstrated that living alone is related to an elevated risk of hip fracture (13). At the same time, living alone increases mortality after hip fracture (15).

When the places where the patients lived were evaluated, while those living in rural areas were more frequently encountered in the control group, those living in urban areas were more prevalent among the patients in the case group. However, these differences were insignificant. In a study by Okubo et al., the relationship between hip fracture and urban and rural settlements was evaluated. No difference was found in men, but an increase in the femoral neck and trochanteric fractures was observed at specific age ranges in women living in urban areas (16). Likewise, a systematic review evaluating the relationship between place of residence and hip fracture showed that the risk of hip fracture in rural areas is lower than in urban areas (17). Ladder usage and multi-story homes can pose a risk for hip fractures. Therefore, making a bar to hold onto the sides is essential. In addition, it is helpful to consider factors such as slippery floors, electronic equipment cables, and the placement of furniture that will tend to fall in the house. The study questioned the type of house and the use of stairs among the participants in the two groups. In both the case and control groups, the proportion of those living in a one-story house and those who did not use ladders was higher and similar. This finding may be explained by the geographical and architectural characteristics of the region where the study was conducted. Ladders were shown to cause hip fractures in the home (18).

Assistive device use rates were found comparable between the two groups of patients. Patients using assistive devices were more common than those who did not in both groups. Stolee et al. reported using assistive devices and unbalanced gait as risk factors for hip fracture (19). Most patients in the two groups were not actively working. When the patients who received help in their daily work were questioned, no significant variation was detected between the groups. A large majority of patients did not receive assistance in their daily work. Smoking is a considerable risk factor for healing and complications before and after hip fracture (20, 21). In the study, it was seen that there was no significant difference between the two groups. The patients were questioned about any fracture history within the last five years and hip fracture history in their first-degree relatives. No significant difference was observed between the groups. A study by Kanis stated that having a family history of hip fracture increases the risk (22). The same study showed that hip fracture risks rise after a fracture in any part of the body. It was reported that this risk increases most after hip and spine fractures. The relationship between hip fractures and chronic diseases has been investigated in the past. Many diseases, such as cognitive disorders, osteoporosis, diseases that impair gait (Parkinson's, vertigo, etc.), malnutrition, morbid obesity, etc., increase the risk of hip fracture (19,22,23). Consistent with the literature, the presence of chronic diseases was encountered at a significantly higher rate in the patients in the case group.

Hip fractures mainly occur after a fall. Therefore, it is estimated that the fear of falling, which was determined to be at a significantly higher rate in the case group, is an expected result. Anxiety in patients may also affect this (24). Fear of falling may cause patients to move less and increase morbidities such as muscle wasting and thromboembolism. It can also increase the use of assistive devices and prolong the rehabilitation process. When it was questioned how the patients evaluated their general health status, a significantly higher rate of the patients with hip fractures described their health status as poor compared to those in the control group. This may be related to the post-traumatic psychology of the patients. A hip fracture can affect patients' physical, social, and emotional functions (25).

Economic competence and educational status are social factors that affect human health. Relationships between these determinants and hip fracture are evaluated. It was reported that individuals with higher education have a lower risk of hip fracture than those with lower education (13). This study showed no statistically significant difference between the education level distributions of the two groups. Those with fixed income and health insurance were significantly higher in the control group. On the other hand, the prevalence of these parameters was also relatively high in the case group. This situation

may be related to the social and economic opportunities of the region where the study was conducted. It was reported that those with good economic status have a lower incidence of hip fractures and a relationship with a hip fracture at older ages (14).

The limitation of this study is that its outcomes cannot be generalized to the general population as it is a case-control study. In addition, the answers given by the participants may have been affected by the memory factor.

CONCLUSION

In conclusion, social determinants are important as risk factors in hip fractures. Social determinants are like iceberg phenomenon in the risk factors of hip fractures. Therefore, clinicians should raise awareness of vulnerable patients about hip fractures in this age population.

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MEDICAL RECORDS-International Medical Journal

Research Article

Investigation of the Opinions of the First-Year Students of Dentistry Who Go to Online Education on Anatomy Education After the Kahramanmaraş Earthquake

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Abstract

Aim: The aim of the study was to examine the opinions of first-year dentistry students who switched to online education after the Kahramanmaraş earthquake on anatomy education.

Material and Methods: A total of 82 students, 38 males and 44 females, participated in the study. The questionnaire consisting of 14 questions was applied online. The questionnaire was Likert-type and calculated as flat coded questions (completely disagree 1 point, disagree 2 points, no idea 3 points, agree 4 points, completely agree 5 points). The questions were calculated as reverse coded because they expressed negativity. There were 13 questions in the questionnaire, except for the open-ended and gender-reporting question, and the highest score was 65 and the lowest score was 13.

Results: The expected frequency of completely agree is 15.3 (40.2%), while the observed frequency is 21 (55.3%). Statistically, there is a difference between expected and observed values ($p<0.05$). In the question "I participated in anatomy courses taught online", the expected frequency of completely agree was 1 (2.3%) while the observed frequency was 0 (0%). Statistically, there is a difference between expected and observed values ($p<0.05$).

Conclusion: Since the anatomy course has too many subjects, the subject contents are difficult to learn, and it is also a basic course, it is important to conduct theoretical and practical lessons face-to-face instead of online.

Keywords: Earthquake, online education, anatomy

INTRODUCTION

Among the goals of higher education institutions is to educate students to be able to take responsibility in the relevant field and to be able to provide active and effective service (1-3). Education is an important process that is living and changing due to its structure and is subject to changes from time to time (4).

Anatomy is one of the basic disciplines of medical education. It is the oldest medical science that provides a lot of information about the human body. It examines the structure, functions, position, and normal shape of the human body (5). Anatomy is a visual science and has an important place in the education and training programs of medical and dental faculties (6). Feedback from students can be shown as an important guiding and driving force during all these changes. Feedback from students has an important place in overcoming the difficulties to be experienced in the face of changes in educational programs and in ensuring better communication between faculty members and students (7). The degree of acquisition of the knowledge aimed to be gained by the students with the anatomy course is the basis for the courses and studies that the students will take in the following years. From this

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point of view, students should understand the subjects given within the scope of this course and be well-trained (8). Factors such as the difficulty in transferring knowledge to students, the difficulties brought by practical education, and the length of the education process have entered a process of change with technology (9). These changes have gained a new dimension with the development of technology and the diversification of instructional materials (5,10).

In our study, the opinions of 82 students studying in the first year of Ordu University Faculty of Dentistry were taken. In the second semester of the first year at Ordu University Faculty of Dentistry, anatomy education is given as 2 hours theoretical and 2 hours practical courses weekly. 1 midterm exam (midterm), 1 final exam and 1 make-up exam are held. Exams are evaluated out of 100 points. 40% of the passing grade is the midterm exam and 60% is the final exam. Students with an average of 60 and above are considered successful. Theoretical courses are lectures with slide support and applied courses are model work and lectures.

The aim of the study was to examine the effects of the first-year dentistry students who received face-to-face education on their anatomy education when they switched to online education after the February 6, 2023 Kahramanmaraş earthquake.

MATERIAL AND METHOD

Before starting the study, ethics committee permission dated 09.06.2023 and numbered 165 was obtained from Ordu University Clinical Research Ethics Committee. In the 2022-2023 academic year, 82 first-year students studying at Ordu University Faculty of Dentistry were included. February 6, 2023 the students who received face-to-face education until the Kahramanmaraş-based earthquake were asked about their opinions on anatomy theoretical and practical courses with the transition to online education after the earthquake. In the study, previous student surveys were utilized while creating the measurement tool.

In the study, 14 questions were asked, one of which was open-ended. The answers to the questions were marked as completely disagree, disagree, no idea, agree, and completely agree. For the safety of the study, students were asked not to write their names and surnames.

Statistical Analysis

IBM SPSS 26 package program was used for statistical analysis. The data in the study were analyzed for normal distribution by considering 5 parameters (Skewness-Kurtosis, Std/Mean, Q-Q Plots, Histogram and Shapiro Wilk Test). Normally distributed parameters with sufficient data were shown as Mean±Std and Independent Samples T Test was used for pairwise comparisons. Fisher's Exact Test (smallest expected value <5) was applied in the frequency analysis of the survey questions according to gender. The questions with the highest and lowest scores were shown in the frequency distribution graph according to gender. In the study, $\alpha=0.05$ and $p<\alpha$ were considered significant.

RESULTS

Of the 82 students who participated in the study, 38 were male and 44 were female (Table 1).

Table 1. Total score by sex

	Score	Sig. (p)
Female	45.19±9.86	0.149
Male	41.64±9.34	

Parametric data were shown as Mean±Standard Deviation (mean±std) and Independent Samples T Test was used for statistical analysis

The Likert-type questionnaire was calculated as flat coded questions (completely disagree 1 point, disagree 2 points, no idea 3 points, agree 4 points, s completely agree 5 points). Since some questions had negative expressions, they were calculated as reverse coded. Reverse-coded questions were calculated as (completely agree 1 point, agree 2 points, no idea 3 points, disagree 4 points and completely disagree 5 points). There were 13 questions in the questionnaire; the highest score was 65 and the lowest score was 13 (Table 2). When the total score was analyzed according to gender, it was seen that the score of women was 45 and 41 for men and the p-value was 0.149. There is no difference between male and female students.

There is no statistical difference between genders in the total score of the questionnaire ($p>0.05$).

The expected frequency of completely agree is 15.3 (40.2%), while the observed frequency is 21 (55.3%). Statistically, there is a difference between expected and observed values ($p<0.05$). In the question "I participated in online anatomy courses", the expected frequency of completely agree was 1 (2.3%) while the observed frequency was 0 (0%). Statistically, there is a difference between expected and observed values ($p<0.05$).

In this study, the question with the highest score was "I watched video recordings of online anatomy lectures that I could not attend" (Figure 1). While 25 students in the female group and 14 students in the male group answered completely agree (5 points), 13 students in the female group and 19 students in the male group answered agree (4 points).

The question with the lowest score in this study was "The lack of face-to-face interaction make learning difficult" (Figure 2). This question was reverse-coded and scored. While 10 students in the female group and 13 students in the male group answered completely agree (1 point), 13 students in the female group and 11 students in the male group answered agree (2 points).

Table 2. The questions were shown as (%) by sex

		Completely disagree	Disagree	No idea	Agree	Completely agree	Sig. (p)
Should have continued face-to-face training after the earthquake disaster *	Female	25	22.7	20.5	27.3	4.5	0.598
	Male	39.5	23.7	10.5	23.7	2.6	Fischer's Exact Test
After the earthquake disaster, it is the right decision for schools to switch to online education	Female	4.5[a]	18.2[a]	18.2[a]	31.8[a]	27.3[a]	0.045
	Male	0[a]	18.4[a]	7.9[a]	18.4[a]	55.3[b]	Fischer's Exact Test
I prefer to teach theoretical anatomy courses face to face *	Female	9.1	11.4	27.3	29.5	22.7	0.724
	Male	18.4	13.2	18.4	26.3	23.7	Fischer's Exact Test
I prefer to teach theoretical anatomy courses on an online platform	Female	13.6	22.7	31.8	18.2	13.6	0.676
	Male	18.4	23.7	18.4	18.4	21.1	Fischer's Exact Test
I participated in online anatomy lectures	Female	20.5[a]	20.5[a]	0a	47.7[a]	11.4[a]	0.042
	Male	5.3[a]	28.9[a]	18.4[a]	4.7[a]	0[b]	Fischer's Exact Test
I watched video recordings of online anatomy lectures that I could not attend	Female	0	6.8	6.8	29.5	56.8	0.177
	Male	2.6	2.6	7.9	50	36.8	Fischer's Exact Test
Online teaching of theoretical anatomy lessons was more useful as the video recordings could be watched again	Female	4.5	6.8	22.7	36.4	29.5	0.855
	Male	5.3	10.5	15.8	31.6	36.8	Fischer's Exact Test
Online teaching of anatomy courses saves time	Female	6.8	20.5	15.9	31.8	25	0.475
	Male	2.6	13.2	18.4	23.7	42.1	Fischer's Exact Test
There was no difference in the quality of education with online or face-to-face teaching of theoretical anatomy courses	Female	22.7	29.5	29.5	11.4	6.8	0.736
	Male	15.8	39.5	21.1	13.2	10.5	Fischer's Exact Test
Lack of face-to-face interaction made learning difficult*	Female	6.8	22.7	18.2	29.5	22.7	0.734
	Male	7.9	13.2	15.8	28.9	34.2	Fischer's Exact Test
It was the right decision to make the theoretical anatomy course exam online	Female	6.8	11.4	13.6	25	43.2	0.658
	Male	2.6	13.2	5.3	26.3	52.6	Fischer's Exact Test
The online anatomy course provides a healthy flow of questions and answers	Female	6.8	13.6	25	38.6	15.9	0.622
	Male	0	15.8	21.1	42.1	21.1	Fischer's Exact Test
The theoretical anatomy lectures given online were sufficient	Female	2.3	9.1	13.6	54.5	20.5	0.518
	Male	0	2.6	15.8	68.4	13.2	Fischer's Exact Test

The difference between expected and observed frequencies according to gender in the questionnaire parameters was evaluated by Chi-Square test. The same letters indicate same group and different letters indicate different groups

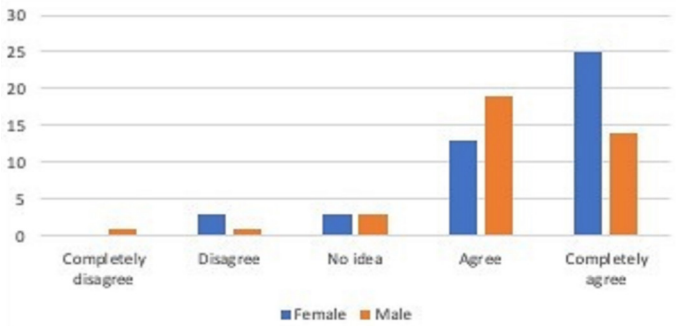

Figure 1. I watched video recordings of online anatomy lectures that I could not attend

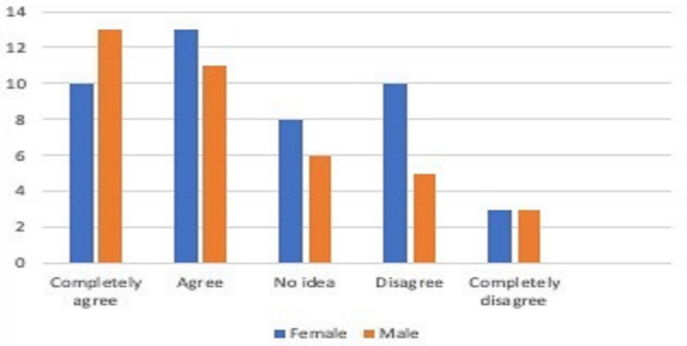

Figure 2. The lack of face-to-face interaction made learning difficult

DISCUSSION

February 6, 2023 The earthquakes centered in Kahramanmaraş affected the education process of universities in the region, as in every field. After the disaster, students' education was disrupted primarily due to the lack of suitable conditions for shelter and studying. Previously, higher education switched to online education on March 6, 2020 due to the COVID-19 pandemic.

The number of dental faculties in Türkiye is increasing and there are differences between them regarding the number of students, buildings, technical equipment and academic staff. Feedback in education is made to get students' opinions for observations, changes and improvement studies related to the education process. In this context, student feedback helps instructors review the educational process and is used by administrators as a source of data on the programs implemented (11). Determining how the quality of education services is perceived by students indicates that the university administration attaches importance to quality studies in education.

Çan et al. In a study, 60 medical and 74 dental students were asked an online questionnaire consisting of four questions. According to the results of the survey, 81.3% of the students expressed anatomy courses with a concrete concept and 18.7% with an abstract concept. The reason for this is that the anatomy course is effective in learning the human body, which consists of tangible, visible structures (12). The study also found that the anatomy course was a major source of burden and stress for students studying dentistry. In addition, almost all students felt that the course was important. The study emphasised the importance of making the anatomy course attractive, avoiding unnecessary detail and detail, and focusing on clinical situations that they will use in their professional lives (12).

In our study, 22.7% of the women completely agreed and 29.5% agreed with the question "lack of face-to-face interaction makes learning difficult", while 34.2% of the men completely agreed and 28.9% agreed.

Mobile learning and e-learning models were developed with the help of technology. A comprehensive strategy for online learning in disaster situations was developed in cooperation with all institutions. This strategy includes making improvements in access to education during disasters, organizing activities to inform students and their families, strengthening the infrastructure, and equipping educators. Considering all these situations, the Kahramanmaraş earthquake brought the importance of online education back to the agenda. Teli et al. argue that in order to make the education system more efficient, appropriate designs and comprehensive strategies should be developed by considering the needs of the student (13).

Singal et al. investigated the challenges of digital anatomy education in India in 2020 among dental and medical students. 58% of the participants stated that they preferred video-recorded distance education (14).

Kelsey et al. concluded that students could pause and resume the video according to their own pace of study, replay the recording, and be free to understand the lesson (15).

Turhan and Yakut asked 64 physiotherapy students the question "I prefer to listen to anatomy lectures on the internet", 54.7% of the students chose to disagree and completely disagree (16).

Similarly, in our study, 52.2% of women and 63.1% of men agreed with the question "lack of face-to-face interaction makes learning difficult". Looking at the survey responses, the participants think that the decision to switch to online education is not beneficial. In addition to the positive effects of online education, it was concluded that participation in anatomy courses taught online was not achieved at the desired rate. When the lowest-scoring answer was evaluated, it was concluded that online education made learning difficult.

Pamay et al. in their 2017 study, they asked the question of how many hours a week dentistry students spend in the anatomy laboratory in North American countries. The rate of 62.50% choosing more than 4 hours and 18.75% choosing 4 hours shows the importance they attach to anatomy practical training (17).

CONCLUSION

As a result, satisfaction levels with anatomy courses were examined in our study. Dental students stated that anatomy education was more efficient face-to-face. Since the anatomy course has too many subjects, it is difficult to learn the subject content, and it is also a basic course, it is important to conduct theoretical and practical courses face-to-face instead of online.

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

Ethical approval: *Before the study, ethical approval was obtained from the Ordu University Clinical Research Ethics Institution (No: 2023/165).*

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Research Article

Where Should We Focus in Emergency Orbital Trauma?

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Abstract

Aim: To describe the most common findings in orbital trauma and to support radiologic decision making by comparing them in 7 pathology regions.

Material and Methods: A total of 190 patients (119 males and 71 females) participated in the study. Orbital injury pathologies were documented and compared in seven regions. The most typical results of orbital tomography were determined. Binominal regression analysis was also performed for each trauma region.

Results: 190 orbital CT scans showed 13.7% orbital bone fractures (n=26), 7.9% bulbus pathology (n=15), 2.6% vitreous pathology (n=5), 2.1% extraocular muscle pathology (n=4), and 6.3% (n=13) retrobulbar pathology. The most common globe pathologies were lens displacement and globe rupture. Retrobulbar fat plane changes (4.2% n=8) were the most common pathology in the region. Periorbital edema was the most common periorbital disease in 86.3% of cases (n=164). When evaluated using cross-tabulations between the seven pathologic regions, the relationship between bone pathology and retrobulbar area and between globe and vitreous was statistically significant ($p<0.05$). In binominal regression analyses, 5 trauma models were significant and showed more than 80 percent success in predicting trauma location ($p<0.05$).

Conclusion: Orbital fractures and pathologies of the retrobulbar space, globe and vitreous are interrelated. Radiologists should be familiar with orbital fracture patterns, potential soft tissue injuries and ocular anomalies and should be able to evaluate the relationship between pathologies.

Keywords: Orbital traumas, orbital tomography, computed tomography, prevalence

INTRODUCTION

Visual acuity and extraocular muscle motility are the two most crucial ophthalmologic functions to be assessed urgently in a patient with severe orbital damage (1). Due to the severity of the head injury, the degree of periorbital soft tissue edema, the inability of certain patients to cooperate, and the lower level of awareness in obtunded people, assessing these abilities can occasionally be challenging. As a result, computed tomography (CT) now plays a significant part in the orbital evaluation of patients with severe trauma (1, 2). Admissions to emergency rooms due to traumatic eye injuries are widespread everywhere. The diagnosis depends on the clinical examination, ocular sonography, and CT (3). Numerous ocular sequelae can result from blunt orbital damage. Ocular trauma more than doubles the risk of lens dislocation and retinal detachment after cataract surgery. The posterior lens can protrude into the vitreous far more frequently than the anterior lens can dislocate. Concomitant ocular injury, such as retinal tear or detachment, hyphema, or globe rupture, may occur in patients with lens displacement (4). A possible blinding complication of craniofacial trauma is retrobulbar bleeding, however prompt ocular examination might be challenging in some circumstances, and there are no established guidelines for canthotomy/cantholysis. Despite being a relatively uncommon sign on CT, tenting of the globe should alert the doctor to the need for action (5). Patients who sustain eyelid or orbital injuries may go to the emergency room or their primary care physician to have their injury assessed. These patients frequently have discomfort and bleeding around their eyes, which may

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make it challenging to assess them. Eyelid tears, orbital hemorrhages, intraorbital foreign objects, and orbital fractures are the most frequent injuries. Many acute eye injuries need quick medical treatment (6).

In this study, we set out to ascertain the frequency of radiological findings in emergency room patients who had orbital damage and had undergone orbital tomography.

MATERIAL AND METHOD

This study was approved by Kafkas University the Clinical Research and Ethics Committee. Due to the retrospective nature of the study, the requirement for written informed consent was waived.

Patients Selection

Orbital CT examinations requested from the emergency department between 01.01.2019 and 01.05.2022 were retrospectively scanned. 210 patients were included in the study. 4 patients were excluded from the study because of diffuse artifact in the images, and 9 patients due to the absence of orbital trauma etiology. Orbital CT reports of all patients were reviewed. Orbital CT reports were divided into 7 groups according to their pathology as Bone, Globe, vitreous, extraocular muscles, retrobulbar area, optic nerve and periorbital area. Orbital pathologies were recorded binomially in 7 regions where they were found. In 7 patients, it was excluded because there was not enough data in all fields in the reports.

Evaluation of CT Images

CT scans were done with Toshiba Alexion 32 Multi-Slice, Canon Medical Systems Corporation (Tochigi, Japan). In our radiology clinic, the orbital CT protocol consisted of 1mm coronal, axial and sagittal sections. Patients' age, gender, the patients' age, gender, orbital pathology in which area, characteristics of orbital pathologies were recorded and compared.

Statistical Analysis

The Statistical Packages for Social Sciences (SPSS Chicago, IL, USA) version 25 was used for data analysis. All variables except age are in categorical variables. Categorical variables were evaluated with cross tables among themselves. There were no outliers or multicollinearity in the data set. To determine the most important categorical variable for each location, a binominal regression model was applied independently to each region. The most significant pathologic location, model success, the amount of variation explained (R2), and the significance of the regression models were all examined. P value <0.05 was considered statistically significant.

RESULTS

In the study, 190 patients, 71 females and 119 males, were evaluated. The mean age of the patients was 35.34±23.24 years. 13.7% (n=26) orbital bone fracture, 7.9% (n=15) bulbus pathology, 2.6% (n=5) vitreous pathology, 2.1% (n=4) extraocular muscle pathology, 1% (n=2) optic nerve pathology, 6.3% (n=12) retrobulbar pathology, were all detected in 190 orbital CT scans (Table 1). In all patients 5.2% (n=10) orbital floor fracture, 3.1% (n=6) medial wall fracture, 2.6% (n=5) orbital roof fracture, 1.6% (n=3) mixed fracture and 1% (n=2) lateral wall fracture was detected. The most frequent globe pathologies were lens displacement and globe rupture. 2.6% (n=5) of the patients had vitreous hemorrhage found. Figure 1-4 presents glob perforation cases, lens dislocation cases and fracture cases. Four individuals (2.1%) had medial rectus muscle thickening. In 2 individuals, the optic nerve had thickened. Retrobulbar fat planes changes (4.2% n=8) were the most prevalent pathology in the region. In 86.3% (n=164) of cases, periorbital edema was the most prevalent periorbital disease. Other results included hemorrhage in the maxillary sinus 5.3% (n=10), foreign body 3.2% (n=6), subcutaneous emphysema 2.6% (n=5), and hematoma 2.6% (n=5).

Table 1. Descriptive findings of 190 patients

		N:	%	N:190
Gender	Female	71	62.6	62.6%
	Male	119	37.4	37.4%
Age	35.34±23.24			
Orbital fracture	Floor	10	38.5	5.2%
	Medial wall	6	23.1	3.1%
	Roof	5	19.2	2.6%
	Mix	3	11.5	1.6%
	Lateral wall	2	7.7	1.0%
Globe	Lens dislocation	6	40.0	3.1%
	Globe rupture	4	26.7	2.1%
	Foreign body	2	13.3	1.0%
	Exophthalmos	2	13.3	1.0%
	Scleral plaques	1	6.7	0.5%
Vitreous	Vitreous hemorrhage	5	100	2.6%
EOM	Thickening of the medial rectus	4	100	2.1%
Optic nerve	Thickening of the optic nerve	2	100	1.0%
Retrobulbar	Heterogeneous retrobulbar fat	8	61.5	4.2%
	Retrobulbar air	3	23.1	1.6%
	Retrobulbar foreign body	2	15.4	1.0%
Periorbital	Edema	164	86.3	86.3%
	Hemorrhage in the maxillary sinus	10	5.3	5.3%
	Foreign body	6	3.2	3.2%
	Hematoma	5	2.6	2.6%
	Subcutaneous emphysema	5	2.6	2.6%

The association between bone pathology and the retrobulbar area, as well as the relationship between the globe and vitreous, were determined to be statistically significant when assessed using cross tables among the seven pathological regions (Table 2). It was shown that the retrobulbar area was impacted by bone fractures in the binominal regression analyses carried out for each location (Table 3). Globe pathologies and vitreous pathologies were significantly correlated. In the periorbital region paradigm, periorbital pathology was often present when the globe was afflicted. In the 5 stated models, more than 80% success was attained.

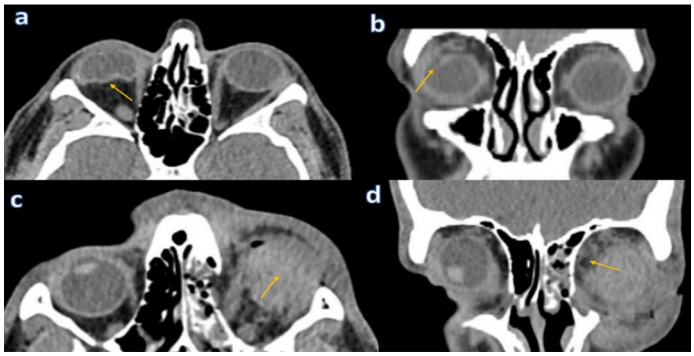

Figure 1. Cases of globe perforation: **1a.** 33 years old male patient with blunt trauma to the right eye showing irregularity in the posterior contour of the globe on axial CT image (arrow) **1b.** Coronal CT image shows a globe posterotemporal defect consistent with perforation (arrow) **1c.** Axial CT image of a 15-year-old male patient portrays increased vitreous density consistent with hemorrhage after trauma (arrow) **1d.** Coronal CT image of the same patient shows an intra-glob air focus (arrow) and contamination of the fat planes

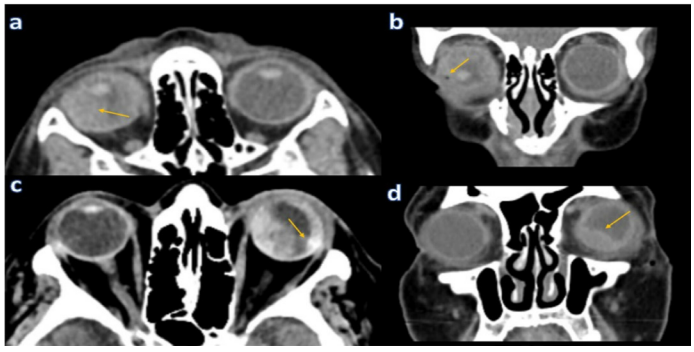

Figure 2. Lens dislocation and vitreous hemorrhage **2a.** A 33-year-old female patient is admitted to the emergency room because of glass in her eye. Axial CT image reveals diffuse vitreous hemorrhage (arrow) **2b.** Coronal CT image demonstrates millimetric air density in the globe consistent with perforation (arrow) **2c.** 69-year-old woman hit her left eye on a nightstand after a fall. The crystalline lens is dislocated posterolaterally in the left eye (arrow) **2d.** Coronal CT image of the same patient presents leveling hemorrhage in the vitreous (arrow)

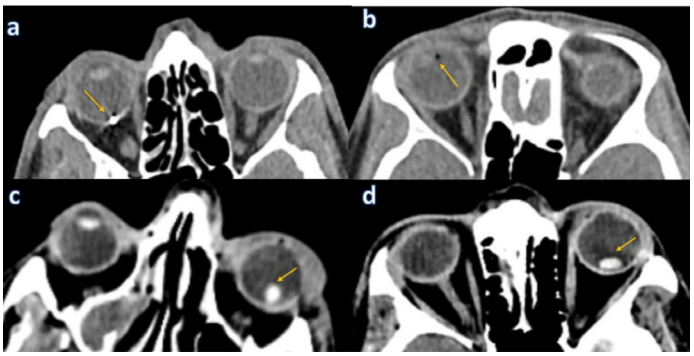

Figure 3. Foreign body, glob air focus and lens dislocation **3a.** 53 years old male patient with foreign body density inside the eye (arrow) **3b.** A 24-year-old woman presented with an intra-globe air focus on an axial CT image with a focus in the eye. Ophthalmologist detected corneal incision and iris problapse. The air finding is consistent with perforation (arrow) **3c.** A 31-year-old male patient is admitted to the emergency room due to battery. Axial orbital CT image reveals a dislocation of the lens of the left eye (arrow) **3d.** A 46-year-old woman has a dislocation of the left eye lens after an object from the kitchen cupboard fell into her eye (arrow)

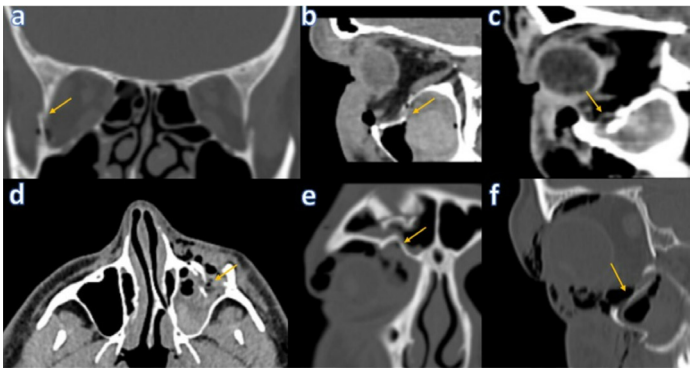

Figure 4. Fracture cases **4a.** Coronal CT image presents a fracture in the orbital lateral wall **4b-f.** Sagittal orbital CT image shows displaced fracture of the orbital inferior wall and air densities **4c-d.** 34 years old male bear attack with diffuse displaced fractures to the inferior wall of the orbit, air images and hemosinus **4e.** Coronal CT image visualized a displaced fracture in the upper wall of the orbit

Table 2. Crosstab of the distribution of orbital pathologies (P values)

	Bone	Glob	Vitreous	EOM	Optic N	Ret	Periorbital
Bone	X	0.967	0.367	0.421	0.571	0.004*	0.046*
Glob	0.967	X	0.000*	0.554	0.026*	0.023*	0.000*
Vitreous	0.367	0.000*	X	0.740	0.815	0.556	0.707
EOM	0.421	0.554	0.740	X	0.835	0.121	0.411
Optic Nerve	0.571	0.026*	0.815	0.835	X	0.004*	0.265
Retrobulbar	0.004*	0.023*	0.556	0.121	0.004*	X	0.016*
Periorbital	0.046*	0.000*	0.707	0.411	0.265	0.016*	X

Table 3: Model successes and most significant variables according to Binomial Regression Analysis

	Model	R^2	Success (%)	Variable	Sig	Exp(B)	%95 CI
Bone	0.025	14%	86.3	Retrobulbar	0.006	7.815	1.819-33.570
Glob	0.000	31%	92.1	Vitreous	0.001	34.661	4.318-278.256
Vitreous	0.039	31%	97.4	Glob	0.001	46.037	5.040-420.508
EOM	0.390	17%	-	-	-	-	-
Retrobulbar	0.000	35%	95.3	Bone	0.005	8.060	1.869-34.755
Periorbital	0.001	20%	85.8	Glob	0.000	10.159	2.786-37.039

DISCUSSION

There was no discernible connection between ocular damage and an orbital wall fracture. Alarm symptoms for more serious visual injuries such retinal tears, detachments, open globe injuries, and extraocular muscle entrapment are all valid reasons to seek emergency ophthalmology care. The majority of orbital fractures do not normally require surgical treatment, pose little harm to eyesight (7). Blowing-in fractures seldom result in globular indentation. In cases of high-velocity trauma to the superolateral orbit accompanied by hypoglobus, motility restriction, and indentation of the globe on dilated examination, clinicians should be wary. Good visual, functional, and aesthetic results can be achieved with early identification and surgical excision of the compressive orbital bone fragments in a multidisciplinary manner (8). Fractures of the medial and orbital walls are frequent midface injuries. Due to the complicated architecture of the related bone and soft tissues, orbital fractures have a unique mechanism of trauma. When treating patients who appear with orbital damage, anatomical knowledge is crucial (9). The purpose of therapy is to reestablish physiologic and aesthetic function. The issue with orbital burst fractures is that they can cause an increase in orbital volume, which can lead to enophthalmos and hypoglobus. Bone fragments may also enter the orbital tissue and inferior rectus muscle, causing diplopia, gaze restriction, and tension. Finally, retinal edema, hyphema, and severe vision loss might result from orbital damage. While some instances can be treated conservatively, others could necessitate surgical intervention (10). In research examining the prevalence of ocular damage related to maxillofacial trauma from 2015 to 2020, a retrospective evaluation of 1677 patients with midface fractures at a Level I trauma center was performed. The most common cause of trauma was being beaten (63.8%). There was a statistically significant correlation between the mechanism of damage and ocular injury. Ocular damage was seen in 44.3% of assault patients and 78.6% of patients with gunshot wounds. 36% of patients experienced minor eye damage, while 10.5% experienced significant ocular injury. In 46.1% of cases, isolated orbital floor fractures were found. All patients with midface fractures should have ophthalmologic exams to help with clinical decision-making and stop further intraoperative eye injury (11). Following an orbital fracture, ocular pathology (OP) can range greatly in complexity and severity. When there has been orbital damage, there are either asymmetrical or symmetrical patterns of extraocular motility (OME) restrictions. 278 orbitals with wall fractures were retrospectively investigated as part of a study to see whether there is any correlation between higher OP after instances of orbital fractures based on the pattern of OME defects. OME restriction was observed to be significantly correlated with greater occlusal pathology following orbital damage. Ocular pathology was more prevalent in instances with symmetrical and asymmetrical OME limitations than in those without them, with odds ratios of 7.9 (95% CI: 2.3-27.2) and 5.22 (95% CI: 1.9-13) times greater respectively. A common finding in cases of orbital fracture is ocular pathology. Although doctors may expect ocular pathology in circumstances of any limitation of OME, symmetrical limitations of OME may increase the likelihood of intraocular damage (12). Radiology focuses on a study examining the clinical manifestation of entrapment and entrapment in the extraocular muscles. 2.8% of patients experienced clinical entrapment, whereas 67% described feeling "stuck" or "trapped." OME herniation was associated with increased risk for entrapment, diplopia, and irregular OME motility, but it also had a 7.9% positive predictive value for clinical entrapment. The independent positive predictive values for fat herniation and OME contour irregularity were 4.2% and 4.8%, respectively. Despite the fact that individuals with OME herniation appear to have a greater chance of being entrapped, this imaging result does not indicate clinical entrapment. The likelihood of entrapment was not increased by fat herniation or abnormal OME contours, and neither were they predictive. Only further CT should be used to support the primary physical examination-based diagnosis of orbital entrapment. Inadvertent inter-site transfers, sub-specialist consultations, and emergency surgical treatments may be carried out as a result of the notion that radiographic data imply orbital crises (13). An intense level one trauma center's treatment of orbital bone fractures was examined for injury patterns and cause. The group identified to be most impacted was between the ages of 20 and 29 (36%). Interpersonal violence was the most frequent cause (55%) followed by falls (20%) and road accidents (12%). The orbital floor was the location of solitary orbital bone fracture most frequently (40%). According to reports, the zygoma is the structure next to the orbit that is most frequently affected by impure orbital fractures (19%) (14). The most frequent cause was blunt injury in research looking at the frequency of major minor ocular damage or orbital fracture. Subconjunctival hemorrhage was the most typical injury (53.5%). Particularly in cases with severe damage coupled with globe rupture, the posterior segment findings of globe rupture (2.9%) and vision-threatening posterior segment symptoms such retinal tear and choroidal rupture (1.3%) were recorded as just one retinal detachment (0.2%) (15). Scleral irregularity was the most frequent CT finding in open globe damage, followed by crystalline lens displacement (54%) and vitreous hemorrhage (51%). The axial, coronal, and combined CT plans had sensitivity values of 74%, 65%, and 79%, respectively. Regardless of the kind and location of the globe damage, there was no significant difference noted between axial and coronal CT scans in the detection of open globe injuries. The sensitivity of identifying open globe injury of the coronal plane is much lower than axial and combined readings for posterior injuries and acute trauma, and the axial CT reading may be as good as a multiplanar reading for open globe injury detection. CT cannot detect open globe injuries with adequate accuracy in the absence of clinical and surgical signs (16). In our study, we showed the most common findings in orbital traumas and which areas may

be related to each other. Primary and secondary lesions may be overlooked in radiology examination. Following clues sometimes helps to find the primary lesion to catch secondary signs. Secondary findings such as intraocular fat herniation, OME trap, bone fragments are important. Improve your understanding of the extraocular muscles' connection to the fracture margins by using the coronal reconstruction.

The radiologist should focus on the orbit apex in patients who report of a sudden post-traumatic reduction in visual acuity to rule out fractures. The purpose of a CT scan in a hyphema case is to evaluate the posterior chamber and determine whether any related injuries are present (17). Look for the presence of foreign bodies and related orbital injuries when the vitreal hemorrhage is evident. The lens's look following cataract surgery should be known to the radiologist. Some ocular abnormalities, such as coloboma and staphyloma, might resemble an open globe damage. Radiologists need to be wary of wooden foreign bodies since they might seem like air and be hypoattenuating and linear (18).

Study Limitations

Our study is a single-center retrospective study. Emergency orbital traumas were evaluated in the secondary care center.

CONCLUSION

Various fracture patterns may develop from orbital trauma. The gold standard for assessing ocular trauma damage and choosing the most effective treatment option is CT. For a quick and precise diagnosis, it's crucial to be aware of the most prevalent pathologies and the related areas. The radiologist must comprehend and be conversant with fracture patterns, potential soft tissue injuries, and anomalies in the eye and globe in order to establish the proper course of therapy.

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Research Article

The Effect of Nomophobic Behaviors on Caring Behaviors in Nurses Working in Intensive Care Clinics

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Abstract

Aim: It is known that nomophobia, which occurs as a result of phone addiction, causes individuals to experience more anxiety, depression and sleep problems than usual, and their quality of life and work performance are adversely affected. In this study, it was aimed to determine the effect of nurses exhibiting nomophobic behaviors on their care behaviors.

Material and Methods: This research was conducted in a descriptive and relationship-seeking type. The minimum sample volume to be reached was calculated as 270 according to the known sample formula. The study was conducted with 284 nurses working in intensive care units. The research data were collected with Google Forms in February-May 2022. Introductory information form, Nomophobia Scale Caring Behaviors Inventory-24 were used to collect data.

Results: Nomophobia scores were moderate with 90.09±28.47, and caring behaviors scores were high with 124.05±18.49. A low negative correlation (r=-0.178, p<0.01) was found between the total score of the Nomophobia and the total score of caring behaviors.

Conclusions: In this research, it was found that nurses' nomophobic behaviors affected their caring behaviors negatively. To eliminate the negative effect of nomophobia on caring behaviors, we recommend that the awareness of intensive care nurses about phone dependency and the effects of this dependency be raised.

Keywords: Care behavior, intensive care clinics, nomophobic behaviors, nursing, smartphone addiction.

INTRODUCTION

It is asserted that almost half of the world's population used social media platforms actively and spent most of their time on the internet. Today, internet and social media use progressively becomes more popular (1,2). According to the results of the household information technologies usage research conducted in Türkiye in 2021, percentages of the Turkish population using mobile phones and the internet were consecutively 96% and 82.6%, and the mean duration of time spent daily on the internet by the Turkish population was approximately eight hours (3,4).

The term, nomophobia, which comes forward as a consequence of phone dependency in line with these high percentages, is derived from the phrase, "NO Mobile PHOBIA", and is illustrated as the case in which individuals have the feelings of distress, worry, anxiety, and anger upon being disconnected from the mobile phone or computer (5,6). As a matter of fact, in previous studies, it is stated that nomophobic individuals experienced more anxiety, depression, and sleep disorders, and additionally, the quality of their lives besides their work performance was negatively affected by nomophobia (7,8). In professions

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where work performance and time management are vital, the development of this dependency is an extremely risky situation. It is stated that internet dependency became more prevalent in nursing, which was one of these professions (9). Intensive care units are the service units where advanced technological monitoring practices need to be closely followed for the follow-up, treatment, and care of critical patients diagnosed with multiple organ failure. In the relevant literature, it is put forward that intensive care units were the service units with high rates of error which, in turn, gave rise to grave consequences (10). As a consequence of having nomophobia, nurses working in special units such as the intensive care service can neglect their care duties and commit medical errors. The committed medical errors extend the duration of the patient's stay at the intensive care unit, increase the care cost per patient, and can lead to consequences disabling the patient and even ending in the patient's death. To prevent the medical errors that are likely to occur, raising the awareness of nurses about phone dependency and the effects of this dependency is important (11-14). In the relevant literature, there were studies about nomophobia in nurses and nursing students (11,13,15) however, there was no study that analyzed the effect of nomophobic behaviors on caring behaviors in nurses who were working in intensive care clinics. In this respect, this study aimed to identify the effect of nomophobic behaviors on caring behaviors in nurses working in intensive care clinics.

MATERIAL AND METHOD

Study Type

This is a descriptive and correlational research.

Research Design and Participants

This study was performed to identify the effect of nomophobic behaviors on caring behaviors in nurses working in intensive care clinics. The research population was the nurses working in intensive care units. Upon the review of the relevant literature (16) the one-sided hypothesis that the nomophobia affected nursing care behaviors was proposed in this study. Research results verified the above hypothesis ($r=-0.178$, $p<0.01$). In the research, the sample size was calculated with the G*Power 3.1.9.7 software. In the calculation performed with a medium effect size ($f2=0.15$), a 5% margin of error, and 80% power ($1-\beta=0.80$), the sample size was found as 270 for the simple linear regression analysis. Nurses who were working in intensive care clinics, had no dyslexia, had no hearing or speaking disorder, and had no mental illness were included in the research. In this regard, a total of 284 intensive care nurses who satisfied the above inclusion criteria took part in the data collection process (17,18).

Data Collection and Measures

The research data were collected with Google Forms in February-May 2022. The data were collected from nurses who were selected with the snowball sampling method through social media platforms from among intensive care nurses satisfying the above inclusion criteria.

Data Collection Tools

In the data collection process, the Personal Information Form, the Nomophobia Questionnaire, and the Caring Behaviors Inventory-24 were used.

The Personal Information Form

Prepared in light of the review of the relevant literature (5,16), the Personal Information Form had a total of 23 questions (7 questions about nurses' socio-demographic characteristics, 10 questions designed to analyze the work conditions at intensive care clinics, and 6 questions about the smartphone use).

The Nomophobia Questionnaire (NMP-Q)

This measure was developed in 2015 by Yıldırım and Correia to evaluate the smartphone dependency in individuals (19). It has four dimensions, that is, (I) not being able to communicate, (II) losing connectedness, (III) not being able to access information, and (IV) giving up convenience. Yıldırım, Sumuer, Adnan et al. performed the validity and reliability study for the NMP-Q in Turkish in 2016 (20). A score below 20 points: no nomophobia, a score of 20-60 points: low-level nomophobia, a score of 60-100 points: medium-level nomophobia, and a score above 100 points: high-level nomophobia. Cronbach's alpha coefficient was found as 0.92, 0.90, 0.74, 0.94, and 0.91 successively for the NMP-Q and its above dimensions. In our study, Cronbach's alpha coefficient was calculated as 0.95, 0.88, 0.86, 0.94, and 0.95 consecutively for the NMP-Q and its above dimensions.

The Caring Behaviors Inventory–24 (CBI-24)

The measure was first developed by Wolf, Giardino, Osborne et al. (21). This measure was later restructured in 2006 (22) and is also known as the short form of the Caring Behaviors Inventory-42. Kurşun and Kanan conducted the validity and reliability study for the short form of the measure, the CBI-24, in Turkish in 2012 (23). The CBI-24 has 24 items and four dimensions (Assurance, Knowledge-Skill, Respectful, and Connectedness). It is stated that, as the score obtained by a nurse from the CBI-24 increases, the nurse has a higher level of care quality perception. Cronbach's alpha coefficient was found as 0.96, 0.95, 0.81, 0.95, and 0.94 successively for the CBI-24 and its above dimensions (23). In the current research, Cronbach's alpha coefficient was calculated as 0.76, 0.74, 0.90, 0.90, and 0.83 consecutively for the NMP-Q and its above dimensions.

Statistical Analysis

The Statistical Package for Social Science for Windows,

Version 22.0, was used in the analysis of the data collected in the context of this study. Skewness (-1.097 – +0.595) and Kurtosis (+1.12–-0.685) values were utilized to evaluate whether the research data were normally distributed. If these values range between -1.5 and +1.5, the data are considered to be normally distributed. Besides descriptive statistics (number, percentage, mean, standard deviation, median, minimum, and maximum), Pearson's correlation coefficient and simple linear regression were used in the statistical analysis. Cronbach's alpha coefficient as the measure of internal consistency was utilized to evaluate the reliability of measurement tools that were used in the study. In the research, the statistical significance was identified if the p-value was below 0.05 ($p<0.05$).

Ethical Endorsement

Before the study was initiated, the ethical endorsement for the research was obtained from the Scientific Research and Publications Ethics Committee of Osmaniye Korkut Ata University of Türkiye (No. 2022/1/11). On the first page of the online survey, an electronic informed consent form was presented to the nurses. Through this first page, nurses were informed that the participation in the study was on a voluntary basis and they were free to quit answering the survey questions any time they wanted to withdraw from the research. During the research, all principles of the Helsinki Declaration were respected.

RESULTS

The Demographic and Smartphone Usage Characteristics of Intensive Care Nurses

Table 1 displayed the breakdown of socio-demographic characteristics of intensive care nurses who were included in the research. Upon the examination of Table 1, it was discerned that the mean age of intensive care nurses was 29.50±5.76 years, and of all participant nurses, 76.8% were female, 57.4% were single, 75% held a bachelor's degree, 56% had an income equaling expenses, 53.5% worked in the nursing profession for 0-5 years, 51.2% worked in surgical intensive care units, 67.6% worked in intensive care units for 0-5 years, 63% worked for 161-191 hours per month, 89.4% worked in shifts, 59.5% voluntarily selected the nursing profession, and lastly, the mean number of beds provided with nursing care by participant nurses was 14.25±4.71 (Table 1).

Next, as per the review of participant nurses' smartphone usage characteristics, it was identified that, of all participant nurses, 94.7% used smartphones for 6 years or longer, 34.2% checked their smartphones 17-33 times per day, 64.1% carried a portable power bank with them, 79.9% checked their smartphones immediately after waking up, 89.8% spent some time with their smartphones before going to bed, and 84.5% did not turn off their smartphones before going to bed (Table 2).

Table 1. Intensive care nurses' socio-demographic characteristics (n=284)

Age	29.50±5.76 years (Min=22, Max=48)	
	n	%
Gender		
Female	218	76.8
Male	66	23.2
Marital status		
Married	121	42.6
Single	163	57.4
Education level		
High school diploma	22	7.7
Associate degree	13	4.6
Bachelor's degree	213	75.0
Master's degree	36	12.7
Perceived income level		
Income below expenses	100	35.2
Income equaling expenses	160	56.3
Income above expenses	24	8.5
Place resided for the longest		
Village	19	6.7
Town	18	6.3
City	247	87.0
Duration of working in the nursing profession		
0-5 years	152	53.5
6-11 years	72	25.4
12 years or above	60	21.1
Current unit of intensive care service		
Internal intensive care clinics	139	48.8
Surgical intensive care clinics	145	51.2
Duration of working in the intensive care unit		
0-5 years	192	67.6
6-11 years	65	22.9
12 years or above	27	9.5
Duration of work per month		
160 hours or below	53	18.7
161-191 hours	179	63.0
192 hours or above	52	18.3
Status of working in shifts in the intensive care unit		
No	30	10.6
Yes	254	89.4
Status of holding an intensive care certificate		
Yes	88	31.0
No	196	69.0
Status of providing patients with nursing care		
Yes	280	98.6
No	4	1.4
Status of selecting the nursing profession voluntarily		
Yes	169	59.5
No	115	40.5
Number of beds in the intensive care unit	14.25±4.71 (Min=4, Max=26)	

Table 2. Intensive care nurses' smartphone usage characteristics (n=284)		
Duration using smartphones		
0-1 year	1	0.4
2-3 years	2	0.7
4-5 years	12	4.2
6 years or above	269	94.7
Frequency of checking the smartphone		
1-16 times	48	16.9
17-33 times	97	34.2
34-50 times	75	26.4
51 times or more	64	22.5
Status of carrying a portable power bank near at hand		
Yes	182	64.1
No	102	35.9
Status of checking the smartphone immediately after waking up		
Yes	227	79.9
No	57	20.1
Status of spending some time with a smartphone before going to bed at night		
Yes	255	89.8
No	29	10.2
Status of turning off the smartphone before going to bed at night		
Yes	44	15.5
No	240	84.5

Total Scores of NMP-Q and CBI-24 Scales and Sub-Dimensions

Table 3 exhibited mean scores, minimum scores, and maximum scores obtained by nurses from the NMP-Q, the CBI-24, and their dimensions. In this respect, first, it was found that the mean of nurses' NMP-Q scores was 90.09±28.47 points, and nurses obtained the maximum score from the NMP-Q Not Being Able to Communicate Dimension (29.10±8.40 points) whereas they obtained the minimum score from the NMP-Q Giving Up Convenience Dimension (18.79±8.85 points). Secondly, it was discerned that the mean of nurses' CBI-24 scores was 124.05±18.49 points, and nurses obtained the maximum score from the CBI-24 Assurance Dimension (40.31±6.89 points) whilst they obtained the minimum score from the CBI-24 Connectedness Dimension (25.78±3.72 points) (Table 3).

Table 3. Mean, minimum, and maximum scores obtained by intensive care nurses from the NMP-Q,the CBI-24, and their dimensions			
The NMP-Q and its dimensions	**Min**	**Max**	**$\bar{X}$±SD**
Not being able to access information	4.00	43.00	20.52±8.47
Losing connectedness	5.00	35.00	21.66±7.58
Not being able to communicate	6.00	42.00	29.10±8.40
Giving up convenience	5.00	35.00	18.79±8.85
NMP-Q	25.00	140.00	90.09±28.47
The CBI-24 and its dimensions	**Min**	**Max**	**$\bar{X}$±SD**
Assurance	21.00	48.00	40.31±6.89
Knowledge-skill	12.00	30.00	26.79±4.08
Respectful	12.00	36.00	31.15±5.06
Connectedness	13.00	30.00	25.78±3.72
CBI-24	58.00	144.00	124.05±18.49

Correlation and Regression Between NMP-Q and CBI-24 Scales

Table 4 showed the analysis of correlations between scores obtained by nurses from the NMP-Q, the CBI-24, and their dimensions. In this regard, firstly, it was identified that there was a statistically significant weak negative correlation between nurses' NMP-Q and CBI-24 scores (r=-0.178, p<0.01). Secondly, it was found that there was a statistically significant highly strong positive correlation between nurses' NMP-Q and its Losing Connectedness Dimension scores (r=0.917, p<0.01). Thirdly, it was discerned that there was a statistically significant highly strong positive correlation between nurses' CBI-24 and its Respectful Dimension scores (r=0.958, p<0.01).

Table 4. Analysis of correlations between research variables

	Correlation Matrix									
Variables	**Not being able to access information**	**Losing connectedness**	**Not being able to communicate**	**Giving up convenience**	**Nomophobia (total)**	**Assurance**	**Knowledge-skill**	**Respectful**	**Connectedness**	**Caring behaviors (total)**
Not being able to access information	1									
Losing connectedness	.650**	1								
Not being able to communicate	.417**	.696**	1							
Giving up convenience	.689**	.811**	.593**	1						
Nomophobia (total)	.808**	.917**	.789**	.907**	1					
Assurance	-.051	-.087	-.113	-.216**	-.139*	1				
Knowledge-skill	-.222**	-.224**	-.104	-.371**	-.272**	.789**	1			
Respectful	-.181**	-.155**	-.079	-.317**	-.217	.838**	.888**	1		
Connectedness	.005	.019	-.023	-.107	-.034	.826**	.760**	.870**	1	
Caring behaviors (total)	-.117*	-.120**	-.091	-.271**	-.178**	.943**	.912**	.958**	.916**	1

*p<0.05, **p<0.01

Lastly, a simple linear regression analysis was conducted to identify the effect of nurses' NMP-Q scores on their CBI-24 scores. As per the examination of the p-value corresponding to the F-value, it was discerned that the simple linear regression model was statistically significant (F=9.238, p<0.05). Next, upon the review of the Beta coefficient, t-value, and p-value for the predictor variable, it was identified that nurses' NMP-Q scores had a statistically significant effect on their CBI-24 scores (p<0.05). Nurses' NMP-Q scores accounted for 32% of the variance in CBI-24 scores (R2=0.320) (Table 5).

Table 5. Results of the simple linear regression analysis conducted to identify the effect of nurses' nomophbia behaviors on their caring behaviors

Dependent variable	Independent variable	B	Std. Error	ß	t	p	R	R2	F	Model p
Caring	Constant	134.479	3.597		37.387	0.000	.178	.320	9.238	0.003
Behaviors	Nomophobia	-0.116	0.038	-.178	-3.309	0.003				

DISCUSSION

Along with the increase in internet usage all over the world, the diversity of social media platforms also increases. Next, in tandem with the increase in this diversity, the time spent by human beings on the internet also increases and human beings develop a dependency on smartphones. Smartphones that move to the center of life in this manner are used in professional life as well (24). The development of this dependency in professions, in which the effective management of time is vital, affects the professional life negatively. It is put forward that the use of the smartphone through a variety of virtual platforms and applications for nonprofessional purposes besides its use in situations relating solely to the profession became prevalent (9). The increase in phone dependency in nurses affects the work performance and service quality negatively. Setbacks experienced in the time management by nurses who work at special clinics such as the intensive care unit can pave the way for vital consequences by reducing the care quality and the reliability and efficiency of care practices (11). In the current research, it was found that intensive care nurses were moderately nomophobic. In the study conducted by Hosgor et al. to identify the relationship between the nomophobia level and the perceived workload in nurses, it is stated that a large majority of the nurses had medium-level nomophobia (11). Likewise, in the study performed by Korkmaz and Aslan to assess whether nurses had nomophobia, it is put forward those nurses had medium-level nomophobia (5). On the other hand, in a study that analyzed the relationship between nurses' personality characteristics and nomophobia, it was identified that nurses had high-level nomophobia (25).

As nomophobia is a relatively new concept in the literature, there is a limited number of studies about the effect of nomophobia on human beings. Studies mostly examined its effect on students with high-level smartphone dependency. Upon the review of studies evaluating the effect of nomophobia on nursing students, it was discerned that the study by Okuyan et al. asserted that nursing students were moderately nomophobic (26) whilst the study by Özdemir et al. stated that nursing students were highly nomophobic (27). Besides, in the study performed by Aguilera-Manrique to analyze the relationship between nursing students' nomophobia levels and their distractibility in clinical practices in association with smartphone use, it was identified that nursing students were moderately nomophobic (28).

In the relevant literature, it is stated that the increase in phone dependency in working individuals was associated with a decrease in work performance (29). In the current study, it was found that there was a statistically significant negative relationship between intensive care nurses' nomophobia levels and caring behaviors, and nomophobia accounted for 32% of the variance in caring behaviors. In the relevant literature, a research study conducted on health workers emphasized that there was a negative relationship between smartphone dependency and work performance (30). Moreover, in a study performed on nurses working in surgery clinics, it was stated that nomophobia reduced the work quality by preventing the patient and health worker from communicating effectively (16). Furthermore, in a study conducted on nurses in Indonesia, it was asserted that nurses with high-level nomophobia had low-level self-efficacy (31). In light of these results, we can state that the development of smartphone dependency in nurses affected nurses' caring behaviors negatively. In a meta-analysis that evaluated internet addiction in health workers, it was put forward that internet addiction affected health workers' caring behaviors (32).

This study had some limitations. The fact that this study had a relatively small sample as the sample was solely comprised of nurses working in a specific unit is the limitation of this research. In this regard, more advanced studies that will have a large sample to compare nurses working in different service units should be performed. On the other hand, the fact that this study was conducted with the participation of intensive care nurses working under challenging conditions during the COVID-19 pandemic is the strength of this research, and additionally, this study is important as it is the first study to evaluate nomophobia in intensive care nurses.

CONCLUSION

In this research, it was found that nurses' nomophobic behaviors affected their caring behaviors negatively. Preventing intensive care nurses from having nomophobia is of importance to the adoption of effective and good-quality caring behaviors by intensive care nurses. To

eliminate the negative effect of nomophobia on caring behaviors, we recommend that the awareness of intensive care nurses about phone dependency and the effects of this dependency be raised. At the same time, it is important to organize training programs on this subject by health institutions and to establish policies that determine the appropriate limits of technology use. In this way, it is thought that nurses will be able to serve their patients better and more sensitively and their working efficiency will increase.

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Research Article

The Effect of an Intensive Hand Exercise Program on Muscle Strength and Hand Functions in Patients with Rheumatoid Arthritis

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Abstract

Aim: This study investigated the effectiveness of classic and intensive exercise programs in patients with rheumatoid arthritis (RA) and their relationship with disease activity and patient functional well-being.

Material and Methods: Sixty patients aged 18 to 65, diagnosed with RA in our clinic, were randomly divided into two groups of 30 each. The first group received an intensive exercise program, while the second group received a classic exercise program. Disease activity was evaluated using erythrocyte sedimentation rate, C-reactive protein, DAS28Sedim, and DAS28Crp. Daily life activities were assessed using the HAQ score and Duruöz hand index. Joint mobility measurements were taken with a goniometer, and muscle strength measurements were taken using a manual dynamometer and pinch meter. Hand and wrist radiographs were taken and evaluated according to Steinbroker stages before exercise therapy.

Results: Improvement was observed in both groups' Visual Analog Scale (VAS) and Health Assessment Questionnaire (HAQ) scores, with a significant improvement in VAS scores favoring the intensive exercise group.

Conclusions: The study concluded that exercise therapy had positive effects on patients' hand functions, and the intensive exercise program was more effective.

Keywords: Rheumatoid arthritis, exercise, disease activity

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disorder that affects multiple joints. It is characterized by an unknown etiology and primarily affects synovial tissues, leading to joint destruction and other tissue damage (1,2). The hands are often among the joints most affected by RA, resulting in significant changes in hand function (3,4). Hand function disability is a significant component due to the hands' vital role in daily activities such as gripping, lifting, and carrying objects (5,6). Research has indicated that individuals with RA experience a significant 75% reduction in hand strength when compared to their healthy counterparts (7). Impairments and limitations in the upper extremities, particularly hand involvement, negatively impact patients' daily activities. Therefore, identifying deficiencies and limitations in the upper extremities, closely monitoring them, and taking early measures to prevent permanent damage are crucia (7,8).

Deformity prevention and treatment require multidisciplinary approaches, including patient education, physical therapy modalities, assistive devices, occupational therapy, energy conservation principles, rehabilitation focused on preserving daily life activities, as well as medical and exercise therapies (9). Recent research

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has shown an increasing interest in intensive exercise programs, contrary to traditional recommendations for gentle exercise therapy. While conventional regimens focus on improving joint mobility and preserving hand strength, intensive exercise programs also strive to augment hand strength (10-12).

The primary objective of this research was to assess and contrast the impacts of an intensive hand exercise program and a traditional hand exercise program on hand strength, joint mobility, pain, and functional ability among individuals diagnosed with RA. Given the lack of similar studies in the literature regarding the applied programs and the diversity of evaluation parameters and follow-up periods, this study aimed to contribute to the existing literature.

MATERIAL AND METHOD

Between January and August 2012, a total of 60 consecutive patients with RA who met the American College of Rheumatology (ACR) diagnostic criteria and were followed up at the Physical Medicine and Rehabilitation Clinic of Istanbul Education and Research Hospital were included in the study. Random selection was employed to include patients within the age range of 18 to 65 years, who had been living with the disease for a minimum of 2 years and a maximum of 10 years. The patients were assigned to groups in a consecutive manner according to their order of admission and then randomized. The classic exercises group (CE) received exercises including squeezing and releasing an object (such as a ball) that could fit in the palm, bringing the fingers closer together and moving them apart while stabilizing the hand on a flat surface (such as a table), performing resistance exercises for 5 seconds while supinating and pronating the hand and forearm, picking up and releasing small objects with index finger and thumb, pressing the hand against a flat surface (such as a table) and resisting for 5 seconds, extension exercises with a water bottle in the palm, and flexion exercises with a water bottle in the palm. The intense exercises (IE) group underwent exercises, including fist clenches and releases, thumb-finger opposition, wrist flexion (bending the wrist downwards), wrist extension (bending the wrist upwards), forearm rotation towards the palm (pronation), and forearm rotation away from the palm (supination). Both exercise programs were performed three times a day, with 30 repetitions for each exercise, five days a week.

Before the exercise therapy, wrist radiographs were taken and evaluated according to the Steinbrocker stages. The disease activity of the patients was evaluated through measurements of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and Disease Activity Score 28 (DAS28) based on both ESR and CRP, and daily life activities were evaluated using the Health Assessment Questionnaire (HAQ) score and Duruöz hand index. During the assessment of the DAS28 score, the following criteria were used to categorize disease activity: remission (≤2.4), low disease activity (2.4-3.6), moderate disease activity (3.6-5.5), and high disease activity (>5.5) (13). The Duruöz hand index is a scale that evaluates activity limitations related to hand function in RA patients. The scale consists of 18 items assessing hand abilities in dressing, kitchen activities, personal hygiene, work, and other daily movements. An increase in the score indicates greater difficulty and more activity limitations. The scoring system ranged from 0 (lowest score) to 90 (highest score) (14). Goniometry was utilized to measure joint range of motion (ROM), while muscle strength assessments were conducted employing a manual dynamometer and a pinch gauge. The assessments of disease activity, daily life activities, muscle strength, and goniometric measurements were conducted at the beginning of the exercise program, and at the end of 8th weeks. Pain intensity was evaluated using the Visual Analog Scale (VAS), where patients were asked to indicate their level of pain by marking along a 10-cm line. One end of the line represented the absence of pain, while the other end represented the most severe pain. The patients were asked to mark the point on the line that represented their current pain level, and the marked section was measured in millimeters (0-100 mm).

Patients with mental, cognitive, or any other neurological diseases, heart failure, tumor, osteomyelitis or any other infectious diseases, spinal deformity or congenital anomalies of the hand, injury or fracture of the forearm and hand, previous hand surgery, vertebral, pelvic or shoulder surgery, nerve laceration, compression or peripheral neuropathy, motor deficits, inflammatory diseases other than RA, contracture deformities and sequelae in the wrist and fingers secondary to RA, RA activation, and participants outside the age range of 18 to 65 years were excluded.

Following comprehensive explanations of the research objectives and study procedures to the participants, formal written consent was acquired from all individuals. The study was conducted in accordance with the ethical principles set forth in the Helsinki Declaration and was duly approved by the institutional ethics committee of the hospital.

Statistical Analysis

The data were analyzed using various statistical methods. Descriptive statistics, such as standard deviation (SD), ratio, mean, and frequency values, were used to summarize the data. To assess the distribution of the data, the Kolmogorov-Smirnov test was employed. Parametric data were subjected to analysis using the t-test, while non-parametric data were analyzed using the Mann-Whitney U test. The chi-square test was applied to analyze proportional data. In cases where the conditions for the chi-square test were not met, the Fischer test was utilized as an alternative. A significance level of $p<0.05$ was considered to determine statistical significance. All statistical analyses were conducted using the SPSS Statistics Standard Concurrent User V 26 (IBM) statistical package program.

RESULTS

The study included patients aged between 18 and 65 years. The mean age was 49.5±8.4 years in the CE group and 47.6±8.6 years in the IE group. The female-to-male ratio was 24/6 in the CE group and 27/3 in the IE group. The proportion of housewives was high in both groups. There were no statistically significant differences in terms of employment status,gender and age between the groups (p>0.05).

Both groups had a dominant right hand, with equal proportions of 28/30. When patients' hand X-rays were evaluated according to the Steinbroker stages, both groups were predominantly classified as stage 1, with a ratio of 28/30. There was no history of trauma in the patients' medical records. There were no statistically significant disparities observed between the CE and IE groups in terms of disease duration, dominant hand side, Steinbroker stages, trauma, presence of other diseases besides RA, and medical treatments (p>0.05) (Table 1).

Table 1. Comparison of the groups based on disease duration, hand dominance, radiological stage, comorbidities, and medication usage before treatment

	Classic exercise group (CE)		Intense exercise group (IE)		P
Disease Duration (years)	5.5±2.3 (Mean±SD)		5.1±2.5 (Mean±SD)		0.520
	N	**%**	**N**	**%**	
Dominant hand					
Right	28	93.3	28	93.3	
Left	2	6.7	2	6.7	>0.05
Steinbrocker					
Class 1	28	93.3	28	93.3	
Class 2	2	6.7	2	6.7	
Co-morbidity	11	36.7	5	16.7	0.08
Methotrexate	22	73.3	16	53.3	0.108
Hydroxychloroquine	5	16.7	5	16.7	>0.05
Leflunomide	6	20	8	26.7	0.542
Steroid	12	40	14	46.7	0.602
NSAID	15	50	11	36.7	0.297
Sulfasalazine	6	20	5	16.7	0.739
Anti TNF	1	3.3	0	0	>0.05
RF +	26	86.6	25	83.3	>0.05
Anti CCP +	27	90	27	90	>0.05

Mean±SD: mean±standard deviation, NSAID: non-steroidal anti-inflammatory drug, RF: rheumatoid factor, Anti CCP: anti-cyclic citrulline peptide, Mean: mean, Chi-square test/ Fischer exact 95% confidence interval

When comparing the pre-exercise and 8th week evaluations of the patients, improvements were observed in terms of HAQ scores and Duruöz scores in both groups. However, no significant difference was found between the two groups (p>0.05) (Table 2).

No statistically significant differences were found between the CE and IE groups in terms of morning stiffness duration, sedimentation, CRP, DAS28Sedim, DAS28CRP, RF, degrees of forearm supination and pronation in the right and left sides, degrees of PIP flexion, degrees of MCP extension, degrees of abduction and flexion of the thumb, degrees of radial and ulnar deviation of the wrist, and degrees of wrist flexion and extension before treatment and at the 8th week (p>0.05).

When examining the VAS scores of the groups before treatment (CE: 6.9, IE: 7.3) and at the 8th week (CE: 6.7, IE: 5.2) a significant decrease was observed in the VAS scores of the IE group after treatment (p<0.05), while there was no significant change in the scores of the CE group (p>0.05). The VAS scores of the CE group (6.7±1.01) were notably greater compared to the intensive exercise group (5.2±0.81) after the treatment (p<0.05) (Table 2).

Table 2. Comparison of the clinical parameters of the groups before and after treatment

		Classic exercise group (CE) (Mean±SD)	Intense exercise group (IE) (Mean±SD)	p
VAS (centimeter)	BT	6.9±8.3	7.3±9.8	0.325
	AT	6.7±10.1	5.2±8.1	0.004
HAQ	BT	1.0±0.6	0.9±0.7	0.327
	AT	0.7±0.5	0.7±0.6	0.446
Duruöz hand index	BT	10.7±6.2	7.1±6.9	0.037
	AT	7.9±5.3	5.3±5.8	0.078
Right-side pinch strength (pound)	BT	14.5±3.4	13.7±4.5	0.439
	AT	16.0±4.1	20.6±5.6	0.001
Left-side pinch strength (pound)	BT	13.4±3.4	13.3±4.9	0.903
	AT	14.8±3.9	20.8±5.8	0.000
Right-side grip strength (pound)	BT	53.4±14.2	47.8±15.0	0.143
	AT	56.0±12.8	56.0±17.2	0.993
Left-side grip strength (pound)	BT	51.7±13.5	45.2±15.0	0.083
	AT	52.8±13.9	53.7±16.4	0.820
Right wrist flexion (degrees)	BT	74.5±4.7	76.6±4.6	0.084
	AT	74.6±4.7	76.9±4.0	0.079
Left wrist flexion (degrees)	BT	74.7±4.7	76.4±4.8	0.064
	AT	74.7±4.7	76.8±4.3	0.054
Right wrist extension (degrees)	BT	65.1±3.3	65.8±4.0	0.464
	AT	65.2±3.3	65.9±4.1	0.387
Left wrist extension (degrees)	BT	64.7±3.4	65.4±4.6	0.468
	AT	64.6±3.5	65.8±4.2	0.270
PIP flexion right (degrees)	BT	91.3±2.9	93.7±4.1	0.754
	AT	91.3±2.9	93.8±4.2	0.668
PIP flexion left (degrees)	BT	90.3±2.5	93.7±4.1	0.856
	AT	90.4±2.6	93.9±4.2	0.835
MCF flexion right (degrees)	BT	84.0±3.5	86.5±3.1	0.877
	AT	84.2±3.7	86.7±2.9	0.829
MCF flexion left (degrees)	BT	83.1±3.5	86.4±3.2	0.454
	AT	83.3±3.8	86.8±2.9	0.466
MCF extension right (degrees)	BT	25.1±4.2	25.3±4.1	0.897
	AT	25.1±4.3	25.3±4.2	0.897
MCF extension left (degrees)	BT	25.2±4.2	25.0±4.2	0.878
	AT	25.2±4.2	25.2±4.1	1.000
Sedimantation mean (mm/hr)	BT	28.4±12.6	31.2±15.9	0.453
	AT	29.1±14.0	37.5±19.2	0.165
CRP mean	BT	0.8±0.7	0.7±0.6	0.542
	AT	1.0±1.0	0.7±0.5	0.532
DAS 28 sedim	BT	2.6±0.3	2.5±0.5	0.383
	AT	2.6±0.2	2.6±0.3	0.138
DAS 28 CRP	BT	1.4±0.2	1.4±0.3	0.126
	AT	1.5±0.2	1.4±0.2	0.236

Mean±SD: mean±standard deviation, BT: before treatment, AT: after treatment, VAS: visual analogue scale, HAQ: health assessment questionnaire score, t-Test 95% confidence interval, Mann-whitney u test, 95% confidence range

The muscle strength values of pinch and grip were compared before and after treatment for the patients. Improvement in muscle strength values of pinch and grip was observed in both groups compared to before treatment. When comparing the CE and IE groups, the right-side pinch strength values were significantly lower in the CE group (16.0±4.1) than in the IE group (20.6±5.6) ($p<0.01$). Similarly, the left-side pinch strength values were significantly lower in the CE group (14.8±3.9) than in the IE group (20.8±5.8) ($p<0.01$). Although both groups showed an increase in grip strength values on the right and left sides compared to before treatment, no statistically significant difference was observed between the groups ($p>0.05$). Correlation analysis between muscle strength and disease duration showed a decrease in pinch and grip strength values as disease duration increased, but his difference was not statistically significant both between and within the groups ($p>0.05$).

DISCUSSION

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disease with a wide range of multi-system involvement and an unclear etiology (15). The course of the disease varies from short-term oligoarticular involvement with minimal joint damage to severe polyarticular involvement leading to significant functional impairment (16). The goal of treatment in RA is to reduce pain, control inflammation, preserve joint function and structure, and ultimately manage systemic involvement in order to maintain the patient's quality of life (17). The hand has a wide range of functions and tasks, including writing, gripping, touching, holding, physical defense, and feeding, among others. In RA patients, hand function deteriorates over time, negatively affecting daily life activities (12). Therefore, early diagnosis should be made whenever possible, and diagnosed patients should be regularly monitored and treated.

Muscle weakness is also a common problem in RA patients. Weakness becomes more pronounced due to disuse, muscle inhibition secondary to joint effusion, or myositis (18). Suomi et al. (19) reported the positive effects of exercise on quality of life. Traditionally, the primary goal of exercise therapy for RA has been to preserve joint ROM and enhance muscle strength.

In our study, it was observed that patients receiving the intensive exercise program showed greater improvement in hand function compared to patients receiving the classic exercise program. At the end of 8 weeks, the pinch values of the CE group improved by 10.6% (from 14.5 to 16) on the right side and 10.4% (from 13.4 to 14.8) on the left side, while the pinch values of the IE group improved by 51% (from 13.7 to 20.6) on the right side and 57% (from 13.3 to 20.8) on the left side (Table 2). At the end of 8 weeks, the grip values of the CE group improved by 4.8% (from 53.4 to 55.3) on the right side and 2.1% (from 51.7 to 52.8) on the left side, while the grip values of the IE group improved by 17% (from 47.8 to 56.0) on the right side and 18.7% (from 45.2 to 53.7) on the left side (Table 2). Similarly, Ronningen et al.(12) reported significant improvements in pinch and grip values in the intensive exercise group compared to the classic exercise group in their study involving 30 patients in each group after 14 weeks. Brorsson et al. (20) provided a 6-week hand exercise program to RA patients and evaluated their muscle strengths. They reported a 40% improvement in grip strength in their study. In the same study, hand muscles were evaluated in cross-section using ultrasound, and significantly increased hypertrophy was observed in patients who received exercise compared to the control group. Hakinken et al. (21) reported an increase in muscle strength in patients who performed home exercises 2-3 times a week in their study.

The average age in our study was 49.5±8.4 in the control group and 47.6±8.6 in the study group. The female-to-male ratio favored women, with 24/6 in the control group and 27/3 in the study group. As the majority of the participants were middle-aged women, housewives ranked first in terms of occupation, and there was homogeneity between the groups. No statistically significant differences were observed between the groups concerning age, gender, dominant hand, radiological stage, presence of additional diseases, and employment status ($p>0.05$) (Table 1).

Goniometric measurements of the participants were performed actively before exercise therapy, and at the end of the 8th week. Measurements were taken for supination, pronation, wrist flexion, wrist extension, MCP flexion, MCP extension, PIP flexion, thumb flexion, thumb abduction, ulnar and radial deviation of the wrist. Except for the left-hand MCP extension degrees of the IE group, all initial measurement values were higher in the intensive exercise group compared to the CE group. The difference in initial ROM values between the groups was not statistically significant. At the end of 8 weeks of exercise, no significant increase was observed in the measurement values of both groups. Hoenig et al. (22) also reported no increase in joint ROM in their study on RA patients who followed a home exercise program for 12 weeks, similar to our results. O'Brien et al. (23) reported no significant difference in upper extremity joint ROM in their study where they followed 67 patients with a home program for 6 months.

When examining the VAS scores of the groups before treatment and 8 week after treatment, a significant decrease was observed in the VAS scores of the IE group after treatment ($p<0.05$), while there was no significant change in the scores of the CE group ($p>0.05$). At the conclusion of the 8th week, the Visual Analog Scale (VAS) scores of the CE group (6.7±1.01) were significantly higher compared to those of the IE group (5.2±8.1). Buljina et al. (7) also reported a more substantial improvement in hand pain scores compared to joint ROM in their study. Hall et al. (24) similarly reported lower pain levels after exercise in their study on RA patients. Hakkinen et al. (25) stated that pain and joint limitations are the most influential symptoms on functional status. Encouraging RA patients to exercise, the physical relief brought by exercise, and individualized attention to the patient's problems have

been reported to reduce chronic patient behavior and alleviate pain (26). In addition to medical treatments, patient education, psychological support, social support, and physical therapy modalities are extremely important in alleviating pain. Various education programs have been developed for this purpose, and their positive effects on pain and limitations have been demonstrated (27,28).

Taştekin et al. (8) reported that hand function, disability level measured by HAQ, hand grip strengths, and joint ROM of the fingers are closely related. In our study, although improvement was observed in HAQ scores in both groups, No statistically significant difference was found between the CE and IE groups regarding HAQ scores ($p>0.05$). Ronningen et al. (12) reported a significant improvement in HAQ scores after exercise in RA patients who received the IE program in their study. Significant improvement was observed in both groups regarding Duruöz hand scale values. However, there was no statistically significant difference between the classic and intensive exercise groups. Our results suggest that both classic and intensive exercises contribute positively to the daily physical activities of the patients.

Morning stiffness, another symptom associated with RA, is particularly associated with synovitis in the joints (29). Yazıcı et al. (30) reported morning stiffness as the most important symptom affecting functionality in their study with 337 RA patients. In the present study, we observed that there was no statistically significant difference in the duration of morning stiffness between the two groups before and after exercise. The results of other studies evaluating morning stiffness with exercise in the literature were also similar to our study (22,31). Although morning stiffness can be expressed to the patient in the best possible way, its evaluation is subjective and dependent on the patient's expression (32). The lack of a significant change in the duration of morning stiffness between the two groups before and after exercise in our study may be related to this subjectivity.

Our study has several limitations that need to be considered. Firstly, the research was conducted in a restricted geographical area, and the population size was relatively small. The higher female-to-male ratio in favor of women is also attributed to the small population. Although efforts were made to ensure compliance of the patients with the program through phone calls and frequent hospital visits, controlling and monitoring home exercise programs is more challenging for physicians compared to treatments provided in the hospital, which is another limitation of our study.

CONCLUSION

In conclusion, our study supports the notion that exercise therapy plays a significant role in improving hand function in RA patients. The implementation of an intensive exercise program may offer better outcomes compared to the classic exercise program. These findings highlight the importance of integrating exercise therapy with medical treatment in the management of RA, contributing to enhanced patient outcomes and overall quality of life. However, further research with larger sample sizes and longer follow-up periods is warranted to corroborate and expand upon our findings.

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MEDICAL RECORDS-International Medical Journal

Research Article

Analysis of Google Trends for Viral Hepatitis A, B, C, D, and E

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Abstract

Aim: Our main objective in this study was to rigorously measure global interest and awareness of viral hepatitis through a systematic evaluation of data collected from Google Trends.

Material and Methods: We compiled and categorized the Search Volume Index (SVI), a quantitative measure covering the global regional distribution associated with the search terms "Hepatitis A", "Hepatitis B", "Hepatitis C", "Hepatitis D" and "Hepatitis E" over a period of approximately ten years from 2013 to 2022.

Results: According to our analysis, there has been a noticeable increase in interest in Hepatitis A and B, while interest in Hepatitis C has declined after peaking in 2015. Meanwhile, interest in Hepatitis D and E continued to show a very low profile. Our rigorous research found that Guatemala recorded the highest rate of interest for Hepatitis A, Ghana for Hepatitis B, Pakistan for Hepatitis C, Kyrgyzstan for Hepatitis D and Namibia for Hepatitis E.

Conclusions: This study highlights the potential for using tools such as Google Trends in organizing public health monitoring and awareness campaigns.

Keywords: Viral hepatitis, trend analysis, public health

INTRODUCTION

Infectious diseases are among the diseases that affect many people worldwide at the same time. Among infectious diseases, viral diseases remain on the agenda due to the ease of transmission routes and difficulties in diagnosis. Among the viral diseases affecting the liver, viral hepatitis is still common in the world and continues to infect people through various transmission routes. Among the viral hepatitis agents, Hepatitis A, B, C, D and E viruses come to the forefront and have their own transmission routes, clinical signs and symptoms and different epidemiological characteristics as in other viral agents (1).

Hepatitis A and Hepatitis E viruses, which are mostly spread by the faecal-oral route, are more prevalent in underdeveloped nations where access to clean, safe water, food sources, and sewerage systems is poor (1). The Hepatitis A and E viruses often cause an acute infection with or without jaundice and do not develop a chronic form in the liver. The main method of transmission for Hepatitis B, C, and D is exposure to blood and bodily fluids, and these infections frequently progress to chronic liver disease. Cirrhosis, hepatocellular carcinoma (HCC), and chronic liver disease are all life-threatening illnesses brought on by these viruses (2).

The widespread use of the Internet has made it easier to access information and to find in-depth information about many diseases. An online tool called Google Trends shows the most popular search terms and tracks interest in related searches over time. Various studies have used Google Trends data analysis to evaluate various diseases and public health issues (3). The purpose of this study is to examine the terms Hepatitis A, B, C, D, and E in a Google search to identify interest in these diseases and raise awareness of the public and health officials in the appropriate field.

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MATERIAL AND METHOD

Between 1 January 2013 and 31 December 2022, we collected search volume data for worldwide Google searches for each of the terms "Hepatitis A", "hepatitis B", "Hepatitis C", "Hepatitis D" and "Hepatitis E" and classified them into worldwide regional distributions. The classified data were further classified into ranges. We also performed time-series analysis of search volumes by examining local regional distributions of search volumes to identify regions of greater interest for each hepatitis type. Local regional distributions of search volumes were also analysed to identify regions of greater interest for each hepatitis type.

RESULTS

Figure 1 visually represents the same data shown in Table 1. This figure clearly shows the change in research for each type of liver disease over the years. It is clear from the graph that interest in Hepatitis A and B generally increased, while interest in Hepatitis C fell after peaking in 2015. Interest in Hepatitis D and Hepatitis E remained rare during the study period. This representation supports the observations in the analysis in Table 1, allowing for easy comparison of study-period subjects for different types of liver disease.

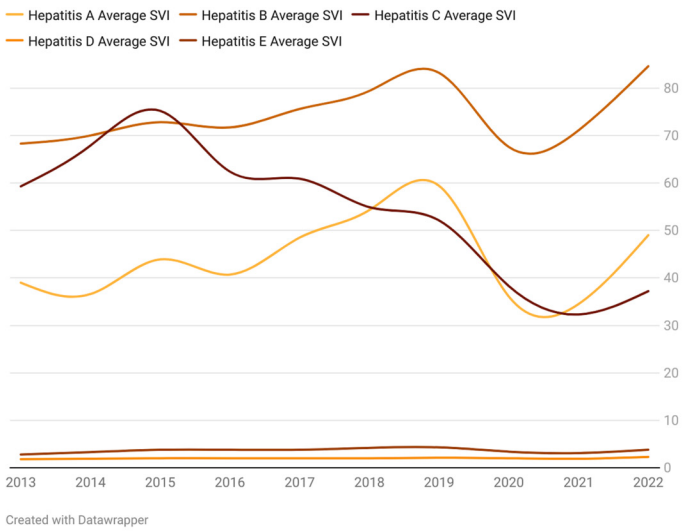

Figure 1. Trends in Average Search Volume Index (SVI) for Hepatitis A, B, C, D, and E from 2013 to 2022

Table 1 shows the average Search Volume Index (SVI) values for each type of liver disease (A, B, C, D, and E) from 2013 to 2022. Overall, SVI values were increased in addition to Hepatitis A. and the effect of Hepatitis B, Hepatitis C appeared after 2015. Find out if SVI values for Hepatitis D and E are low and stable over time.

Table 1. Average SVI values for Hepatitis A, B, C, D, and E by year

Years	Hepatitis A Average SVI	Hepatitis B Average SVI	Hepatitis C Average SVI	Hepatitis D Average SVI	Hepatitis E Average SVI
2013	39.0	68.3	59.3	1.8	2.8
2014	36.6	70.0	67.9	1.9	3.3
2015	43.9	72.8	75.2	2.0	3.8
2016	40.7	71.7	62.4	2.0	3.8
2017	48.5	75.6	60.9	2.0	3.8
2018	54.3	79.4	54.9	2.0	4.2
2019	59.4	83.2	52.1	2.1	4.3
2020	36.1	67.6	38.3	2.0	3.4
2021	34.5	71.1	32.3	1.9	3.1
2022	49.0	84.6	37.2	2.3	3.8

Table 2 shows the ranking of the top 10 countries with the highest SVI values for each viral hepatitis agent separately. Guatemala has the highest SVI for Hepatitis A, while Ghana has the highest SVI for Hepatitis B. Pakistan has the highest SVI for hepatitis C, Kyrgyzstan for Hepatitis D and Namibia for Hepatitis E.

The highest search interest for Hepatitis A is predominantly in Central and South America with Guatemala leading, for Hepatitis B it's concentrated in Africa with Ghana at the forefront, for Hepatitis C it's diverse globally with Pakistan showing the highest SVI, for Hepatitis D it's noted across Asia, Africa, and the Americas with Kyrgyzstan leading, and for Hepatitis E, Namibia in Africa records the highest interest, followed by countries in Asia and Europe (Figure 2).

Based on the Google Trends data, the highest search volume index (SVI) for Hepatitis A comes primarily from the Americas, particularly from Central and South America. Guatemala leads the list, followed by Venezuela, Peru, Honduras, Bolivia, Ecuador, Mexico, Costa Rica, and Puerto Rico. This interest could be associated with the region's efforts to improve sanitation and vaccination against hepatitis A or outbreaks that may have occurred (Figure 3).

Table 2. Top 10 countries with the highest SVI values for Hepatitis A, B, C, D, and E

Ranking	Hepatitis A (SVI)	Hepatitis B (SVI)	Hepatitis C (SVI)	Hepatitis D (SVI)	Hepatitis E (SVI)
1	Guatemala (100)	Ghana (100)	Pakistan (100)	Kyrgyzstan (100)	Namibia (100)
2	Venezuela (96)	Uganda (54)	Puerto Rico (85)	Nigeria (95)	Pakistan (12)
3	Ghana (92)	Nigeria (49)	United States (69)	Bolivia (85)	Nepal (11)
4	Peru (86)	Ethiopia (37)	Dominican Republic (59)	Pakistan (76)	Germany (9)
5	Honduras (84)	Zambia (34)	Nigeria (57)	Nepal (74)	Ghana (8)
6	Bolivia (83)	Cameroon (30)	Ghana (54)	Venezuela (71)	Uganda (8)
7	Ecuador (76)	Kenya (21)	Serbia (47)	Dominican Republic (65)	Kyrgyzstan (6)
8	Mexico (72)	Tanzania (21)	Bosnia and Herzegovina (46)	Ecuador (57)	Bolivia (6)
9	Costa Rica (69)	Dominican Republic (18)	Spain (44)	Peru (52)	Netherlands (5)
10	Puerto Rico (66)	Nepal (18)	Austria (43)	Mexico (52)	Dominican Republic (5)

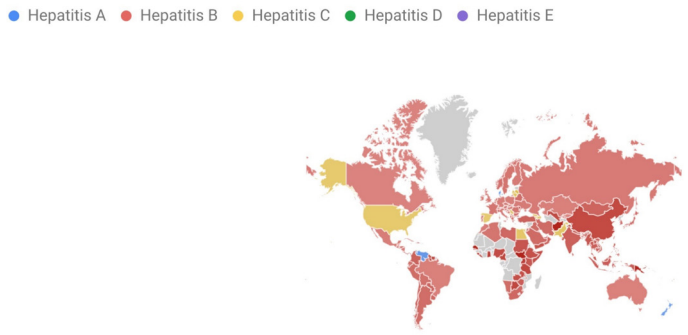

Figure 2. Worldwide search intensity for the terms Hepatitis A, B, C, D and E (Colour intensity represents percentage of searches)

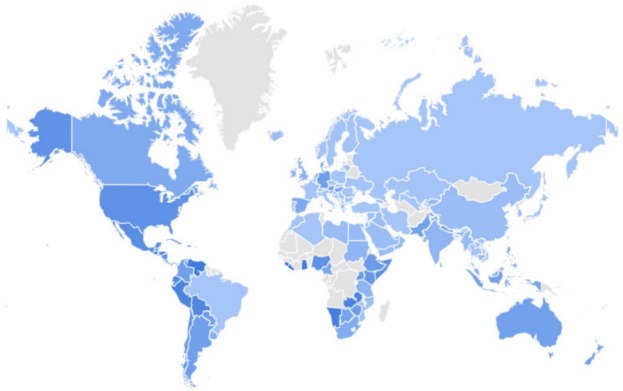

Figure 3. Search intensity of the term Hepatitis A worldwide (Colour intensity represents percentage of searches)

The search interest for Hepatitis B is remarkable in Africa, with Ghana having the highest SVI for hepatitis B among African countries. Other African countries such as Uganda, Nigeria, Ethiopia, Zambia, Cameroon, Kenya and Tanzania are also showing high search interest. This indicates that hepatitis B is still a major public health problem in these regions (Figure 4).

The search interest for Hepatitis C is diverse and spread across multiple continents. Pakistan exhibits the highest SVI, followed by Puerto Rico in the Americas, the United States, and the Dominican Republic. European countries like Serbia, Spain, Bosnia-Herzegovina, and Austria also show substantial search interest. This could be reflective of the global distribution of Hepatitis C, which is commonly associated with injected drug use in many developed countries and unsafe medical practices in developing countries (Figure 5).

The highest SVI for Hepatitis D comes from Kyrgyzstan, followed by Nigeria, Bolivia, Pakistan, Nepal, Venezuela, the Dominican Republic, Ecuador, Peru, and Mexico. This suggests a higher search interest in Asia, Africa, and the Americas. Hepatitis D, being a defective virus requiring Hepatitis B for its replication, tends to be searched in regions where Hepatitis B is also prevalent (Figure 6).

Interestingly, the highest SVI for Hepatitis E comes from Namibia, a country in Africa, followed by Pakistan and Nepal in Asia. The search interest then drops significantly with Germany in Europe, and then back to Africa with Ghana and Uganda. This may reflect the epidemiology of Hepatitis E, which is often associated with large outbreaks in developing countries, particularly in regions with poor sanitation, but is less common in developed countries (Figure 7).

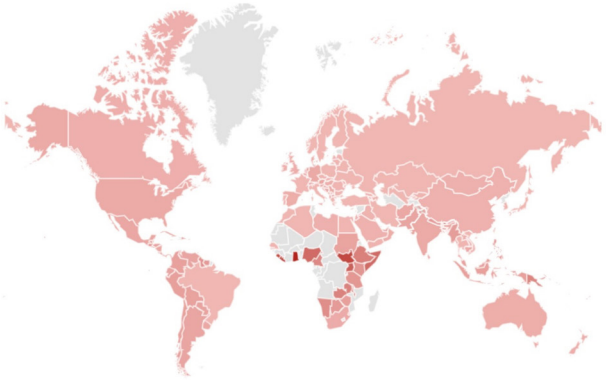

Figure 4. Search intensity of the term Hepatitis B worldwide (Colour intensity represents percentage of searches)

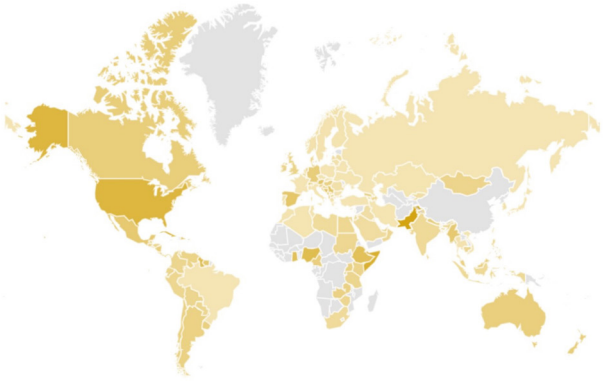

Figure 5. Search intensity of the term Hepatitis C worldwide (Colour intensity represents percentage of searches)

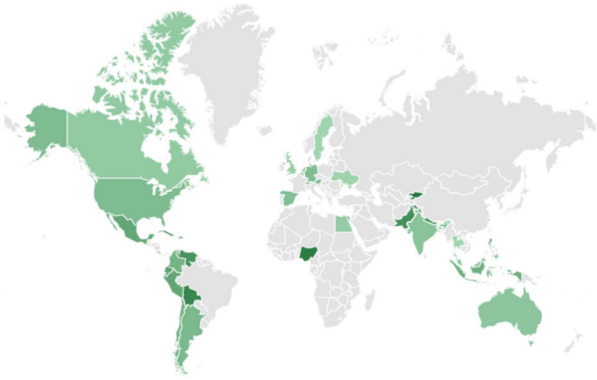

Figure 6. Search intensity of the term Hepatitis D (Colour intensity represents percentage of searches)

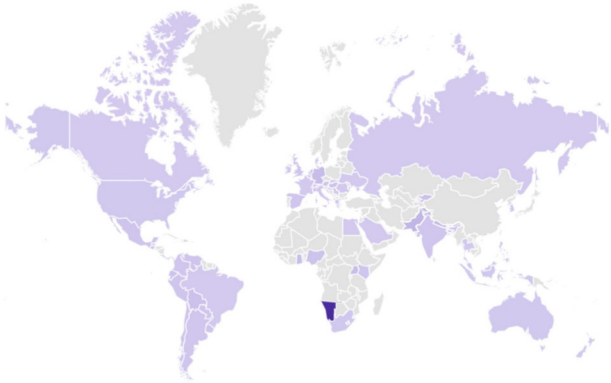

Figure 7. Search intensity of the term Hepatitis E (Colour intensity represents percentage of searches)

DISCUSSION

The analysis of Google Trends data in this study offers critical insights into the global awareness and perceived relevance of different types of hepatitis - A, B, C, D, and E. The geographical diversity and variance in the Search Volume Index (SVI) suggest a correlation with the regional prevalence of these diseases, public health interventions, disease outbreak responses, or general health literacy.

The high SVI values for Hepatitis A searches predominantly originating from Central and South America can be correlated with the region's significant efforts to improve sanitation and promote vaccination, key preventive measures against Hepatitis A. The World Health Organization (WHO) data supports this observation, indicating high endemicity of Hepatitis A in these regions (4). However, it is also crucial to consider the impact of socioeconomic factors and accessibility to digital infrastructure influencing these results (5).

For Hepatitis B, the elevated search interest from Africa aligns with the high prevalence rates of this disease in the region. Despite global efforts to increase Hepatitis B vaccination, the disease remains a significant public health concern in Africa (6). Therefore, the high SVI values could reflect the need for information about the disease, prevention methods, and available treatments. This finding calls for more proactive public health initiatives and vaccination programs in these regions (7).

Hepatitis C shows a diverse geographical distribution in search interest, which can be reflective of its global prevalence. The highest SVI comes from Pakistan, followed by countries from the Americas and Europe. The diversity in countries and continents shows the global scale of Hepatitis C, which is linked to unsafe medical practices, drug use, and transfusion of unscreened blood and blood products (5). This diverse interest underscores the necessity of universal prevention strategies, including harm reduction services for people who inject drugs and ensuring safe blood supply and safe healthcare procedures (8,9).

The highest SVI for Hepatitis D is observed in Kyrgyzstan, followed by countries in Africa and the Americas. Given that Hepatitis D is a defective virus requiring Hepatitis B for its replication, the data underscores the link between the two diseases (10). The high search interest in regions where Hepatitis B is also prevalent suggests a potential co-infection scenario, emphasizing the need for integrated strategies to combat Hepatitis B and D (11).

The highest search interest for Hepatitis E comes from Namibia, followed by countries in Asia. Hepatitis E is typically associated with large-scale outbreaks in developing countries and regions with poor sanitation (12). However, the lower search interest from developed countries could reflect the lower incidence of Hepatitis E in these regions (13).

While this study provides a unique perspective on global

awareness about different types of hepatitis, some limitations must be acknowledged. The SVI values are relative to the total number of Google searches conducted over time, and thus, they do not reflect the absolute search volume. Also, factors such as internet penetration, digital literacy, language preference, and age distribution can significantly influence these values.

CONCLUSION

In conclusion, this study illustrates the potential of using Google Trends as a tool for gauging public interest and awareness about different types of hepatitis worldwide. The insights obtained from this analysis could help guide public health authorities in tailoring disease awareness and prevention strategies to align with the information-seeking behavior of the population.

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

Ethical approval: *Ethical approval was not required for this study as it solely involves the analysis of publicly available Google Trends data without any direct involvement of human subjects or identifiable personal data.*

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MEDICAL RECORDS-International Medical Journal

Research Article

Implications of Gastric Diverticulum in the Incidence of Metaplasia: An Analysis of 37 Cases

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Abstract

Aim: The present study aimed to investigate the potential association between gastric fundus diverticulum and metaplasia by retrospectively analysing patient data and biopsy results.

Material and Methods: 37 patients with gastric fundus diverticulum were examined, with their data compared to a control group of 50 patients without it. All diagnoses were made endoscopically. Demographic information, laboratory parameters, and endoscopic biopsy results were compared between the groups.

Results: No significant differences were identified between the two groups concerning several laboratory parameters. However, there were significant differences in lymphocytes, urea, albumin, Na, and K values ($p<0.05$). Helicobacter pylori and atrophy distributions did not differ between the groups ($p>0.05$), while a notable difference was seen in the distribution of metaplasia ($p<0.05$). Metaplasia positivity was found to be 16% in patients without gastric diverticulum and 43.2% in patients with gastric diverticulum.

Conclusions: This study found a higher prevalence of metaplasia positivity in patients with gastric diverticulum than those without. These findings suggest a potentially significant link between the gastric diverticulum and the occurrence of metaplasia, which warrants further research to better understand the underlying mechanisms and implications for patient management.

Keywords: Gastric diverticula, metaplasia, gastric biopsy, endoscopy, gastroenterology

INTRODUCTION

Gastric diverticula, while relatively rare, have been a topic of increased interest in recent years. Defined as herniations of the gastric mucosa through the muscular layer, and often discovered incidentally during endoscopic examinations (1,2). Recent advancements in endoscopic technology have improved our ability to identify and analyse the characteristics of gastric diverticula. They are typically asymptomatic but can occasionally present with non-specific symptoms such as abdominal pain, belching, bloating, and severe complications like bleeding or perforation (3-5).

Despite its rare occurrence, gastric diverticula hold potential implications in the onset of various gastrointestinal complications. Among these is metaplasia, a reversible transformation of one differentiated cell type to another, often as a response to chronic injury or irritation (6). While not malignant, this process has been associated with an increased risk of neoplastic transformation in various organs, including the stomach (7-10).

Recent studies have highlighted the possible connection between gastric diverticula and metaplasia (11). However, the specific mechanisms underlying this association remain elusive, suggesting the need for further investigation. Moreover, deepening our understanding of how this relationship can influence patient management and potential therapeutic approaches is crucial.

The present study aims to contribute to this growing

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body of research by conducting a retrospective analysis of patients diagnosed with gastric fundus diverticulum. By comparing these patients' laboratory and biopsy results with those of a control group, we seek to uncover potential differences that may indicate an increased risk of metaplasia among patients with gastric diverticulum.

MATERIAL AND METHOD

The local ethics committee of Giresun Training and Research Hospital approved the study protocol. Informed patient consent was waived due to the retrospective design of the study. This study was conducted on the relevant ethical principles of the Declaration of Helsinki, revised in 2013. The study was conducted at Giresun Training and Research Hospital in Giresun province.

This retrospective study was conducted on 87 patients who underwent upper gastrointestinal endoscopy at our institution from January 2020 to December 2022. Among them, 37 patients were diagnosed with gastric fundus diverticulum, while 50 patients with similar demographic characteristics but without gastric diverticulum served as the control group.

A gastric diverticulum was established using endoscopic examination, defined by the presence of a pouch protruding from the gastric wall. The location, size, and appearance of the diverticula were documented. The control group comprised patients who underwent endoscopy for similar complaints but were found not to have a gastric diverticulum.

Demographic information of the patients, including age and gender, was extracted from the patient records. Laboratory parameters including white blood cell (Wbc), haemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), platelet (Plt), glucose, alanine transaminase (ALT), aspartate transaminase (AST), calcium (Ca), lymphocytes (Lymp), creatine, urea, albumin, sodium (Na) and potassium (K) values were obtained from the laboratory records. Biopsies were taken from all patients during the endoscopy. The specimens were immediately fixed in 10% formalin and were sent for histopathological examination. Helicobacter pylori (H. pylori), atrophy, and metaplasia were evaluated and recorded by experienced pathologists blinded to the clinical data.

Statistical Analysis

Data was analysed using the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics package program. The suitability of the numerical variables of the patients to the normal distribution was determined by looking at the skewness values. Except for glucose, urea, ALT and albumin values, it was observed to comply with the rules of normal distribution. The reference value in the normal distribution is between ±1.5. The chi-square test was used to compare patients' descriptive features and pathology findings with and without gastric diverticulum. The Independent Sample T Test or Mann Whitney U test was used to compare patients' age and laboratory parameters with and without gastric diverticulum. Pearson or Spearman Correlation tests were used to examine the relationships between gastric diverticulum disease and age, gender, laboratory and pathology findings. Correlation coefficient; A relationship between 0.00-0.30 was considered as low, between 0.30-0.70 as a medium level, and between 0.70-1.00 as a high-level relationship. Logistic regression analysis results were used to estimate the probability of having a gastric diverticulum. The significance levels were carried out in the study by considering the values of 0.05 and 0.01.

RESULTS

Eighty-seven patients were included in the study. 57.5% of the patients were without gastric diverticulum, and 42.5% were patients with gastric diverticulum. Of the patients without gastric diverticulum, 70% (35 patients) were female, 30% (15 patients) were male, and of the patients with gastric diverticulum, 62.2% (23 patients) were female, 37.8% (14 patients) were male. Of the patients without gastric diverticulum, 52% (26 patients) were under 60 years of age, 48% (24 patients) were 60 years and older, and 51.4% (19 patients) of patients with gastric diverticulum were younger than 60 years, 48%, 6 (18 patients) are 60 years old and above. In addition, the mean age of patients without gastric diverticulum is 58.90 years, and that of patients with gastric diverticulum is 62.89 years. These results showed that the gender and age distribution of patients with and without gastric diverticulum did not differ ($p>0.05$). In other words, the gender and age distributions of the patients in both groups are homogeneous. All gastric diverticulums were in fundus localisation. The comparison of the characteristics of patients with and without gastric diverticulum is shown in Table 1.

In the comparison of laboratory parameters of patients between the two groups, there was no significant difference between Wbc, Hgb, Htc, MCV, Plt, glucose, creatine, ALT, AST and Ca values of patients with and without gastric diverticulum ($p>0.05$). There was a significant difference between the lymphocytes, urea, albumin, Na and K values of patients with and without gastric diverticulum ($p<0.05$). The comparison of laboratory parameters of patients with and without gastric diverticulum is shown in Table 2.

The distribution of H. pylori and atrophy in patients with and without gastric diverticulum did not differ ($p>0.05$). Metaplasia positivity is 16% in patients without gastric diverticulum and 43.2% in patients with gastric diverticulum. According to these findings, metaplasia positivity in patients with gastric diverticulum was considerably higher than in patients without gastric diverticulum. The pathology findings of patients with and without gastric diverticulum are shown in Table 3.

Regression analysis was performed to estimate the probability of having a gastric diverticulum. The patients' lymphocyte, urea, albumin, Na, K and metaplasia parameters were determined as independent variables.

The created logistic regression model was found to be statistically significant (χ2(6)=37.82, p=0.000, p<0.01). Independent variables explain 35.6, according to Cox & Snell and 47.8, according to Nagelkerke, of the changes in the probability of gastric diverticulum. When lymphocyte and albumin variables and the effects of other independent variables were controlled, it was seen that there was no significant variable in estimating the probability of gastric diverticulum in the patient (p>0.05). Urea, Na, K and metaplasia variables were significant in estimating the patient's gastric diverticulum probability when the effects of other independent variables were controlled (p<0.05). When beta coefficients are examined, It was observed that the most influential variable on gastric diverticulum, from largest to smallest, was K, metaplasia, Na and urea. In this context, the logistic regression analysis results for estimating the probability of gastric diverticulum are shown in Table 4.

Table 1. Comparison of characteristics of patients with and without gastric diverticulum

Patients' characteristics		Patient without gastric diverticulum (n:50)		Patient with gastric diverticulum (n:37)		p
		Number	%	Number	%	
Gender	Female	35	70.0	23	62.2	0.591
	Male	15	30.0	14	37.8	
Age	< 60	26	52.0	19	51.4	1.000
	≥ 60	24	48.0	18	48.6	
		Med±SD Med (Min-Max)		Med±SD Med (Min-Max)		
Age[t]		58.90±16.15 58.5 (22-86)		62.89±19.34 59 (27-96)		0.298

*p<0.05, **p<0.01, χ2: chi-square test (categorical data), t: independent sample T test, Med: median, SD: standart deviation. Min: minimum. Max: maximum

Table 2. Comparison of laboratory parameters of patients between groups

Laboratory parameters	Patient without gastric diverticulum (n:50)	Patient with gastric diverticulum (n:37)	p
	Med±SD	Med±SD	
Wbc[t]	6935.80±1869.00	7125.68±3107.62	0.743
Hgb[t]	12.61±1.76	12.18±2.03	0.298
Htc[z]	38.32±4.70 39.05 (25.5-45)	37.01±5.47 39 (23-48.70)	0.196
MCV[t]	85.09±7.22	87.16±4.82	0.134
Plt[t]	264.74±79.42	253.81±65.91	0.498
Lymp[t]	2.09±0.61	1.74±0.71	**0.015***
Glucose[z]	108.82±32.58 100 (65-245)	126.86±57.48 102 (54-254)	0.424
Urea[z]	29.40±8.91 28 (12-59)	43.70±31.75 33 (15-179)	**0.008****
Creatine[t]	.74±0.19	.80±0.21	0.239
ALT[z]	16.64±8.91 15 (6-55)	15.22±10.28 12 (5-55)	0.104
AST[t]	19.52±5.73	20.08±9.21	0.745
Albumin	44.22±7.47 44 (4.5-52.2)	38.66±8.81 41 (10-49)	**0.000****
Na[t]	140.82±2.30	139.46±2.91	**0.017***
K[t]	4.48±0.36	4.19±0.39	**0.001****
Ca[t]	9.54±0.42	9.30±0.74	0.062

*p<0.05, **p<0.01, Med: median, SD: standart deviation, t: independent sample T test, z: Mann Whitney U test (mean and standard deviation values of the data, as well as median, minimum and maximum values are given)

Table 3. Comparison of pathology findings of patients between groups

Pathology findings		Patient without gastric diverticulum (n:50)		Patient with gastric diverticulum (n:37)		p
		Number	%	Number	%	
H.pylori	Negative	38	76.0	29	78.4	0.998
	Positive	12	24.0	8	21.6	
Atrophy	Negative	47	94.0	31	83.8	0.234
	Positive	3	6.0	6	16.2	
Metaplasia	Negative	42	84.0	**21**	56.8	**0.010****
	Positive	8	16.0	16	43.2	

*p<0.05, **p<0.01, $\mathcal{X}2$: chi-square test

Table 4. Results of regression analysis for estimating the probability of gastric diverticulum occurrence in patients

Predictive variable	β	SE	p	Odds ratio	Confidence intervals 95 C.I.for OR	
					Lower	Upper
Lymphocytes	-0.387	0.447	0.387	0.679	0.283	1.631
Urea	0.054	0.027	**0.050**	1.055	1.000	1.113
Albumin	-0.019	0.038	0.614	0.981	0.911	1.056
Na	-0.300	0.147	**0.041**	0.741	0.556	0.987
K	-2.492	0.804	**0.002**	0.083	0.017	0.400
Metaplasia	1.396	0.622	**0.025**	4.040	1.193	13.682
Constant value	52.014	21.253	0.014	$3.8x10^{22}$		

Dependent variable: having gastric diverticulum, β: beta coefficient, SE: standart error, +: positivity, OR: odds ratio

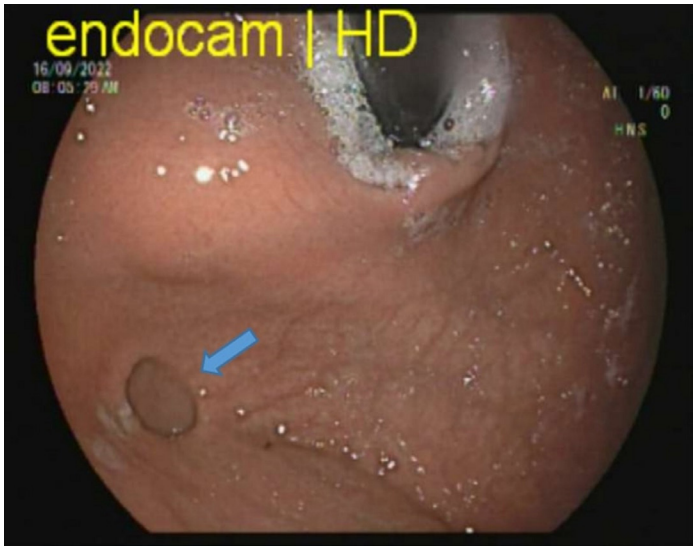

Figure 1. Endoscopic view of the gastric fundus diverticulum

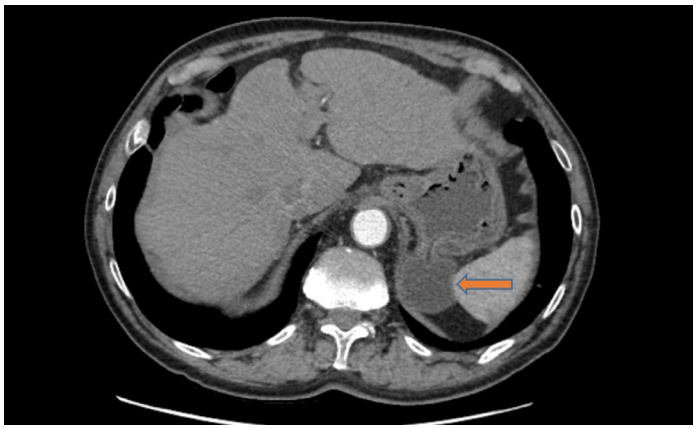

Figure 2. Computed tomography image of gastric fundus diverticulum

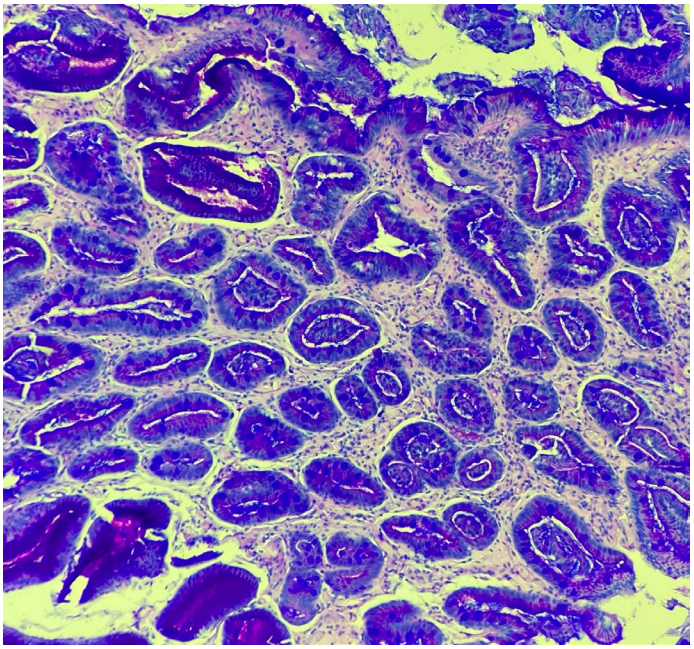

Figure 3. Gastric biopsy showing intestinal metaplasia. Magnification 100×

DISCUSSION

This study is one of the first to explore the relationship between gastric fundus diverticulum and metaplasia in English literature. The significant association between gastric diverticula and metaplasia uncovered in our study is noteworthy, given the established link between metaplasia and the progression to gastric cancer, one of the most lethal malignancies worldwide. While the exact mechanism behind this relationship remains unclear, it is plausible that the diverticulum's structure might promote

bacterial overgrowth, inflammation, and subsequent metaplastic changes. It aligns with the 'Correa cascade', a widely accepted pathogenic model of gastric cancer development, where chronic inflammation can lead to atrophic gastritis, intestinal metaplasia, dysplasia, and eventually, cancer (12).

One could speculate that the altered anatomy and physiology in the area of the diverticulum might lead to the stagnation of gastric contents, promoting metaplasia (13-15). Alternatively, the diverticulum could result from a weakened gastric wall in response to a prolonged inflammatory stimulus, such as H. pylori infection, also known as a risk factor for metaplasia. Although our study found no significant difference in the distribution of H. pylori between the two groups, previous literature described a link between H. pylori infection and gastric metaplasia (12). Given H. pylori's known role in the pathogenesis of gastric cancer, future research could further investigate the relationship between H. pylori, gastric diverticulum, and metaplasia.

A similar mechanism has been suggested in the case of intestinal diverticulosis, where inflammation within the diverticula has been associated with colonic mucosal dysplasia and adenocarcinoma (16). Other instance, colorectal diverticula have been associated with an increased risk of colorectal neoplasia, a pathogenesis thought to result from chronic inflammation (17). These parallel observations underscore the potential significance of gastric diverticulum and metaplasia and the need for further research.

It is also worth noting that there were significant differences in some laboratory parameters between the groups, namely lymphocytes, urea, albumin, Na, and K values. These findings could suggest a systemic influence of gastric diverticulum, possibly related to inflammation, nutritional status, or electrolyte balance. However, further studies are needed to elucidate the potential implications of these variations.

Study Limitations

While our study presents novel insights into the potential association between gastric fundus diverticulum and metaplasia, it is important to acknowledge its limitations.

Firstly, the retrospective nature of our study may introduce selection bias and limit the ability to establish a causal relationship between gastric diverticulum and metaplasia. Secondly, although our sample size is larger than many previous studies on this topic, it remains relatively small, given the rarity of the gastric diverticulum. This limited sample size may reduce our findings' statistical power and the results' generalizability to the broader population. Thirdly, due to the design of our study, we could not account for potential confounding factors such as the patients' dietary habits, medication use, and other lifestyle factors that might influence the risk of metaplasia. Lastly, the lack of follow-up data in our study means we cannot ascertain whether the patients with metaplasia progressed to dysplasia or gastric cancer, which limits our understanding of the clinical implications of our findings.

CONCLUSION

This study uncovers a novel association between gastric fundus diverticulum and increased metaplasia positivity, potentially implicating gastric diverticulum as a risk factor in gastric cancer development. This highlights the importance of vigilant surveillance in patients with gastric diverticulum and invites further investigation into the underlying mechanisms. The identified discrepancies in laboratory parameters further extend the potential clinical implications of this condition. Future prospective studies with larger cohorts are warranted to corroborate these findings and pave the way for improved patient care and prognosis.

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

Ethical approval: *The study was conducted in accordance with the Helsinki Declaration principles and was approved by our Corporate Ethics Committee Giresun Training and Research Hospital (2023/KAEK-93).*

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Research Article

Relationship Between Chronic Spontaneous Urticaria and Fibromyalgia Syndrome

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Abstract

Aim: Autoimmunity, peripheral nerve dysfunction, and neurogenic inflammation are common mechanisms in chronic spontaneous urticaria (CSU) and fibromyalgia syndrome (FMS). We aimed to detect the prevalence of FMS in patients with CSU and to determine whether this prevalence was affected by the severity of urticaria, and dermatology life quality.

Material and Methods: Fifty-three patients with CSU and 49 controls were enrolled in this prospective, controlled, cross-sectional study. The severity of CSU was assessed using Urticaria Activity Scores (UAS), and Dermatology Life Quality Index (DLQI) scores were recorded. The 2016 fibromyalgia diagnostic criteria were used for the diagnosis of FMS, and FMS-related functional disability was assessed using the Fibromyalgia Impact Questionnaire (FIQ).

Results: Fibromiyalgia prevalence and the FIQ scores were higher in the CSU group than in the control (p=0.033 and p=0.004, respectively). There was no statistically significant difference between the urticaria durations and UAS of CSU with and without FMS (p>0.05), but DLQI scores were statistically significantly higher in CSU with FMS (p=0.007). A statistically significant moderate positive correlation was present between DLQI and FIQ, Widespread Pain Index, and Symptom Severity Scale scores (r=0.500, r=0.408, r=0.469, r=0.507, respectively).

Conclusions: The prevalence of FMS and the disability due to FMS was increased in CSU. Furthermore, the FMS prevalence was not affected by the duration and severity of urticaria; however, it was associated with decreased quality of life.

Keywords: Fibromyalgia syndrome, chronic urticaria, quality of life

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a skin disorder characterized by itchy wheals and/or angioedema for 6 weeks or more in the absence of identifiable physical or other stimuli and accounts for half to three-quarters of all cases of chronic urticaria. It is most common between the ages of 20 and 40, with a higher incidence in women. Although CSU etiopathogenesis is not yet clear, immunological and inflammatory mechanisms have been shown to play a considerable role (1). Chronic spontaneous urticaria has been associated with various autoimmune and chronic inflammatory diseases such as autoimmune thyroiditis and connective tissue diseases (2). Depression, anxiety, and psychological stress play a role in the CSU etiology and might lead to exacerbations (3). Peripheral nerves have been shown to contribute to the pathophysiology of chronic urticaria, and some neuropeptides exacerbate the disease (4). It has been shown that there is a network that communicates between cutaneous sensory nerve fibers and immune system cells in the skin. The neuropeptides secreted from the nerve endings affect the target cells and are responsible for erythema, edema, temperature increase, and itching. Mast cells, one of the most crucial cells involved in the pathogenesis of chronic urticaria, play a critical role in this

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neuroimmune bond (5).

Fibromyalgia syndrome (FMS) is a chronic pain syndrome characterized by widespread and chronic musculoskeletal pain, accompanied by sleep disturbance, fatigue, morning stiffness, and cognitive disorders. Its prevalence varies from 0.2–6.6%, with a more common incidence in women (6). Fibromyalgia syndrome has been shown to coexist with diseases wherein emotional factors play a role in the etiology, such as dysmenorrhea, depression, migraine, and irritable bowel syndrome, and chronic inflammatory and autoimmune diseases, such as psoriasis and systemic lupus erythematosus (7-9). Although the pathophysiology of FMS has not been fully elucidated, it is thought that the disease may be associated with changes and dysfunction in peripheral cutaneous nerve fibers. In addition, neurogenic inflammation is higher in skin biopsy samples obtained from FMS patients than in those from non-FMS individuals (10). Again, previous studies have reported that mast cells play a significant role in FMS development (11). No routine blood test or imaging technique is recommended for diagnosing FMS. The 1990 FMS diagnostic criteria of the American College of Rheumatology (ACR), based on tender point examination, have been used in FMS diagnosis for many years. However, since these criteria are difficult to apply in clinical practice and do not include symptoms such as fatigue, sleep disturbance, and cognitive impairment, these criteria have been revised over the years, which led to the emergence of ACR 2010, 2013, and 2016 diagnostic criteria (12).

Neurogenic inflammation is a common pathogenetic factor in both CSU and FMS. Furthermore, the association of both these diseases with autoimmunity, chronic inflammation, and psychological stress is clear (2,3,7-9). Hence, we aimed to investigate FMS prevalence in CSU patients and the relationship of FMS incidence with urticaria activity and dermatology quality of life. Several studies have investigated the relationship between chronic urticaria and FMS. However, unlike these studies, we used the ACR 2016 diagnostic criteria for FMS diagnosis in the current study.

MATERIAL AND METHOD

Ethical Aspects

The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Hatay Mustafa Kemal University (approval number: 2022/75, date: 22.08.2022).

Study Design

This study was conducted in Dermatology and Physical Therapy and Rehabilitation outpatient clinics of Giresun University Giresun Training and Research Hospital between September 1, 2022 and March 1, 2023. Fifty-three patients diagnosed with CSU and 49 healthy volunteers matched according to age and sex were recruited in this prospective, controlled, cross-sectional study. Patients with a history of malignancy; musculoskeletal, neurological, endocrinological, or rheumatic diseases; severe depression; congestive heart failure; psoriasis; chronic episodic urticaria; or chronic inducible urticaria were excluded from the study.

The urticaria activity score (UAS) was used to determine the disease activity in the CSU group. Urticaria activity score was determined based on the approximate number of urticaria plaques (0=none; 1=mild, ≤20 plaques/24 h; 2=moderate, 21–50 plaques/24 h; and 3=severe, >50 plaques/24 h) and the severity of pruritus (0=none, 1=mild, 2=moderate, and 3=severe) in the previous week from the statements of the patients (1).

Then, all patients were given the dermatology life quality index (DQLI) questionnaire. Dermatology life quality index comprised 10 questions that evaluated the daily activities of a person in the last week, including the way they spend their free time, their relationships, and their feelings. The first and the second questions of the questionnaire are about symptoms and emotions; the third and fourth questions are about daily activities; the fifth and sixth questions are about leisure activities; the seventh question is about work and school; the eighth and ninth questions are about interpersonal relationships; and the tenth question is about treatment. The scoring was as follows: “quite a lot=3 points”, “a lot=2 points”, “mild=1 point”, “none=0 point”, “not related=0 points”, and the total score of the scale, which can vary between 0 and 30, is the sum of the scores of each question. High scores in DLQI indicate low quality of life (13).

Physical examination for FMS diagnosis was performed by experienced physical medicine and rehabilitation specialists. The ACR 2016 diagnostic criteria were used as diagnostic criteria in this study. The scale used in the 2016 ACR diagnostic criteria comprised two parts: the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS). The sum of WPI and SSS scores gives the Fibromyalgia Score (FS). Widespread Pain Index indicates in how many of the 19 lower regions (left upper, right upper, left lower, right lower, and axial) there was pain in the last week. The total score in WPI can be between 0 and 19. In SSS scale, fatigue, waking up restless, and cognitive symptoms are evaluated from 0–3 points depending on the severity of the symptoms that existed in the last week, and whether there is pain and cramping in the abdomen, depression, and headache in the last 6 months (0–1 points) is questioned. The total score lies between 0 and 12. According to the 2016 diagnostic criteria, FMS is diagnosed in patients and volunteers who experienced generalized pain and other symptoms for three months. Generalized pain was defined as having pain in at least four of the five regions, except for the chin, chest, and abdomen. Moreover, the patients also needed to have WPI≥7 and SSS≥5, or WPI 4–6 and SSS≥9 (12). In addition, a 10-item fibromyalgia impact questionnaire (FIQ) was administered to all participants to determine the FMS-

related effect rate and functional restriction. The first item of the questionnaire includes 11 Likert-type questions evaluating the daily activities of the patients, and the questions are scored from 0–3; the total score is the average of the scores of all 11 questions. In the second item, the patient is questioned about the day they felt good in the last week. In the third item, they are questioned about the day when they could not go to work in the last week. The scores of the first three items are normalized (the score obtained from the first item is multiplied by 3.3, and the scores obtained from the second and the third items are each multiplied by 1.4). The remaining seven questions are related to the severity of symptoms, pain, fatigue, restless sleep, stiffness, anxiety, and depression, and the responses are evaluated on a 10-point scale. A total score of 0–100 is possible from the survey. The average score of a patient diagnosed with FMS is 50, and a higher score means more severe disease (14).

Statistical Analysis

Statistical analyses were performed using the SPSS software version 23. Parametric, nonparametric, and categorical parameters were presented respectively as mean±standard deviation (SD), median (interquartile range (IQR), and numbers (%). The Shapiro-Wilk test was used for testing assumption of normality in numerical variables. Pearson's Chi-square test or Fisher's exact test was used to compare the categorical data. The chi-square and Fisher's exact tests were used to identify the significance of the relationships between categorical variables. To compare the data between two independent groups, Student's t-test was used for variables with a normal distribution and the Mann-Whitney U-test for variables without a normal distribution. The Spearman correlation coefficient was used to evaluate the relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Fifty-three CSU patients and 49 healthy controls were included in this study. There was no difference in the demographic characteristics of the two groups (Table 1). The incidence of FMS in the CSU group (n=14, 26.4%) was significantly higher than in the control group (n=4, 8.2%) (p=0.016). Further, 92.8% of the CSU patients diagnosed with FMS were women, while all FMS patients in the control group were women. Among all patients diagnosed with FMS, the female/male ratio was 17/1. The FIQ score was significantly higher in the CSU group than in the control group (p=0.004, Table 1).

Next, we compared the CSU patients with and without FMS (Table 2). The mean age of CSU patients diagnosed with FMS (47.14±8.87 years) was higher than that of the non-FMS CSU group (38.00±13.84 years, p=0.026). There was no significant difference between these two groups in terms of sex, body mass index, duration of urticaria, family history, or status of receiving treatment for urticaria. A significantly higher number of CSU patients with fibromyalgia were in secondary school or below (n=14, 100%) compared to those without fibromyalgia (n=18, 46.2%; p<0.001). While there was no difference between the two groups in terms of urticaria duration and UAS, the DQLI scores were significantly higher in the group with fibromyalgia (10.21±4.74) than in the group without fibromyalgia (6.38±4.25, p=0.007).

The relationships between urticaria duration, UAS and DLQI, FIQ, WPI, SSS scores, and FS are presented in Table 3. Accordingly, a statistically significant moderate positive correlation was present between DLQI and FIQ, WPI, SSS scores, and FS (r=0.500, r=0.408, r=0.469, r=0.507, respectively).

Table 1. Comparison of chronic spontaneous urticaria and control groups according to their demographic characteristics, dermatology life quality index, fibromyalgia impact questionnaire scores, and the presence of the fibromyalgia syndrome

	Urticaria (n=53)	Control (n=49)	p-value
Age (years)	40.42±13.35	40.39±13.29	0.992
Sex			0.463
Female	47 (88.7)	41 (83.7)	
Male	6 (11.3)	8 (16.3)	
BMI (kg/m²)	26.81 (23.87-31.02)	24.61 (22.83-27.99)	0.086
DLQI	7.00 (4.00-10.50)	0.00 (0.00-2.00)	**<0.001**
Diagnosed with FMS	14 (26.4)	4 (8.2)	**0.016**
Female	13 (92.8)	4 (100)	
Male	1 (7.2)	0 (0)	
FIQ score	36.10 (16.88-56.94)	19.01 (9.50-36.83)	**0.004**

BMI: body mass index, DLQI: dermatology life quality index, FMS: fibromyalgia syndrome, FIQ: fibromyalgia impact questionnaire

Table 2. Comparison of patients with and without fibromyalgia syndrome according to the demographic and clinical characteristics in the patients with chronic urticaria

	Fibromyalgia+(n=14)	Fibromyalgia-(n=39)	p-value
Age (years)	47.14±8.87	38.00±13.84	0.026
Sex			1.00
Female	13 (92.9)	34 (87.2)	
Male	1 (7.1%)	5 (12.8)	
Education			**<0.001**
Secondary school and below	14 (100.0)	18 (46.2)	
High school and above	0 (0.0)	21 (53.8)	
BMI (kg/m²)	29.82±3.45	26.71±5.65	0.060
Disease duration (months)	9.50 (5.50-48.00)	24.00 (6.00-48.0)	0.598
Urticaria history in the family			0.649
Yes	2 (14.3)	4 (10.3)	
No	12 (85.7)	35 (89.7)	
Status of treatment			0.182
Receiving	12 (85.7)	25 (65.1)	
Not receiving	2 (14.3)	14 (34.9)	
UAS	22.43±9.44	20.10±12.17	0.520
DLQI	10.21±4.74	6.38±4.25	**0.007**
FIQ score	78.93±15.52	26.56±16.16	**<0.001**
FS (WPI+SSS)	23.00 (17.75-27.25)	4.00 (2.00-7.00)	**<0.001**
WPI score	13.50 (8.00-15.25)	0.00 (0.00-2.00)	**<0.001**
SSS score	12.00 (8.75-12.00)	3.00 (1.00-5.00)	**<0.001**

BMI: body mass index, FIQ: fibromyalgia impact questionnaire, WPI: widespread pain index; SSS: symptom severity scale, FS: fibromyalgia score (WPI+SSS), UAS: urticaria activity score; DLQI: dermatology life quality index

Table 3. Relationship between the duration of urticaria, urticaria activity score, and Dermatology life quality index and fibromyalgia impact questionnaire, widespread pain index, and symptom severity scale scores in patients with chronic urticaria (n=53)

	FIQ score	WPI score	SSS score	FS
Duration of urticaria	0.098	-0.004	0.019	0.048
UAS	0.147	0.081	(0.214)	0.192
DLQI	0.500	0.408**	0.469	0.507**

FIQ: fibromyalgia impact questionnaire, WPI: widespread pain index, SSS: symptom severity scale, FS: fibromyalgia score, UAS: urticaria activity score, DLQI: dermatology life quality index; ** p<0.001

DISCUSSION

In the current study, the FMS incidence in CSU patients (26.4%) was significantly higher than in the control group (8.2%). Similar studies comparing FMS prevalence in patients with chronic urticaria and healthy volunteers have shown that the FMS incidence in the urticaria group varied between 9.7% and 70.6% (15-20). In all these studies, a higher FMS prevalence was observed in the urticaria group than in the control group, and, similar to our study, the difference in FMS prevalence between these two groups was statistically significant (15-19). Torresani et al. compared 126 patients with chronic urticaria with 50 controls and used ACR 1990 criteria for diagnosing FMS. Similar to the current study, Torresani et al. reported a significantly higher FMS prevalence in the chronic urticaria group (70.6% in the chronic urticaria group and 16% in the control group). Based on their findings, the authors suggested that the neuropeptides secreted from

the dysfunctional nerve fibers in FMS patients cause vasodilation and extravasation in the dermal vessels. These neuropeptides stimulate the nerve endings and trigger mast cell degranulation, leading to a higher release of neuropeptides. Moreover, FMS triggers cutaneous neurogenic inflammation, leading to chronic urticaria (15). In addition, the FMS incidence observed by Torresani et al. in the chronic urticaria group (70.6%) was much higher than that observed in the CSU group of our study (26.4%). The higher FMS incidence in the former study might be attributed to the inclusion of patients with autoimmune diseases, such as autoimmune thyroiditis, type 1 diabetes mellitus, and vitiligo, by Torresani et al. In another study, Hapa et al. compared 50 patients with chronic urticaria with 48 controls. They found that 26% of the urticaria patients and 20.8% of the individuals in the control group had FMS, suggesting no significant difference between the two groups (20). While the FMS prevalence in their urticaria group was similar to that observed in our chronic urticaria group, Hapa et al. reported a much higher FMS prevalence in the control group than that observed in our control group. According to Hapa et al., such high FMS prevalence in the control group might be attributed to the selection of the female sex in the control group in the foreground. In our study, although the number of women in the control group was high in order to obtain a sex-matched group to the patient group, no such results were obtained. Hence, we postulate that this discrepancy in the FMS prevalence in the control groups of the two studies might be attributed to the inclusion of individuals with other dermatological diseases in the control group by Hapa et al.

On comparing CSU patients with FMS with those without FMS, we found that the mean age of the patients with FMS was significantly higher. This finding was consistent with the previous findings that FMS was less common at a young age and that its prevalence increased with age (21-23). Many studies have reported low education levels and low socioeconomic status as risk factors for FMS and other chronic pain syndromes (22-24). Corroborating these findings, our results also showed that the education level of patients with FMS was lower than those without FMS.

Similarly, Hapa et al. found no relationship between urticaria duration and UAS and FMS prevalence (20). Contrarily, Koca et al. reported that UAS was significantly higher in urticaria patients with FMS. They also reported a positive correlation between the UAS and FIQ scores. They did not use the DLQI questionnaire but administered the Pittsburgh Sleep Quality Index and Beck Depression Scale to the patients. They reported a positive correlation between the UAS and the scores of these scales. Based on their findings, Koca et al. stated that as the severity of urticaria increases, FMS prevalence, anxiety, and depression increase in the patients. Thus, common pathogenetic mechanisms involved in both diseases warrant further elucidation (18). Yener et al., unlike our study, reported a positive correlation between both urticaria duration and UAS; and DLQI score, FMS prevalence, FMS duration, and the number of sensitive points. They attributed the relationship between chronic urticaria and FMS to underlying common etiopathogeneses, such as autoimmunity and cutaneous neurogenic inflammation (19). In our study, no significant difference was observed in urticaria duration, urticaria treatment status, or UAS between the CSU patients with and without FMS. Yet, the DLQI score was significantly higher in CSU patients diagnosed with FMS. Moreover, we found that the duration of urticaria and UAS did not correlate well with FIQ, WPI, and SSS scores. Nevertheless, these scores positively correlated with DLQI. Hence, FMS incidence was not related to the severity and activity of urticaria but was associated with the psychosocial impact rate of urticaria. Accordingly, we predict that rather than the common pathophysiologic pathway, the relationship between the two diseases may be due to emotional and psychosocial factors, which play a critical role in both.

CONCLUSION

In this study, FMS prevalence and the impact rate of fibromyalgia were found to be higher in CSU patients. This prevalence was not affected by the duration or severity of urticaria. However, it was associated with a drop in the quality of life. Outcomes of our study support that CSU with FMS possesses more restrictions in their daily life than CSU alone, and the association of two diseases might be due to common psychosocial factors. However, there is a need for extensive studies involving more patients to support this hypothesis.

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

Ethical approval: *The present study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Hatay Mustafa Kemal University (approval number: 2022/75, date: 22.08.2022).*

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Research Article

Does $MgSO_4$ Treatment Affect Maternal Aspartate Aminotransferase to Platelet Ratio Index (APRI) Score in Preterm Labor?

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Abstract

Aim: This study evaluated the association between magnesium sulfate treatment for fetal neuroprotection on APRI scores in pregnant women with the preterm birth threat.

Material and Methods: Thirty-one pregnant women hospitalized and received $MgSO_4$ for preterm birth risk in the Obstetrics and Gynecology Department, between 2019-2022 were included, and the patient records were evaluated retrospectively. The fetal neuroprotective $MgSO_4$ treatment protocol included administering a loading infusion dose of 4 grams/30 minutes followed by a 1 gram/hour infusion for 24 hours to pregnant women hospitalized for a threat of preterm labor. In addition, the electrocardiography, hemogram, and hepatic and renal functions were evaluated upon hospitalization before $MgSO_4$ administration, and patients were monitored closely. Women who gave birth before completion of 24 hours of $MgSO_4$ administration, multiple pregnancies, patients with comorbid deteriorated liver or kidney functions, preeclampsia, intrauterine growth retardation, fetal abnormalities, gestational diabetes mellitus, chorioamnionitis, adolescent and advanced age pregnancies or any other obstetric complications were excluded from analyses. The APRI score was calculated and compared between the results of the biochemical analyses performed at initiation (basal) and 12th hour of $MgSO_4$ administration.

Results: The mean APRI score at the 12th hour of administration (0.45±0.07) was significantly higher than the basal values (0.31±0.07) ($p<0.001$), but hemoglobin, hematocrit, and platelet values were similar ($p>0.05$ for all).

Conclusions: Magnesium sulfate treatment for preterm birth threat significantly increases APRI score at the 12th hour of administration.

Keywords: APRI score, $MgSO_4$ treatment, neuroprotective effect, preterm birth

INTRODUCTION

Preterm birth is a significant cause of newborn morbidity and mortality and the most frequent reason for antenatal hospitalization. In addition, premature neonates are vulnerable to long-term complications, particularly cerebral palsy. Randomized-controlled trials and meta-analyses revealed that antenatal magnesium sulfate ($MgSO_4$) administration for fetal neuroprotection when preterm birth is anticipated might decrease the neurological morbidities, including cerebral palsy and severe motor dysfunction. The $MgSO_4$ administration within 24 hours of risk of preterm delivery is also recommended by the American College of Obstetricians and Gynecologists (ACOG), World Health Organization (WHO), and several other associations (1-6).

The aspartate aminotransferase (AST) to platelet ratio index (APRI) score is a non-invasive scoring system. It is frequently used to assess liver inflammation and cellular damage and grade hepatic fibrosis. It is calculated using the AST and platelet values in routine blood sample analyses. The APRI score is more frequently used for gastrointestinal conditions but has come into gynecology-obstetrics practice recently, and this non-invasive bioindicator provides valuable information in clinical applications (7-10).

CITATION

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The $MgSO_4$ treatment has rare side effects and is safe for both mother and fetus when administered in the therapeutic range. It is primarily eliminated from kidneys, but there is no precise data regarding its use in hepatic failure (11). Also, there is no data on neuroprotective $MgSO_4$ administration on maternal APRI scores. Thus, this study aimed to evaluate the changes in APRI scores in pregnant women who received $MgSO_4$ for neuroprotective purposes.

MATERIAL AND METHOD

Thirty-one pregnant women hospitalized and received $MgSO_4$ for preterm birth risk in the Obstetrics and Gynecology Department of the Ankara Liv Hospital of Yuksek Ihtisas University, Faculty of Medicine, between 2019-2022 were included, and the patient records were evaluated retrospectively. The study protocol was approved by the Ethics Committee of Yuksek Ihtisas University (Date: 18/05/2023; Approval No: 2023/03/07).

The fetal neuroprotective $MgSO_4$ treatment protocol included administering a loading infusion dose of 4 grams/30 minutes followed by a 1 gram/hour infusion for 24 hours to pregnant women hospitalized for a threat of preterm labor. In addition, the electrocardiography, hemogram, and hepatic and renal functions were evaluated upon hospitalization before $MgSO_4$ administration, and patients were monitored closely. Hourly urine excretion and deep-tendon reflexes were followed for any adverse event. Women who gave birth before completion of 24 hours of $MgSO_4$ administration, multiple pregnancies, patients with comorbid deteriorated liver or kidney functions, preeclampsia, intrauterine growth retardation, fetal abnormalities, gestational diabetes mellitus, chorioamnionitis, adolescent and advanced age pregnancies or any other obstetric complications were excluded from analyses. Demographic characteristics of the patients, medical and obstetric histories, weeks of gestation, hemogram and biochemical test results, delivery types were were collected retrospectively from patient records. Fetal well-being of all hospitalized patients was checked with ultrasound and NST during hospitalization.

The APRI score was calculated from the results of the biochemical analyses performed at initiation (basal) and 12th hour of $MgSO_4$ administration, using the formula by Wai et al. (12), as follows:

$$APRI = \frac{AST\ (IU/L) \Big/ AST\ (ULN)}{Platelet\ (10^9/L)} \times 100$$

Statistical Analyses

Descriptive analyses were presented using mean±standard deviation after controlling for normal distribution assumptions using normality tests and visual inspections of histograms and detrended Q-Q plots for continuous variables, and frequency and percent for categorical variables. Continuous variables were compared with the Wilcoxon signed-rank test between two consecutive measurements. Statistical analyses were done in SPSS 25 (IBM Inc., Armonk, NY, USA), and a type-I error level of 5% was considered a statistical significance threshold.

RESULTS

A total of 31 patients were included in the study. The mean age of patients, the gestational week at $MgSO_4$ administration, and neonate birth weight were 29.2±5.6 years, 28.5±1.9 weeks, and 1225.2±307.6 grams, respectively. Seventeen (54.8%) patients were nulliparous, while 14 (45.2%) patients were multiparous. Eight (25.8%) patients had a spontaneous vaginal delivery, and the remaining 23 (74.2%) patients had cesarean section delivery. The sociodemographic and clinical characteristics of patients are presented in Table 1.

Table 1. Demographic and clinical characteristics of patients

	Mean±SD
Age, years	29.16±5.60
Gestational age, weeks	28.45±1.91
Birth weight, grams	1225.16±307.60
	n (%)
Parity	
Nulliparous	17 (54.8)
Multiparous	14 (45.2)
Delivery mode	
Normal	8 (25.8)
C/S	23 (74.2)

Biochemical analyses revealed that the AST levels at the 12th hour were significantly higher than the basal levels (p<0.001). However, there were no significant differences between basal and 12th-hour hemoglobin (p=0.97), hematocrit (p=0.21), and platelet (p=0.25) levels. The APRI score at the 12th hour was significantly higher than the APRI score at basal measurements (p<0.001) (Table 2).

Table 2. Biochemical analyses at initiation and 12th hour of $MgSO_4$ administration

	Basal	12th hour	p
	Mean±SD	Mean±SD	
Magnesium (mEq/L)	-	4.8±0.4	-
Hemoglobin g/dL	11.3±1.4	11.3±1.3	0.97
Hematocrit (%)	32.2±3.2	33.3±3.6	0.21
Platelet (×109/L)	241.6±19.2	240.3±18.4	0.25
AST (IU/L)	29.7±6.7	42.8±5.4	<0.001
APRI Score	0.31±0.07	0.45±0.07	<0.001

DISCUSSION

This is the first study that evaluates the effects of $MgSO_4$ on the maternal APRI scores when administered for neuroprotection in preterm labors. The analyses showed

that $MgSO_4$ administration significantly increases the APRI scores at 12th hours of administration following the loading dose. Our findings showed that APRI score of the pregnant patients can change with the administration of MgSO4. Results of this study may support the current clinical practice and usage of APRI score in the patient follow up in the treatment of magnesium sulfate.

The $MgSO_4$ administration is the first choice of intervention to manage severe preeclampsia and eclampsia. However, it has been more used for neuroprotective purposes in recent years. Many tocolytic drugs for women are used in preterm labor to prolong pregnancy and reduce birth damage associated with prematurity. It has a neuroprotective effect in the newborn, when magnesium sulfate ($MgSO_4$) is used prenatally in mothers at risk of preterm delivery. Therefore, $MgSO_4$ is frequently used for tocolytic purposes.

The research showed that in-utero exposure to $MgSO_4$ before early preterm delivery decreases the incidence and severity of cerebral palsy. It is also considered safe or might cause more favorable or manageable side effects when administered in therapeutic doses (13-14). No complications were observed in our study due to $MgSO_4$ administration.

Several mechanisms were suggested for the neuroprotective features of $MgSO_4$ administration, including stabilization of cerebral circulation by stabilizing blood pressure and normalizing cerebral blood flow, prevention of excitatory injury by stabilizing neuronal membranes and blockade excitatory neurotransmitters, such as glutamate. Moreover, $MgSO_4$ is a robust antioxidant with significant anti-inflammatory effects (15).

Several previous studies reported data on the effects of $MgSO_4$ administration on the immune and inflammatory responses. In one of those, Sugimoto et al. showed that $MgSO_4$ administration decreases the TNF-α and IL-6 production, which has roles in inflammatory processes (16), which was also demonstrated by other studies (17). Another study by Haruka Suzuki-Kakisaka reported reductions in the levels of TNF-α and IL-6 (18). An animal model has recently evaluated the lipopolysaccharide-simulated inflammation in brain tissue during pregnancy and reported that $MgSO_4$ administration decreased proinflammatory cytokine production (19). Another study found that maternal $MgSO_4$ administration prevents brain damage in the neonate, but without any decreases in the cerebral IL-1β levels, contrary to other studies, which suggests that the neuroprotective effects of $MgSO_4$ administration are not mediated by the inhibition of inflammatory cytokine production (20). Nevertheless, a recent study reported that $MgSO_4$ administration increases the inflammatory indexes, contrary to others. Orgul et al. evaluated 63 pregnant women hospitalized for preterm labor, and reported that $MgSO_4$ administration increases the inflammatory indexes including neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index at 6th hour of administration, which contradicts with other studies regarding the inflammatory characteristics of magnesium, and concluded that preterm labor is an inflammatory process per se, might be affected from many factors, and may change rapidly (21).

A recent study has evaluated the effects of $MgSO_4$ on the hepatic ischemia/reperfusion damage in a rat model, and the results from 32 adult female Wistar-Albino rats revealed that $MgSO_4$ administration pretreatment moderately decreased the liver damage through its anti-inflammatory and anti-oxidant effects (22).

There are only limited number of studies on the effects of $MgSO_4$ treatment on the liver functions. In one of those studies from 2018, the effects of $MgSO_4$ treatment on liver functions in major depressive disorder cases were evaluated, and no significant effects were found (23). In contrary to that study, we found that AST levels were increased 12 hours after the initiation of $MgSO_4$ infusion. Nevertheless, this increase was temporary, and we observed normal hepatic functions at the postpartum 2^{nd} day. The increase in the APRI score following $MgSO_4$ administration that we observed has not been reported in the literature. Although the $MgSO_4$ is metabolized from kidneys, our results also suggests that it might have effects also on liver. Further studies with larger sample sizes may warrant better elucidation of these effects.

Recently; The APRI score, which is frequently the subject of research in inflammation, malignancies, cardiovascular diseases, and infections such as covid 19, continues to be the subject of new research in the field of obstetrics. Especially in viral infections such as covid 19, the APRI score, which can show the severity of the infection, continues to be interesting (24,25). In our study, it will be instrumental in putting forward the idea that the APRI score can be put into practical use in the field of obstetrics. If these findings are supported by larger studies, a low-cost and practical scoring system will contribute to the clinic. In a similar article in which some non-invasive and low-cost biomarkers, such as APRI, determined from blood parameters, were examined in preterm births in obstetric practice. The idea of integrating such low-cost biomarkers into clinical usage was discussed (26).

Besides its promising results, our study is not without some limitations. First, the sample size is relatively low due to the study design, and our results needs confirmation by further studies with larger sample sizes. In addition, another limitation is that the study was a single center study. Supporting our findings with multicenter studies will provide broader contributions to the literature. Last but not least, we could only evaluate the short-term outcomes of $MgSO_4$ treatment, thus long-term outcomes need to be evaluated in future studies with longer follow-up periods.

Nevertheless, despite its limitations, our study will also be beneficial in terms of opening up new horizons for

clinicians. It is a research that gives us the idea that a treatment protocol such as $MgSO_4$ that can cause potential toxicity can be predicted with a simple non-invasive biomarker and necessary precautions can be provided.

CONCLUSION

The APRI score significantly increases at the 12th hour of $MgSO_4$ infusion administered for neuroprotective purposes in preterm labors. Further prospective studies may be helpful to understand the pathophysiological effect of neuroprotective magnesium sulfate administration on maternal APRI Score levels.

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Research Article

Examining the Influence of the COVID-19 Pandemic Process on Nurses and Society's Perception of the Nursing Image

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Abstract

Aim: The purpose of this study was to conduct comparative examination of the influence of the COVID-19 pandemic process on the nursing image perceptions of nurses and individuals forming the society.

Material and Methods: This study was carried out using the cross-sectional descriptive research design. The study was conducted online between November 2020 and June 2021 due to the COVID-19 pandemic process. The research sample consisted of 710 people, and the data were collected with the Personal Identification Form and the Nursing Image Scale.

Results: The nurses' nursing image scale total score was found to be statistically significantly higher than the scores of the individuals representing the society ($p<0.05$). On the other hand, it was found that when compared to nurses, individuals representing the society considered nursing more to be a profession and that the pandemic had positively changed nurses' perspective on the nursing profession. In addition, according to the results, the pandemic made the nursing profession visible, and the awareness of the place of the nursing profession in the society increased due to the pandemic. Moreover, the results also showed that nurses considered themselves to be an important member of the health staff as they were always in the field with their caregiver roles ($p<0.05$).

Conclusions: The nursing image mean scores of the nurses and those of the individuals representing the society were found to be highly positive compared to the pre-pandemic period. In the study, it was revealed that the way the nurses did their job professionally was perceived by the society with the COVID-19 pandemic process and that with this rising awareness, the society's perception of the nursing image increased positively. It is recommended that researchers conduct studies on how to further develop the perception of nursing professional image through social media.

Keywords: Nurses, nursing image, perception, COVID 19, pandemics, society

INTRODUCTION

The COVID-19 outbreak originated in China and had a significant impact on nurses due to its spread, mortality rate and care burden (1). It was pointed out that during the COVID-19 pandemic, most nurses had to work in emergency and intensive care units where they had no experience and that this situation caused them to experience many problems (2). Countries were in lockdown with the COVID-19 pandemic, and chronically underfunded healthcare systems were dangerously close to meltdown (3). However, stories of inspiration and innovation as well as achievements related to the nursing care provided emerged through the pessimism caused by the pandemic (4). Especially nurses constitute more than half of the global healthcare workforce worldwide, and they are regarded as the backbone of the healthcare system (5,6). The knowledge, experience and counseling of the nursing profession has become an important part of the strategy of controlling the pandemic, and the practice of nursing now acts as a basis for the care and survival of patients severely affected by COVID-19 (3). For this reason, it is thought that the image of nursing might have been affected during the COVID-19 process.

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The nursing image has important influence on the development of nursing competence and on the quality of nursing care (7). Nurses' positive and negative perceptions of their public image are related to their self-concept, self-esteem, job satisfaction and their performances. It is also important that nurses, who have an important place in the health system, have a positive perception of themselves and of their profession (8). The opinion of the society about the image of nursing affects the nursing profession, members of the profession and candidates of the profession in a positive or negative way. The society still does not know enough about the contemporary roles and responsibilities, education, and economic and social aspects of the nursing profession. People think that the duties of nurses are only to take blood from the patient, to measure blood pressure and so on (9). The COVID-19 pandemic process will be a period in which the dignity and autonomy of nurses will be revealed with the recognition of the importance of nursing in our country and in the world and with the understanding of its indispensable place in the delivery of health care services (10). It is important to contribute to the reinforcement of the professional identity of nursing, which is considered a critical resource, and to determine and evaluate the image of nursing in terms of its position in the society (11). In one study, it was found important to improve the nursing image perception of the society and the nurses' own professional image perceptions in a positive way in order to increase nurses' job performance and to reduce their intention to quit the job (12). When the literature was examined, no study could be found that compared the nursing image perception of the society and of nurses. In this respect, the purpose of this study was to compare the two groups with respect to the impact of the COVID-19 pandemic process on the nursing image perceptions of nurses and of individuals forming the society.

MATERIAL AND METHOD

Research Design

This study was carried out using the cross-sectional descriptive research design.

Place and Time of the Study

The study was conducted online between November 2020 and June 2021 due to the COVID-19 pandemic process.

Research Sample

A total of 710 people, who were nurses and individuals in the society, were included in the research sample. In the study, the snowball sampling method, one of the non-probabilistic sampling methods, was used to reach individuals in the society through social media tools. The criteria for inclusion in the sample were volunteering to participate in the study, being 18 years old or older, being literate and being able to communicate. In the study, G*Power version 3.1 was used for calculating the sample size (13). At the end of the study, the power of the study was calculated with the G* Power program using the data obtained in this study. In the G*Power program, the power of the study was found to be “1” when the effect size was 0.92, α=0.05 and the sample size was 311 for the group of nurses and 399 for the society.

Data Collection Tools

Personal Identification Form

The form was developed by the researchers in line with the related literature. In the form, there were questions regarding the participant's age, gender, the presence of a nurse in the family and so on (14,15).

Nursing Image Scale

The scale was developed as a questionnaire by Özsoy (2000), yet its psychometric properties were not examined (16). Later, it was turned into a scale by Çınar and Demir (2009) by conducting its validity and reliability analyses. In order to measure the nursing image of the society, the scale consisted of 28 items regarding the individuals’ views about the image of the nursing profession. There were three sub-dimensions in the scale: "Appearance, Communication and Vocational and Educational Qualifications”. The internal consistency Cronbach alpha reliability coefficient of the scale was .81. The lowest score to be obtained from the scale was 28, and the highest score was 84. The item-total score correlation values varied between .64-.30. In this study, the total scale score was grouped by the authors as weak (between 28-47 points), moderate (between 46.5-65 points) and high (between 66-84 points) for the evaluation/interpretation of the scale findings more easily. An increase in the total score indicated that the image of nursing was positive (16,17). For this study, the Cronbach alpha value was found to be .86.

Data Collection Process

The survey forms created with Google forms were shared via social media tools (such as WhatsApp, Instagram, twitter), and those who responded to the survey were asked to share with other people. For each of the items in the Nursing Image Scale, one of the data collection tools, the individuals were expected to evaluate their perceptions during the pandemic process. It took an average of 10 minutes to fill out the questionnaire.

Analysis of the Research Data

The data were analyzed in computer environment using the statistical software of SPSS 25.0 (IBM SPSS Statistics, Chicago, IL, USA). Student t test and Chi-square analysis for the independent groups were applied for the comparison of the perceptions of the nurses and society regarding nursing and their professional image perceptions during the COVID-19 process. In the study, the statistical significance level for the variables was taken as $p<0.05$.

Research Ethics

In order to conduct the research process, the approval of the non-invasive clinical research ethics committee of the Medicine Faculty of a University was obtained. Moreover, permission from the Turkish Ministry of Health was taken for the present study. In addition, consent of the authors who adapted the scale was obtained. In addition, online consents of the individuals who met the criteria for inclusion in the study and who agreed to participate in the study were taken as well. Permission from the research sample; The consent of the research sample was obtained via the Informed Consent Form, which included information about the purpose of the study, the implementation process, data collection, voluntary participation in the study, the participants' freedom of leaving the research process at any time, and confidentiality of the participants' names.

RESULTS

The average age of the nurses in the research sample was 26.28±7.37, while it was 33.95±10.73 for the individuals representing the society. According to the results, 80.7% of the nurses were women; 96.5% had a bachelor's degree or higher; and 58.8% perceived their income as equal to their expenses. The results also showed that in the research sample, 66.9% of the individuals representing the society were women; 79.2% had a bachelor's degree or higher; and 49.1% perceived their income as equal to their expenses (Table 1).

It was revealed that there was news/information attracting the attention of the nurses about any development or difficulties they experienced regarding the nursing profession during the pandemic compared to the individuals in the society and that the sources of their knowledge were social media. Moreover, it was seen that the profession of nursing reminded them of heroes during the pandemic and that they thought nurses were important members of healthcare teams in the pandemic process. Furthermore, the they knew it was a year declared by WHO as 'Year of Nursing' ($p<0.05$). On the other hand, when compared to the nurses, the individuals representing the society thought that the pandemic reminded them of the profession more and that the pandemic changed the viewpoint about the nursing profession positively. Additionally, the pandemic made the nursing profession visible, and the awareness of the place of the nursing profession in the society increased due to the pandemic. Moreover, it was seen that nurses were important members of the healthcare team during the pandemic process as they were always in the field with their caregiver roles ($p<0.05$). In addition, it was revealed that the nurses' nursing image scale total score was statistically significantly higher than the scores of the individuals representing the society ($p<0.05$). There was no statistical difference between the nurses and individuals representing the society in terms of the change caused by the pandemic in the viewpoint about the nursing profession ($p>0.05$) (Table 2).

Table 1. Examining the introductory characteristics of the nurses and of the individuals in the society (n: 710)

Variables	Nurses (n: 311) n (%)	Society (Non-health professions/non-working individuals) (n: 399) n (%)
Gender		
Female	251 (80.7)	267 (66.9)
Male	60 (19.3)	132 (33.1)
Educational background		
Literate/elementary school	0 (0)	21 (5.3)
High school	11 (3.5)	62 (15.5)
Bachelor's degree and higher	300 (96.5)	316 (79.2)
Economical situation		
Income lower than expenses	82 (26.4)	121 (30.3)
Income equal to expenses	183 (58.8)	196 (49.1)
Income higher than expenses	46 (14.8)	82 (20.6)
Marital status		
Single	231 (74.3)	192 (48.1)
Married	80 (25.7)	207 (51.9)
Region of accommodation		
Southeast Anatolia region	175 (56.3)	170 (42.6)
Eastern Anatolia region	13 (42.0)	14 (3.5)
Central Anatolia region	21 (6.8)	46 (11.5)
Marmara region	16 (5.1)	41 (10.3)
Aegean region	15 (4.8)	49 (12.3)
Mediterranean region	66 (21.4)	70 (17.5)
Black Sea region	5 (1.6)	9 (2.3)
Having an acquaintance around who is a nurse		
Yes	264 (84.9)	326 (81.7)
No	47 (15.1)	73 (18.3)
Having received a nursing service before		
Yes	250 (80.4)	242 (60.7)
No	61 (19.6)	157 (39.3)
Previous companionship		
Yes	228 (73.3)	309 (77.4)
No	83 (26.7)	90 (22.6)
	$\bar{x}$±SS (Min-Max)	$\bar{x}$±SS (Min-Max)
Age	26.28±7.37 (18.00-56.00)	33.95±10.73 (18.00-66.00)

Table 2. Comparison of the mean scores of the nurses and individuals in the society regarding the nursing image scale and its sub-dimensions and their views about the nursing profession during the COVID-19 pandemic period (n:710)

Views about the nursing profession	Nurses (n: 311) n (%)	Society (Non-health professions/ individuals) (n: 399) n (%)	Test; p value
News/information drawing their attention about any development or difficulties experienced in relation to the nursing profession during the pandemic.			
Yes	287 (92.3)	345 (86.5)	χ^2=6.047 p=0.014
No	24 (7.7)	54 (13.5)	
***Source of news/information**			
Social media	184 (59.2)	231 (57.9)	χ^2=22.419 p=0.000
Press releases of professional organizations	64 (20.6)	40 (10.0)	
Television	63 (20.3)	128 (32.1)	
What the profession of nursing reminded of before the pandemic?			
Profession of caregiving	88 (28.3)	44 (11.0)	χ^2=45.595 p=0.000
An overburdened and exploited profession	3 (1.0)	2 (0.5)	
doctor's assistant	43 (13.8)	102 (25.6)	
Hero	23 (7.4)	29 (7.3)	
Sister	1 (0.3)	9 (2.3)	
Profession	153 (49.2)	213 (53.4)	
What the profession of nursing reminded of during the pandemic?			
Profession of caregiving	52 (16.7)	27 (6.8)	χ^2=44.787 p=0.000
An overburdened and exploited profession	13 (4.2)	2 (0.5)	
Doctor's assistant	12 (3.9)	48 (12.0)	
Hero	173 (55.6)	217 (54.4)	
Sister	2 (0.6)	7 (1.8)	
Profession	59 (19.0)	98 (24.6)	
Willingness to become a nurse before the pandemic			
Yes	162 (52.1)	122 (30.6)	χ^2=89.196 p=0.000
I never wanted	44 (14.1)	182 (45.6)	
I'm undecided	53 (17.0)	67 (16.8)	
I wanted to before the pandemic, but I don't want it now	52 (16.7)	28 (7.0)	
The pandemic changing the viewpoint about the nursing profession *			
Changed	174 (56.0)	222 (55.6)	χ^2=0.073 p=0.964
Partly changed	53 (17.0)	71 (17.8)	
No change	84 (27.0)	106 (26.6)	
*****Is the change in the viewpoint about the nursing profession positive due to the pandemic?**			
Yes	130 (62.2)	220 (81.2)	χ^2=54.948 p=0.000
No	60 (28.7)	12 (4.4)	
Partly	19 (9.1)	39 (14.4)	
Thinking that the pandemic made the nursing profession visible			
Yes	192 (61.7)	290 (72.7)	χ^2=23.586 p=0.000
No	54 (17.4)	24 (6.0)	
Partly	65 (20.9)	85 (21.3)	
Thinking that awareness of the place of the nursing profession in the society has increased due to the pandemic.			
Yes	108 (34.7)	216 (54.1)	χ^2=47.118 p=0.000
No	87 (28.0)	39 (9.8)	
Partly	116 (37.3)	144 (36.1)	
Thinking that the nurse is an important member of the healthcare team during the pandemic process.			
Yes	301 (96.8)	370 (92.7)	χ^2=5.530 p=0.019
No	10 (3.2)	29 (7.3)	
The reason why the nurse is an important member of the healthcare team during the pandemic process			
The burden they take is too much, and they are responsible for caregiving	14 (6.1)	16 (6.1)	χ^2=25.672 p=0.019
They were always in the field with their caregiver roles	163 (71.2)	200 (76.3)	
They worked at the cost of their lives	8 (3.5)	29 (11.1)	
They worked in close contact with patients	44 (19.2)	17 (6.5)	
Knowing that 2020 was declared as the 'Year of Nursing' by the World Health Organization			
Knows	237 (76.2)	181 (45.4)	χ^2=68.664 p=0.000
Does not know	74 (23.8)	218 (54.6)	
	Mean±SD	**Mean±SD**	**Test; p value**
Nursing image scale total score	74.14±6.60	68.15±7.98	t=10.935* p=0.000

*Chi-square analysis, ** student t-test for independent groups, *** those reporting a change in viewpoint responded

DISCUSSION

Nurses' Image Perception

In the study, it was found that there was news/information attracting the attention of nurses about any development or difficulties they experienced regarding the nursing profession during the pandemic compared to the individuals in the society. In addition, it was revealed that the sources of their knowledge were social media and that the profession of nursing reminded them of heroes during the pandemic. Furthermore, they thought nurses were important members of a healthcare team in the pandemic process, and they knew it was a year declared by WHO as 'Year of Nursing'. In their study, O'Leary, et al. (2021) examined the tweets shared by 2790 people and by various organizations during the COVID-19 pandemic. In the study, it was revealed that in addition to the disseminating information, nurses tried to reach political and health service leaders through social media in order to solve the problems experienced during the COVID-19 process (18). The problems experienced during the COVID-19 pandemic exposed nurses to psychological stress, burnout, depression and so on (19,20). On the other hand, the expression of the problems experienced by nurses in the media and the search for solutions to the problems experienced by the relevant professional organizations left their mark on the media (21,22-25). Many artistic images of the courage and sacrifices of nurses during the COVID-19 pandemic were shared on social media, and they became a legend in the war against Corona (23). The reason for this situation is thought to be because the nurses were at the forefront of the war against the COVID-19 pandemic because the health institutions lacked the necessary material and/or staff as well as because there were nurse deaths during their efforts for solving the problems they experienced and for following up the situation.

The total score of the nurses in the nursing image scale was found to be statistically significantly higher than the scores of the individuals representing the society ($p<0.05$). In many studies examining the professional image perceptions of nurses before the pandemic, it was revealed that the image perception of the nurses compared to the society was moderately positive (15, 26-28). Takase, Maude & Manias, (2006), in their study, found that the nurses' perception of professional leadership and professional image was more positive than the perception of society. As the nurses' perception of professional image increased, there was an increase in their job performance and a decrease in their intention to quit the profession (26). In a study conducted with nursing intern students during the pandemic, it was seen that they had moderate levels of professional image perceptions (29). In the present study, it was found that during the COVID-19 process, the nurses had high levels of professional image perceptions (74.14±6.60), which were statistically more positive when compared to the society's nursing image perception. In a study, it was reported that the nurses involved in the care of COVID-19 patients had a significantly higher level of professional identity when compared to the nurses who did not give care to COVID-19 patients (30). In a qualitative study examining the nurses' perceptions of professionalism in the COVID-19 process through their social media accounts, one of the nurses stated that "We are nurses, and we have a major role in educating people about COVID-19", while another nurse pointed out that "Patients with corona are terrified and anxious, and it is our responsibility to stand with them during this difficult time." In the present study carried out via social media, it was seen that despite the difficulties brought about by COVID-19, the nurses acted professionally by being conscious of the COVID-19 process and of their professional responsibility for their patients (31). In a study, it was found that the nursing students who chose the nursing profession voluntarily had more positive perceptions of professional image when compared to the students who chose the nursing profession unwillingly (32). In this study, it was thought that there were two reasons why the professional image perception scores of the nurses were statistically significantly higher when compared to those of the society. One of these reasons could be the fact that the COVID-19 pandemic developed/increased the professional identity of the nurses, and another reason might be the fact that more than half of the nurses participating in the study chose the profession willingly (Table 2).

Image Perception of the Society

It was found that nursing reminded the individuals representing the society of the profession to a higher extent before the pandemic when compared to the nurses and that the society perceived the nursing image perception highly positively. In literature, there are several studies conducted to examine the society's perception of the nursing image before the pandemic in Turkey. Some studies revealed that the society had moderately positive perceptions regarding the nursing image (12,15,33), while some other studies demonstrated that the society had negative perceptions regarding the nursing image (34). In a study carried out by Tan, Yuncu, Şentürk & Yıldız (2007), the negative perception of the nursing image might be due to the sample difference. In another study conducted with the same scale used in this study in Turkey before the pandemic, it was found that the society perceived the professional image of nursing as moderately positive (35). In another study carried out by Şahan, Yıldız, & Ergin (2021), who evaluated the society's perception of nursing image via the social media tool of Twitter, it was revealed that 373 tweets about the nursing profession were shared before the pandemic and that 35.65% of these tweets contained positive messages, while 64.35% contained negative messages. On the other hand, it was found that 1006 tweets were shared during the COVID-19 pandemic and that 91.94% of these tweets included positive messages while the remaining 8.06% contained negative messages (36). In this study, it was found that the society's

perceptions of the nurses' professional image during the COVID-19 pandemic were perceived highly positive, similar to the results reported in related literature.

Other findings related to the society's perception of nursing professional image were as follows: The pandemic changed the society's viewpoint about the nursing profession; the pandemic made the nursing profession visible; awareness of the place of the nursing profession in the society increased due to the pandemic; and nurses became important members of health teams during the pandemic because they were always in the field with their caregiver roles. One of the methods used in the promotion of a profession in image studies is the media (37,38). In a study examining the status of nursing in the media, all the nursing-related news, web-based publications and press releases in English on an international scale on 18 March-18 April 2020 reached by using the keyword of "nursing" were compared with those published in the same period in 2019. The comparison revealed that the news about nursing increased almost three times in the media in the stated time period in 2020 (39). In a study conducted by Ateş, Önal, Çolak and Öztürk (2021), news about healthcare workers during the COVID-19 pandemic was examined. In addition, news about the appreciation of health staff and news about the positive social image constituted 18.64% of the content of the news about the social image of health staff. When the details of the news about professional image were examined, it was seen that there were statements including positive image elements and appreciation of health staff like "…Turkey applauded and thanked the healthcare workers fighting the coronavirus on the frontline…", "… No words can summarize the efforts of the doctors, nurses and other health personnel who did their best day and night during our ongoing treatment and healed us…", "…We would like to express our gratitude to our healthcare workers who sacrificed their lives for our families and beloved we left behind, while we are here on the homeland watching…." (24). Similarly, in this study, it was found that the society's viewpoint about the nursing profession changed positively with the pandemic. The reason for this positive change might be the increased awareness of the society with the news shared in the media together with the pandemic.

CONCLUSION

It was found that the nurses and the individuals representing the society had extremely high mean scores regarding the image of nursing when compared to the pre-pandemic period. In addition, the nurses had statistically significantly higher image mean scores than the individuals representing the society. In this study, it was revealed that there was news/information attracting the attention of nurses about any development or difficulties they experienced regarding the nursing profession during the pandemic compared to the individuals in the society. The other findings related to the society's perception of nursing professional image revealed that the pandemic changed the society's viewpoint about the nursing profession positively, made the nursing profession visible and increased the awareness of the place of the nursing profession in the society. The findings also showed that nurses were thought to be important members of health teams during the pandemic as they were always in the field with their caregiver roles. Accordingly, as the nursing image perceptions of nurses and of the society are important in terms of their job performance, motivation and intention to quit their job, countries could take effective initiatives concerning the media (public advertisements, social media, and so on) to improve nurses' professional image perceptions. In addition, attempts should be made to ensure that nursing professional organizations play an active role in the legislative proposals related to nursing in order to improve nursing services.

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Case Report

The Effect of Vagus Nerve Stimulation Applications on Taste and Smell Loss in COVID-19 Syndrome: Case Report

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Abstract

Loss of the sense of taste and smell is a common side effect of Covid 19. It is thought that transcutaneous ear vagus nerve stimulation may affect taste and smell as a result of neural connections. We present a 27-year-old female participant diagnosed with loss of taste and smell for more than 1 year. The Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test was used to test the sense of smell. To test the sense of taste, 3 drops of taste test were applied. It was found that during the application period of 1 session per day for 15 days, there was a progressive improvement in the sense of taste and smell. However, it was found that the effect was not significant in restoring the sense of smell and the ability to distinguish odors.

Keywords: COVID-19, vagus nerve stimulation, anosmia, ageusia

INTRODUCTION

Coronavirus has emerged as a global health threat due to its accelerating geographical spread in the last two decades. The virus is believed to be derived from a zoonotic source and is thought to be transmitted directly and by contact. The symptomatic phase is characterized by severe respiratory failure with fever, cough, and myalgia. Diagnosis is confirmed using reverse transcriptase PCR (1). Anosmia, loss or alteration of the sense of smell, is one of the most common symptoms of COVID-19, affecting around 53% of people (2). The acute loss of sense of taste and smell after COVID-19 is the hallmark symptom, affecting between 20 and 85 percent of patients. However, the pathophysiology and potential treatments for Covid-19-related taste and smell loss are not fully understood. Reviewing potential pathological pathways and treatment options for COVID-19 smell and taste loss may be an option in the treatment of persistent dysfunction (3).

CASE REPORT

In November 2020, a 27-year-old female patient who applied to the COVID-19 outpatient clinic as a contact with complaints of runny nose, fever, and headache, SarCovV2 nasopharyngeal swab test was positive and grounded glass image was found on CT examination. At the end of the 7th day, the patient's symptoms worsened and blood tests revealed CRP 14.55 (ref. 0-5), Ferritin 9 (ref. 13-150), Blood urea nitrogen (BUN) 25mg/dl (ref. 5-50), Creatinine 0.66mg/dl (ref. 0,3-1,4), Aspartate Transaminase 13U/l (ref. 5-50), Alanine Aminotransferase 13U/l (ref. 5-50), Troponin-T 3ng/l (ref. 0-14), lactic dehydrogenase 131U/l (ref. 50-480). During the treatment, the patient used Favicovir for 7 days and continued his treatment at home. The person started to experience loss of taste and smell from the 3rd day of the disease. At the end of the 14th day, the test was negative, but the sense of taste had been partially restored and the patient had completely lost his sense of smell. Afterward, the loss of taste and smell continued steadily for more than 1 year and transcutaneous auricular vagus nerve stimulation (taVSS) was initiated.

The study was designed in accordance with the Declaration of Helsinki and approval no. 2021/4 was received from Gümüşhane University Scientific Research and Publication Ethics on 09.06.2021.

taVSS is a stimulant application that can be easily applied

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to healthy individuals to provide autonomic nervous system regulation, and; is actively used to improve general health status including sportive performance. The application was performed as noninvasive transcutaneous auricular vagus nerve stimulation from both ears and the application parameters were; Frequency: 10 Hz, Transition time: 300 micro sec, and application time: 20 min. The applications were performed with Vagustim device (Figure 1).

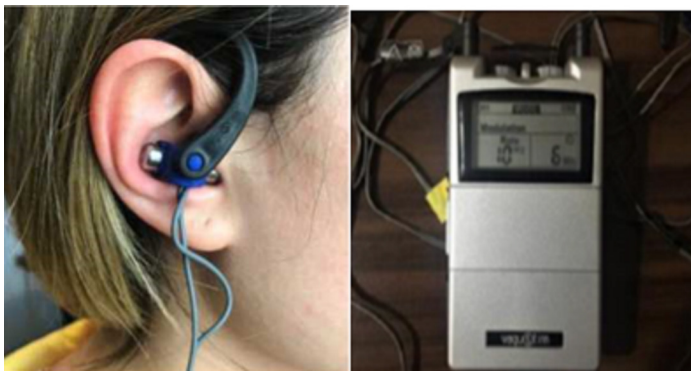

Figure 1. taVNS with Vagustim device

The application was performed in a total of 15 sessions, 5 days a week. Evaluation measurements were carried out before and after the application on each application day, and the evaluation methods were applied as follows;

To test the participants' sense of smell, the Connecticut Chemosensory Clinical Research Centre (CCCRC) Odor Test was used before and after application. The CCCRC test consists of the n-butanol odor threshold test and the odor identification test. For the n-butanol test, butanol solutions numbered from zero to seven were used and pure water was used as a control. The bottle containing 4% n-butanol was numbered zero. The other bottles contained 1/3 dilutions of the previous concentration prepared with distilled water. The threshold was defined as the correct preference for the butanol bottle on 4 consecutive trials and the N-butanol test was scored out of 7(4).

For the odor identification test, cinnamon, chocolate, coffee, soap, peanut, baby powder, naphthalene, and Viks odors were used to test olfactory nerve stimulation and trigeminal nerve stimulation as determined by Veyseller et al. The participant was asked to identify the correct odor from a list of odors that included a distractor response. After evaluation of the N-butanol and odor tests, the values for each nostril were divided by 4 to obtain the mean value, which was between 0 and 7, for each nostril (5).

A global test method, the "three drops" method, was used to assess the participant's 4 taste sensations: sweet (sucrose), salty (sodium chloride), sour (citric acid), and bitter (quinine sulfate). Three drops of liquid (two drops of pure water and one drop of sweetener) were pipetted onto the participant before and after each application. For each of the 4 taste qualities, the test was started with a dilution below the threshold of detection and was gradually increased. The flavor concentrations used were sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose, salty: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride, sour: 0.075, 0.041, 0.0225, 0.0125 g/ml citric acid, bitter: 0.0015, 0.0006, 0.0002, 0.0001 quinine hydrochloride. The lowest-density solution is numbered 1 and the highest-density solution is numbered 4. The participant was asked to identify the flavored drop and rate the taste quality using a visual analog rating scale. The relative scaling for "very low density / very high density" was assessed in the range of 0 to +100, represented by a physical length of 200 mm at each scale (6).

IBM SPSS Statistics 22 was used for statistical analysis in the evaluation of the results obtained in the study. Shapiro-Wilks tests were used to assess the compatibility of the parameters with normal distribution, and it was found that the parameters did not have a normal distribution. Wilcoxon sign test was used for changes in parameters after taVSS compared to before taVSS.

There was no statistically significant change in the value of sweet 1 in the taste evaluation after the application compared to the period before the application ($p>0.05$). The increase in the taste score of the sweet 2 value after the application compared to the value before the taVSS application is statistically significant ($p:0.015$; $p<0.05$). The increase in post-application taste scores compared to pre-application taVSS is statistically significant for sweet 3 ($p:0.048$; $p<0.05$). The increase in taste scores after application compared to before the taVSS application is statistically significant for the sweet 4 score ($p:0.041$; $p<0.05$) (Table 1).

Table 1: Evaluation of taste changes before and after taVSS treatment

	Before taVSS	After taVSS	
	mean±SD (median)	mean±SD (median)	p
Sweet 1	14.7±6.4 (10)	18.7±5.2 (20)	0.058
Sweet 2	23.3±12.9 (20)	32±7.7 (30)	0.015*
Sweet 3	48.7±12.5 (50)	56.7±8.2 (60)	0.048*
Sweet 4	74.7±16 (80)	82.7±8.8 (80)	0.041*
Salty 1	23.3±11.8 (20)	22±6.8 (20)	0.705
Salty 2	44.7±16.8 (40)	47.3±8.8 (50)	0.150
Salty 3	70.7±12.2 (70)	75.3±9.9 (80)	0.124
Salty 4	96±8.3 (100)	98.7±3.5 (100)	0.102
Sour 1	25.3±9.2 (20)	26.7±6.2 (30)	0.608
Sour 2	44±13.5 (40)	49.3±8.8 (50)	0.085
Sour 3	66±11.2 (60)	70±9.3 (70)	0.207
Sour 4	92±7.7 (90)	92.7±7 (90)	0.763
Bitter 1	11.3±7.4 (10)	13.3±6.2 (10)	0.317
Bitter 2	32.7±13.3 (30)	34.7±10.6 (40)	0.438
Bitter 3	77.3±20.5 (80)	75.3±16 (80)	0.715
Bitter 4	96.7±7.2 (100)	90±12.5 (90)	0.026*

taVSS: transcutaneous auricular vagus nerve stimulation, SD: standard deviation, Wilcoxon sign test, *p<0.05

Salty 1, salty 2, salty 3, and salty 4 values did not show a statistically significant change in taste evaluation after the application compared to before the taVSS application (p>0.05) (Table 1).

Sour 1, sour 2, sour 3, and sour 4 values did not show a statistically significant change in the taste evaluation after the application compared to before the taVSS application (p>0.05) (Table 1).

There was no statistically significant change in the taste evaluation of bitter 1, bitter 2, and bitter 3 values after the application compared to before the taVSS application (p>0.05). The decrease in taste scoring in the bitter 4 value after application compared to before the taVSS application is statistically significant (p:0.026; p<0.05) (Table 1).

There was no statistically significant change in the score of the odor assessment in threshold test 1 after the application compared to before the taVSS application (p>0.05). There was no statistically significant change in threshold 2 score odor assessment after application compared to before taVSS application (p>0.05). There was no statistically significant change in the identification scores after the application compared to the pre-application (p>0.05). Compared to before the taVSS application, there was no statistically significant change in CCRC scores after application (p>0.05) (Table 2).

Table 2: Evaluation of odour changes before and after taVSS treatment

	Before taVSS	After taVSS	
	mean±SD (median)	mean±SD (median)	p
Threshold test 1 score	3.5±2 (3)	4.1±2 (4)	0.142
Threshold test 2 score	2.3±1.5 (2)	2±1.1 (2)	0.356
Identification	1.4±0.7 (1)	1.7±0.6 (2)	0.166
CCCRC score	2.5±1.3 (2)	2.9±1.1 (3)	0.094

taVSS: transcutaneous auricular vagus nerve stimulation, CCCRC: connecticut chemosensory clinical research centre, SD: standard deviation, Wilcoxon sign test,*p<0.05

DISCUSSION

COVID-19, which has become a global pandemic, is characterized by symptoms such as fever, cough, difficulty breathing, as well as loss of taste and smell (7). Loss of taste and smell occur together, more than 80% of COVID-19 patients with smell loss also experienced taste disturbance, but did not report taste loss alone. However, loss of taste may be attributable to retronasal olfactory impairment rather than impaired gustation (taste) (8). Research using taste tests is needed to determine conclusively whether SARS-CoV-2 can damage taste transmitters or brain regions related to the taste centers of the brain (9). This confusion of taste- and olfactory-mediated sensations often makes both smell and taste tests necessary to accurately diagnose chemosensory disorders (10).

A quarter of individuals with COVID-19 had some degree of loss of olfactory function by the end of the acute recovery period (9). As in the case in the literature, only sweet and bitter taste sensations were found to be impaired by the 3-drop taste test, and no impairment was observed in salty and sour tastes. Again, our patient was evaluated as anosmia as a result of the CCCRC odor test.

If the loss of odor lasts longer than 2 weeks, treatment should be considered. The effectiveness of current treatments for patients experiencing odor loss associated with COVID-19 is unknown (7). Vagus nerve electrical stimulation may be clinically effective for COVID-19 complications (11). Significant changes were observed in cerebral regions involved in odor and taste processing caused by VSS administration (12), failed to show significant changes in olfactory perception during stimulation in a study in depressed patients (6). Although it is known that the taste sensation of the back of the tongue is associated with the vagus nerve, there is insufficient data on the interaction between vagal nerve stimulation and the olfactory and gustatory systems. In our study, improvement was observed in sweet and bitter taste sensations after VSS application, while no change was observed in salty and sour taste sensations. There was no statistically significant difference in the sense of smell. However, the patient's sense of smell increased. In addition, auricular vagus nerve stimulation was well tolerated by the patient and no side effects were observed during the study period.

CONCLUSION

In this case report, we thought to reveal that taVSS applications are one of the possible methods to be used in the loss of taste and odor after COVID-19. Our study shows that taVSS is a promising application, especially for the improvement of taste parameters. In this direction, a pilot study should first be designed with more cases, and then a randomized controlled study should be carried out by increasing the number of cases further. This case report is not inclusive because it was performed on a single case, but the positive result is promising for further research.

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Review Article

Gamma Delta T Cells and Organ Transplantation: A Review of Recent Studies

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Abstract

Gamma delta (γδ) T cells have gained a lot of attention in the field of cancer immunotherapy due to their unique innate and adaptive immune properties. However, until recently, their potential significance in organ transplantation went unnoticed. This review highlights the effector roles and potential advantages of γδ T cells in organ transplantation by examining recent studies examining the connection between T cells and organ transplantation. Recent studies have shown that high γδ T-cell immune reconstitution following organ transplantation is associated with a significantly greater overall survival rate and a lower incidence of acute graft-versus-host disease (GVHD), despite prior studies' contradictory findings. These results suggest that γδ T cells might be a useful addition to the current transplantation procedures. The effector activities of γδ T cells and their putative modes of action following organ transplantation will be covered in this review. We also provide a summary of the most recent research on the connection between γδ T cells and organ transplant outcomes, such as acute GVHD and graft survival. Finally, we point out the areas that still need to be studied in order to fully comprehend how γδ T cells function after organ donation.

Keywords: Phase angle, diabetes mellitus, fasting glucose, hemoglobin A1c

INTRODUCTION

A distinct subpopulation of lymphocytes known as gamma delta (γδ) T cells possess both innate and adaptive immunological features. In contrast to the alpha-beta (αβ) TCR expressed by typical T cells, they express a T-cell receptor (TCR) made up of gamma and delta chains (1). It is well recognized that γδ T cells are essential for a number of immunological responses, including tumor surveillance, pathogen removal, and tissue homeostasis (2). γδ T cells may play a part in organ transplantation, according to recent investigations (3).

The most successful course of action for end-stage organ failure is organ transplantation. Immune rejection, in which the recipient's immune system perceives the transplanted organ as foreign and develops an immunological response against it, limits the success of organ transplantation. Drugs that suppress the immune system are used to prevent immunological rejection, but long-term usage is linked to a number of problems, including infections and cancers (4). To enhance the results of organ transplantation, it is, therefore, necessary to investigate new immunotherapy options.

γδ T cells may have a function in organ transplantation, according to current studies. The effects of γδ T cells on organ transplantation have been studied in the past, but the findings have been mixed. While some research indicated that γδ T cells had a positive effect, other investigations found no effect or possibly a negative effect (5,6). To better appreciate the potential advantages

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and disadvantages of γδ T cells and organ donation, it is necessary to analyze the available evidence.

In this essay, we examine the most recent research on the function of γδ T cells after organ donation. We talk about the effector capabilities of γδ T cells and possible organ transplantation strategies they might employ. We also provide a summary of the most recent research on the association between γδ T cells and organ transplant outcomes, such as acute GVHD and graft survival. Finally, we point out the areas that still need to be studied to fully comprehend how γδ T cells function after organ donation.

γδ T cells

T lymphocytes have a special subgroup known as γδ T cells, which contain TCR γ and δ chains (7). γδ T cells can detect antigens in a TCR-dependent or -independent way, in contrast to traditional αβ T cells (8). The liver, gut, and epithelial tissues are only a few of the tissues where they can be found (9).

Based on how their TCRs are expressed, Vγ9Vδ2 T cells and non-Vγ9Vδ2 T cells are the two main categories of γδ T cells (10). The most prevalent type of γδ T-cell subset in peripheral blood is Vγ9Vδ2 T cells, which accounts for up to 5% of circulating T cells in healthy people (11). They detect phosphorylated non-peptidic antigens produced by different bacteria and tumor cells, such as isopentenyl pyrophosphate (IPP) (12). Although less well understood, non-Vγ9Vδ2 T cells are capable of recognizing a wide range of antigens, including self-antigens and stress-induced molecules (13).

Recent research has also raised the possibility of tissue-resident γδ T cells, which are essential for immune surveillance and tissue homeostasis (14). These tissue-resident γδ T cells differ from the circulating γδ T cells in that they have a high level of tissue selectivity (15).

γδ T cells and organ transplantation

Early studies on the organ transplant effect of γδ T cells: the role of γδ T cells in organ transplantation has been investigated since the 1990s. Early studies suggested that γδ T cells might contribute to graft rejection due to their potent cytotoxic activity and pro-inflammatory cytokine production (16). However, other studies reported conflicting results, with some indicating that γδ T cells might have a protective role in graft survival (17).

Recent studies on γδ T cells immune reconstitution after organ transplantation: the favorable impact of γδ T cells in organ transplantation has been demonstrated by more recent investigations. Studies have confirmed that patients, who received bone marrow transplantation and had high levels of γδ T cells experienced considerably lower incidences of GVHD and greater overall survival rates (18). Similar findings were made regarding kidney transplant recipients, where it was discovered that higher levels of circulating γδ T cells were linked to improved graft function and a lower risk of acute rejection (19).

γδ T cells have also been demonstrated to be important in the immune system's recovery following organ transplantation. The recovery of γδ T cells in peripheral blood was linked to a lower risk of post-transplant infections in a study of liver transplant recipients (20). Similarly, early γδ T cells recovery after heart transplantation was linked to a lower risk of infection and better graft survival (21).

These studies collectively imply that γδ T cells might be useful in organ transplantation. To clarify the underlying mechanisms and decide when and how much to provide γδ T cells-based treatments, more investigation is required.

Effector mechanisms, subtypes in several organ transplantations

A diverse group of T cells known as γδ T cells possess both innate and adaptive immunological capabilities. They are capable of identifying and reacting to a variety of antigens, including self-antigens produced by stress and non-peptidic antigens delivered by non-classical major histocompatibility complex (MHC) molecules (22, 23).

The effector mechanisms and γδ T cell subtypes in the setting of organ transplantation have been the subject of numerous research. According to one study, Vδ1 T cells, a subtype of γδ T cells, were protective against acute rejection and were selectively increased in the peripheral blood of kidney transplant recipients (23). The most common T-cell subset in human blood, Vδ2 T cells, was discovered to play a cytotoxic role in the rejection of liver transplants in another investigation (24).

Furthermore, diverse subsets of γδ T cells have been discovered to have various effector capabilities. For instance, some γδ T-cell subsets create anti-inflammatory cytokines like interleukin (IL)-10, while others produce pro-inflammatory cytokines like interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) (25). Additionally, it has been discovered that some T-cell subsets possess regulatory abilities, such as the capacity to inhibit T-cell growth and control dendritic cell activity (26).

Liver transplantation is a life-saving treatment for diverse etiologies of end-stage liver disease. Immunosuppression (IS) therapy must be administered for the remainder of a patient's life to maintain the function of an allograft liver. Patients on lifelong IS therapy had a higher mortality rate than the normal population because of infections, cancers, cardiovascular problems, and incomplete liver function preservation (27). γδ T cells after liver transplantation have both good and bad consequences, according to studies. Patients with liver transplant rejection have been found to have the presence of γδ2+ T cells, and it is considered that these γδ2 T cells may be the cause of allograft rejection. As one of T cells' beneficial effects, they lower the likelihood of GVHD, which worsens with organ damage as a result of an intense immune response mediated by healthy T lymphocytes. Intolerant liver recipients show an increase in γδ1+ T cell infiltration. It has been observed that it causes the release of interleukin (IL)-4 and IL-10, which results in the protection of allografts, particularly in the liver (28) (Figure 1).

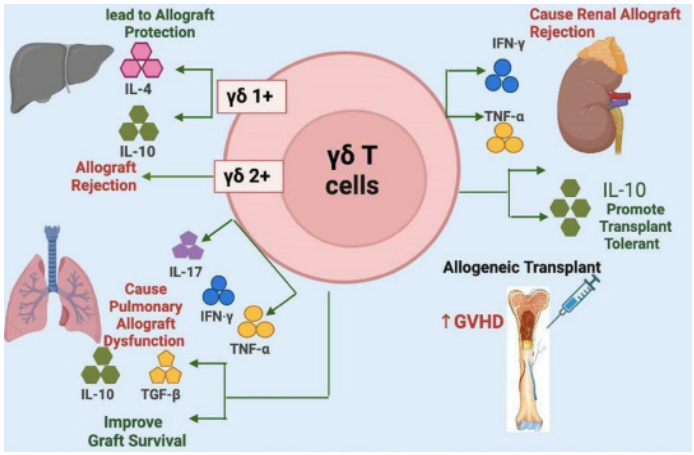

Figure 1: γδ T cells following liver transplantation have both good and bad consequences. Rejection of liver allografts has been linked to the presence of γδ2+ T cells. However, IL-4 and IL-10 are secreted when a γδ1+ T cells is activated, protecting the liver allograft. IL-17 from γδ T cells contributes to acute and chronic allograft dysfunction in lung transplants. The acute rejection of lung allografts and the early phases of renal allograft rejection is accompanied by an increase in TNF-α and IFN-γ production. In hematopoietic stem cell transplantation, acute GVHD is more common and is correlated with γδ T cells

Renal transplantation is chosen in individuals with end-stage renal failure as a therapeutic option. Transplantation necessitates long-term chronic immunosuppression to prevent acute rejection and increase graft survival. Studies have demonstrated that by releasing pro-inflammatory cytokines such as IFN-γ and TNF-α, γδ T cells can influence the early stages of renal allograft rejection (29). Additionally, during acute rejection episodes, it has been observed that γδ T cells infiltrate the renal graft, indicating their possible role in the etiology of renal allograft rejection (30).

On the other side, it has also been demonstrated that γδ T cells contribute to the development of tolerance to renal allografts. For instance, it has been discovered that γδ T cells can secrete immunoregulatory cytokines like IL-10, which can inhibit the activation of conventional T cells and encourage tolerance (31). Furthermore, some research has indicated that, under specific conditions, γδ T cells might contribute to the induction of transplant tolerance. A specific γδ T cell agonist was reported to be able to prolong the survival of cardiac allografts in mice in one investigation, indicating the potential therapeutic role of γδ T cells in fostering transplant tolerance (32).

Overall, γδ T cells have a complex and context-specific role in renal transplantation. Although they have the potential to cause acute rejection and inflammation, they can also foster tolerance and long-term graft survival (Figure 1).

Allogeneic hematopoietic stem cell transplantation is a therapeutic approach that is increasingly being employed with individuals who have hematological malignancies. γδ T cells are a distinct subset of lymphocytes that play a key role in innate immunity against a range of illnesses and have strong anticancer activity (33). They quickly regenerate following bone marrow transplantation, in contrast to αβ T cells, which take longer to mend and lead to an immunological deficit in the months immediately following transplantation. It is highly debatable whether or not γδ T cells play a role in GVHD prevention or promotion, which is one of the most frequent causes of posttransplant mortality after bone marrow transplantation. This is because distinct subsets of γδ T cells may have conflicting effects. While some research suggests that having more γδ T cells is linked to an increased frequency of acute GVHD, other research contends that there is no link between having more γδ T cells and GVHD or that having fewer cells is linked to a greater incidence of condition (34). As a result of their involvement in leukemia and infection control, γδ T cells are also expected to contribute significantly to the efficacy and safety of bone marrow transplantation, increasing patient survival (35) (Figure 1).

Pulmonary transplantation is a treatment that can treat terminal lung disease and save lives. With a median life of only 6.5 years, pulmonary transplant recipients had a worse long-term survival rate than those of other solid organ transplant recipients. Meanwhile, research has demonstrated that interleukin (IL)-17+ γδ T cells during mouse pulmonary transplantation, after 21 days of transplantation, it has been noted that it makes up a sizable fraction of the infiltrating immune cells, and in small animal lung transplant models, the generation of IL-17 by γδ T cells also plays a role in acute and chronic allograft failure (36).

In accordance with findings from additional research, γδ T cells have a role in both the early and late stages of pulmonary allograft rejection. Additionally, their presence in lung tissue is linked to an increase in inflammation and tissue damage. According to one study, acute pulmonary allograft rejection resulted in a large increase in γδ T cells, and their activation was linked to an increase in the production of pro-inflammatory cytokines like TNF-α and IFN-γ (37).

γδ T cells have been linked to promoting tolerance to pulmonary allografts in addition to their pro-inflammatory function. These cells can release immunoregulatory cytokines including IL-10 and transforming growth factor beta (TGF-β), and studies have linked their presence to lower rates of acute rejection and better long-term graft survival (38) (Figure 1).

The effector mechanisms and γδ T cell subtypes involved in organ transplantation are intricate and varied overall. To clarify the functional functions of various γδ T-cell subsets in certain transplant situations and to identify the most effective methods for influencing γδ T-cell responses for therapeutic goals, more study is required.

CONCLUSION

In conclusion, γδ T cells represent a diverse population of lymphocytes with innate and adaptive immunological characteristics. They play a complex and multidimensional function in organ transplantation, with early investigations yielding contradictory findings. However, recent research

has indicated that strong γδ T-cell immune reconstitution following organ transplantation has an advantageous outcome. High γδ T-cell counts had a considerably greater survival rate and lesser acute GVHD cases. It is still unclear how effector mechanisms and different types of γδ T cells function after organ transplantation; some subsets play protective functions while others play cytotoxic roles during rejection. To completely comprehend the functional functions of various γδ T-cell subsets in certain transplant contexts and to identify the most effective methods for influencing γδ T-cell responses for therapeutic reasons in organ transplantation, more study is required. Overall, immunomodulatory medicines in organ transplantation may find success with targeting γδ T cells.

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